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Microbial Volatile Organic Compounds

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Microbial volatile organic compounds (MVOCs) are a variety of compounds formed in the metabolism of fungi and bacteria. Of more than 200 compounds identified as MVOCs in laboratory experiments, none can be regarded as exclusively of microbial origin or as specific for certain microbial species. Thus, the recognition of microbially contaminated areas by MVOC measurements is not successful with current methods. In this review, the basic physical and chemical properties of 96 typical MVOCs have been summarised. Of these, toxicological and exposure data were gathered for the 15 MVOCs most often analysed and reported in buildings with moisture and microbial damage. The most obvious health effect of MVOC exposure is eye and upper-airway irritation. However, in human experimental exposure studies, symptoms of irritation have appeared at MVOC concentrations several orders of magnitude higher than those measured indoors (single MVOC levels in indoor environments have ranged from a few ng/m^3 up to 1 mg/m^3). This is also supported by dose-dependent sensory-irritation response, as determined by the American Society for Testing and Materials mouse bioassay. On the other hand, the toxicological database is poor even for the 15 examined MVOCs. There may be more potent compounds and other endpoints not yet evaluated

Keywords Health effect, occupational exposure limit, risk assessment, sensory irritation, toxicity

INTRODUCTION

Microbial volatile organic compounds (MVOCs) are produced in the metabolism of micro-organisms such as fungi and bacteria. They are formed during both the primary metabolism (from the synthesis of DNA and amino and fatty acids, for example) and the secondary metabolism (from intermediates of the primary metabolism) as side-products, mainly in the metabolic oxidation of glucose from various intermediates (Berry, 1988). Thus, the production of MVOCs is greatly affected by microbial species, growth phase and conditions such as nutrients, pH, humidity, and temperature (Larsen and Frisvad, 1994; Batterman, 1995; Whillans and Lamont, 1995). More than 200 compounds are regarded as MVOCs in the literature. The compounds also have other environmental sources besides microbial metabolism. Thus, compounds originating solely from microbial metabolism hardly exist.

The interest in using MVOCs as indicators of biocontamination was originally raised by the food-processing industry in the 1970s, when analysis of unpleasant-smelling MVOCs was suggested as a practical and rapid tool to detect undesirable or spoilage processes caused by micro-organisms during the storage or processing of foodstuffs (Kaminski et al., 1972, 1974; Miller et al., 1973; Lee et al., 1979; Dainty et al., 1984, 1989; Börjesson et al., 1989, 1992; Wilkins and Scholl, 1989). Later, MVOC analyses and profiles were applied to the taxonomy research to identify and separate microbial (mainly fungal) species or strains (Zeringue et al., 1993; Jelen et al., 1995; Larsen and Frisvad, 1995a, 1995b; Fischer et al., 1999; Wilkins et al., 2000; Karlshøj and Larsen, 2005). MVOCs were analysed in indoor-air environments for the first time in the 1990s (Bayer and Crow, 1994; Ström et al., 1994; Wessén and Schoeps, 1996a, 1996b; Morey et al., 1997; Wilkins et al., 1997). With MVOC analysis, a possible means of detecting hidden microbial growth

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behind interior surfaces without opening building structures was presented. It was assumed that, as gases, MVOCs may enter the indoor air (e.g. through water-vapour barriers) more easily than spores (Ström et al., 1994; Wessén et al., 1999; Lorenz et al., 2002). Concern about possible health risks related to MVOC exposure in indoor environments was also raised in the 1990s. As eye and upper-respiratory-tract irritation was frequently reported by occupants in buildings with moisture and mould damage, these symptoms were concluded to be associated with exposure to irritative substances of microbial origin (Burge, 1990). Interestingly enough, much less attention has been paid to MVOCs and their possible adverse health effects in work environments with productive microbial sources or high levels of contamination, where the occurrence of at least some MVOCs is obviously more abundant than in indoor environments.

This document reviews the literature on the compounds most frequently denoted as MVOCs. From 96 typical MVOCs listed, 15 compounds were chosen for closer toxicological evaluation (Tables 1 and 2). The toxicological data on the individual compounds presented in this document are condensed, focusing on inhalation studies and the lowest administered doses, and are largely based on toxicological reviews and literature retrieved by means of TOXNET®. Generally, high-dose effects of individual compounds are not dealt with, as they are considered

TABLE 1
Most-often reported microbial volatile organic compounds (MVOCs) in living environments, and conversion factors (National Institute for Occupational Safety and Health, 2006)

	Conversion factors (25°C, 101.3 kPa)		
Compound	1 ppm =	1 mg/m^3 =	Reference
2-Methyl-1-propanol	3.03 mg/m^3	0.330 ppm	Ström et al. (1994), Kim et al. (2007), Wieslander et al. (2007)
3-Methyl-1-butanol	3.61 mg/m^3	0.277 ppm	Ström et al. (1994), Smedje et al. (1996), Morey et al. (1997, 2000), Fedoruk et al. (1999), Lorenz et al. (2002), Mehrer and Lorenz (2005)
3-Methyl-2-butanol	3.61 mg/m^3	0.277 ppm	Ström et al. (1994)
2-Pentanol	3.61 mg/m^3	0.277 ppm	Ström et al. (1994), Smedje et al. (1996), Fedoruk et al. (1999), Lorenz et al. (2002), Mehrer and Lorenz (2005), Wieslander et al. (2007)
3-Octanol	5.33 mg/m^3	0.188 ppm	Ström et al. (1994), Smedje et al. (1996), Carlson and Quraishi (1999), Fedoruk et al. (1999)
1-Octen-3-ol	5.24 mg/m^3	0.191 ppm	Ström et al. (1994), Smedje et al. (1996), Morey et al. (1997), Carlson and Quraishi (1999), Fedoruk et al. (1999), Lorenz et al. (2002), Norbäck et al. (2003), Mehrer and Lorenz (2005), Wieslander et al. (2007)
2-Octen-1-ol	5.24 mg/m^3	0.191 ppm	Ström et al. (1994), Smedje et al. (1996), Morey et al. (1997, 2000), Carlson and Quraishi (1999), Fedoruk et al. (1999)
3-Methylfuran	3.36 mg/m^3	0.298 ppm	Ström et al. (1994), Smedje et al. (1996), Morey et al. (1997), Lorenz et al. (2002), Norbäck et al. (2003), Mehrer and Lorenz (2005), Wieslander et al. (2007)
2-Hexanone	4.10 mg/m^3	0.244 ppm	Ström et al. (1994), Fedoruk et al. (1999), Lorenz et al. (2002), Kim et al. (2007), Wieslander et al. (2007)
2-Heptanone	4.67 mg/m^3	0.214 ppm	Ström et al. (1994), Smedje et al. (1996), Morey et al. (1997, 2000), Fedoruk et al. (1999), Lorenz et al. (2002), Kim et al. (2007), Wieslander et al. (2007)
3-Octanone	5.24 mg/m^3	0.191 ppm	Ström et al. (1994), Smedje et al. (1996), Fedoruk et al. (1999), Lorenz et al. (2002), Mehrer and Lorenz (2005), Wieslander et al. (2007)
2-Methylisoborneol	6.88 mg/m^3	0.145 ppm	Ström et al. (1994), Smedje et al. (1996)
2-Isopropyl-3-methoxy-pyrazine	6.22 mg/m^3	0.161 ppm	Ström et al. (1994), Smedje et al. (1996)
Geosmin	7.46 mg/m^3	0.134 ppm	Ström et al. (1994), Smedje et al. (1996)
Dimethyl disulphide	3.85 mg/m^3	0.260 ppm	Lorenz et al. (2002), Mehrer and Lorenz (2005), Wieslander et al. (2007)

TABLE 2

Chemical identification, based on laboratory studies, of the compounds frequently reported as microbial volatile organic compounds (MVOCs) of fungi and bacteria common in the environment. The 15 substances selected for further investigation are in bold face type (ChemBioFinder, 2005; CHEMINFO, 2005; The Physical and Theoretical Chemistry Laboratory, Oxford University, 2005)

Category	Common name or name used in review	IUPAC-name	Synonyms (selected)	Chemical formula	Molecular weight	CAS-number
Alcohols	1-Butanol	Butan-1-ol	*n*-Butanol; *n*-butyl alcohol; propyl carbinol	$C_4H_{10}O$	74.12	71-36-3
	4-Decanol	Decan-4-ol	—	$C_{10}H_{22}O$	158.28	2051-31-2
	Ethanol	Ethanol	Ethyl alcohol; ethyl hydroxide; methyl carbinol; spirit	C_2H_6O	46.07	64-17-5
	2-Ethyl-1-hexanol	2-Ethylhexan-1-ol	2-Ethylhexanol	$C_8H_{18}O$	130.23	104-76-7
	2-Heptanol	Heptan-2-ol	*sec*-Heptyl alcohol; 2-heptyl alcohol; isoheptyl alcohol; 2-hydroxyheptane; 1-methylhexanol; methyl pentyl carbinol; methyl *n*-amyl carbinol	$C_7H_{16}O$	116.20	543-49-7
	1-Hexanol	Hexan-1-ol	1-Hexyl alcohol; *n*-hexyl alcohol; *n*-hexanol; amyl carbinol	$C_6H_{14}O$	102.18	111-27-3
	2-Methyl-1-propanol	2-Methylpropan-1-ol	1-Hydroxymethylpropane; 2-methylpropyl alcohol; isobutanol; isobutyl alcohol; isopropyl carbinol	$C_4H_{10}O$	74.12	78-83-1
	2-Methyl-1-butanol	2-Methylbutan-1-ol	*Sec*-Butyl carbinol	$C_5H_{12}O$	88.15	137-32-6
	3-Methyl-1-butanol	3-Methylbutan-1-ol	1-Hydroxy-3-methylbutane; 2-methyl-butanol-4; 3-methylbutanol; isoamyl alcohol; isobutyl carbinol; isopentanol; isopentyl alcohol	$C_5H_{12}O$	88.15	123-51-3
	3-Methyl-2-butanol	3-Methylbutan-2-ol	2-Hydroxy-3-methylbutane; *sec*-isoamyl alcohol; methylisopropylcarbinol	$C_5H_{12}O$	88.15	598-75-4
	1-Octanol	Octan-1-ol	1-Octyl alcohol; *n*-octanol; *n*-octyl alcohol; 1-hydroxyoctane; heptyl carbinol; caprylic alcohol	$C_8H_{18}O$	130.23	111-87-5
	3-Octanol	Octan-3-ol	*n*-Octan-3-ol; 1-ethyl-1-hexanol; *n*-amyl ethyl carbinol	$C_8H_{18}O$	130.23	589-98-0 and 20296-29-1
	1-Octen-3-ol	Oct-1-en-3-ol	3-Octenol; octen-3-ol; vinyl hexanol; 3-hydroxy-1-octene; *n*-oct-1-en-3-ol; amyl vinyl carbinol; pentyl vinyl carbinol	$C_8H_{16}O$	128.21	3391-86-4
	2-Octen-1-ol	Oct-2-en-1-ol	2-Octenol; 4-butyl-2-buten-1-ol	$C_8H_{16}O$	128.21	22104-78-5
	1-Pentanol	Pentan-1-ol	1-Pentol; pentanol-1; *n*-pentan-1-ol; *n*-pentyl alcohol; *n*-pentanol; *n*-amyl alcohol; *n*-butyl carbinol	$C_5H_{12}O$	88.15	71-41-0

(Continued on next page)

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Category	Common name or name used in review	IUPAC-name	Synonyms (selected)	Chemical formula	Molecular weight	CAS-number
	2-Pentanol	Pentan-2-ol	Pentanol-2; *sec*-amyl alcohol; methyl propyl carbinol; *sec*-pentyl alcohol	$C_5H_{12}O$	88.15	6032-29-7
	1-Propanol	Propan-1-ol	*n*-Propyl alcohol; *n*-propanol; ethyl carbinol	C_3H_8O	60.10	71-23-8
Aldehydes	Acetaldehyde	Acetaldehyde	Acetic aldehyde; acetylaldehyde; ethanal; ethyl aldehyde	C_2H_4O	44.05	75-07-0
	Acrolein	Prop-2-enal	2-Propen-1-one; 2-propenal; prop-2-en-1-al; acraldehyde; acrylaldehyde; acrylic aldehyde; allyl aldehyde; ethylene aldehyde; propenal; propenaldehyde; propylene aldehyde; *trans*-acrolein	C_3H_4O	56.06	107-02-8
	Benzaldehyde	Benzaldehyde	Benzoic aldehyde; benzoyl hydride; phenylmethanal	C_7H_6O	106.12	100-52-7
	Decanal	Decanal	Decyl aldehyde; decaldehyde; decanaldehyde; decylic aldehyde; *n*-decylaldehyde; *n*-decanal; capric aldehyde	$C_{10}H_{20}O$	156.27	112-31-2
	Formaldehyde	Formaldehyde	Formic aldehyde; methanal; methaldehyde; methyl aldehyde; methylene oxide; oxomethane; oxomethylene; oxymethylene	CH_2O	30.03	50-00-0
	Heptanal	Heptanal	*n*-Heptaldehyde; *n*-heptanaldehyde; *n*-heptyl aldehyde; *n*-heptanal; enanthic aldehyde	$C_7H_{14}O$	114.19	111-71-7
	Hexanal	Hexanal	1-Hexanal; hexaldehyde; hexoic aldehyde; *n*-hexanal; *n*-hexyl aldehyde; caproic aldehyde	$C_6H_{12}O$	100.16	66-25-1
	Nonanal	Nonanal	1-Nonaldehyde; 1-nonanal; 1-nonyl aldehyde; *n*-nonyl aldehyde; nonanoic aldehyde; nonoic aldehyde	$C_9H_{18}O$	142.24	124-19-6
	Octanal	Octanal	1-Octaldehyde; 1-octanal; 1-octylaldehyde; *n*-octaldehyde; *n*-octanal; *n*-octyl aldehyde; octanoic aldehyde; caprylic aldehyde	$C_8H_{16}O$	128.21	124-13-0
	Phenylacetaldehyde	2-Phenylacetaldehyde	1-Oxo-2-phenyl ethane; alpha-tolualdehyde; alpha-toluic aldehyde; benzeneacetaldehyde; benzyl carboxaldehyde; phenyl acetic aldehyde; phenylethanal	C_8H_8O	120.15	122-78-1

Hydrocarbons	Benzene	Benzene	Benzol; cyclohexatriene; phenyl hydride	C_6H_6	78.11	71-43-2
	Ethylbenzene	Ethylbenzene	Ethylbenzol; phenylethane	C_8H_{10}	106.17	100-41-4
	1-Heptene	Hept-1-ene	*n*-Heptene; *n*-hept-1-ene	C_7H_{14}	98.19	592-76-7
	Toluene	Toluene	Methyl benzene; methylbenzol; phenyl methane; toluol	C_7H_8	92.14	108-88-3
	1-Methyl-4-methylethyl benzene	*p*-Cymene	1-Methyl-4-isopropylbenzene; 1-methyl-4-(methylethyl)-benzene; *para*-cymene; 4-isopropyltoluene; *p*-methyl cumene; 4-methyl isopropylbenzene	$C_{10}H_{14}$	134.22	99-87-6
	2-Methyl-1,3-butadiene	2-Methylbuta-1,3-diene	2-Methylbutadiene; beta-methylbivinyl; isopentadiene; isoprene	C_5H_8	68.12	78-79-5
	1-Nonene	Non-1-ene	—	C_9H_{18}	126.24	124-11-8
	1,3-Octadiene	Octa-1,3-diene	—	C_8H_{14}	110.20	1002-33-1
	1-Octene	Oct-1-ene	—	C_8H_{16}	112.21	111-66-0
	Styrene	Styrene	Ethenylbenzene; phenylethene; phenylethylene; styrol; vinyl benzene; vinylbenzol	C_8H_8	104.15	100-42-5
	Xylenes	*o*-, *m*-, *p*-Xylene	Dimethylbenzenes; xylols; methyltoluenes	C_8H_{10} 1 xylene	106.17 1 xylene	1330-20-7
Acids	Acetic acid	Acetic acid	Ethylic acid; methanecarboxylic acid	$C_2H_4O_2$	60.05	64-19-7
	Octanoic acid	Octanoic acid	1-Heptanecarboxylic acid; *n*-octanoic acid; *n*-octylic acid	$C_8H_{16}O_2$	144.21	124-07-2
Ethers	Anisole	Anisole	Methoxybenzene; methyl phenyl ether; phenyl methyl ether	C_7H_8O	108.14	100-66-3
	1,3-Dimethoxybenzene	1,3-Dimethoxybenzene	*m*-Dimethoxybenzene; dimethylresorcinol	$C_8H_{10}O_2$	138.17	151-10-0
	2,5-Dimethylfuran	2,5-Dimethylfuran	—	C_6H_8O	96.13	625-86-5
	1-Methoxy-3-methylbenzene	1-Methoxy-3-methylbenzene	3-Methylanisole; *m*-methoxytoluene; *m*-methylanisole; 3-cresol methyl ether; 3-methoxytoluene; 3-methyl-1-methoxybenzene; *m*-cresol methyl ether; *m*-cresyl methyl ether; methyl *m*-tolyl ether	$C_8H_{10}O$	122.17	100-84-5
	1-Methoxy-3-methylbutane	1-Methoxy-3-methylbutane	4-Methoxy-2-methylbutane; isopentyl methyl ether; methyl isopentyl ether	$C_6H_{14}O$	102.17	626-91-5
	2-Methylfuran	2-Methylfuran	5-Methylfuran; alpha-methylfuran; methyl furan	C_5H_6O	82.10	534-22-5
	3-Methylfuran	3-Methylfuran	—	C_5H_6O	82.10	930-27-8
	2,3,5-Trimethylfuran	2,3,5-Trimethylfuran	—	$C_7H_{10}O$	110.15	10504-04-8

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Category	Common name or name used in review	IUPAC-name	Synonyms (selected)	Chemical formula	Molecular weight	CAS-number
Esters	Ethyl acetate	Ethyl acetate	Acetoxyethane; ethyl acetic ester	$C_4H_8O_2$	88.11	141-78-6
	Ethyl-2 methyl propionate	Ethyl 2-methyl propanoate	2-Methylpropanoic acid ethyl ester; ethyl isobutyrate	$C_6H_{12}O_2$	116.16	97-62-1
	Ethyl propionate	Ethyl propanoate	Ethyl *n*-propanoate; propanoic acid ethyl ester	$C_5H_{10}O_2$	102.13	105-37-3
	Methyl acetate	Methyl acetate	Acetic acid methyl ester; methyl acetic ester; methyl ester acetic acid; methyl ethanoate	$C_3H_6O_2$	74.08	79-20-9
	3-Methyl-1-butyl acetate	3-Methylbutyl acetate	3-Methyl-1-butanol acetate; acetic acid 3-methyl butyl ester; isoamyl ethanoate; isopentyl ester acetic acid; isopentyl acetate; isoamyl acetate	$C_7H_{14}O_2$	130.19	123-92-2
	Methyl-2-methylpropionate	Methyl 2-methylpropanoate	Methyl isobutyrate; 2-methylpropanoic acid methyl ester; methyl 2,2-dimethylacetate	$C_5H_{10}O_2$	102.13	547-63-7
	Propyl acetate	Propyl acetate	1-Propyl acetate; *n*-propyl acetate; *n*-propyl ethanoate	$C_5H_{10}O_2$	102.13	109-60-4
Ketones	Acetone	Acetone	2-Propanone; propanone; dimethyl ketone; beta-ketopropane; ketone propane	C_3H_6O	58.08	67-64-1
	2-Butanone	Butan-2-one	Ethyl methyl ketone; methyl acetone; methyl ethyl ketone; oxobutane	C_4H_8O	72.11	78-93-3
	Cyclopentanone	Cyclopentanone	Ketocyclopentane	C_5H_8O	84.12	120-92-3
	2-Heptanone	Heptan-2-one	Butyl acetone; methyl *n*-amyl ketone; *n*-amyl methyl ketone; methyl pentyl ketone	$C_7H_{14}O$	114.19	110-43-0
	2-Hexanone	Hexan-2-one	*n*-Butyl methyl ketone; methyl *n*-butyl ketone; propylacetone	$C_6H_{12}O$	100.16	591-78-6
	3-Hydroxy-2-butanone	3-Hydroxybutan-2-one	2,3-Butanolone; 2-butanol-3-one; gamma-hydroxy-beta-oxobutane	$C_4H_8O_2$	88.11	513-86-0
	3-Methyl-2-butanone	3-Methylbutan-2-one	Isopropyl methyl ketone; methyl isopropyl ketone	$C_5H_{10}O$	86.13	563-80-4
	3-Methyl-2-pentanone	3-Methylpentan-2-one	*Sec*-Butyl methyl ketone; methyl 1-methylpropyl ketone; methyl *sec*-butyl ketone	$C_6H_{12}O$	100.16	565-61-7
	4-Methyl-3-hexanone	4-Methylhexan-3-one	Ethyl isobutyl ketone	$C_7H_{14}O$	114.19	17042-16-9

	2-Nonanone	Nonan-2-one	Methyl heptyl ketone; *n*-heptyl methyl ketone	$C_9H_{18}O$	142.24	821-55-6
	2-Octanone	Octan-2-one	Hexyl methyl ketone; methyl *n*-hexyl ketone; 2-oxooctane	$C_8H_{16}O$	128.21	111-13-7
	3-Octanone	Octan-3-one	Ethyl amyl ketone; *n*-amyl ethyl ketone; ethyl pentyl ketone	$C_8H_{16}O$	128.21	106-68-3
	2-Pentanone	Pentan-2-one	Ethyl acetone; methyl *n*-propyl ketone; propyl methyl ketone	$C_5H_{10}O$	86.13	107-87-9
	3-Pentanone	Pentan-3-one	Diethyl ketone; dimethyl acetone; ethyl ketone; methacetone	$C_5H_{10}O$	86.13	96-22-0
	2-Undecanone	Undecan-2-one	Methyl nonyl ketone; undecanone	$C_{11}H_{22}O$	170.29	112-12-9
Lactones	*Gamma*-Decalactone	5-Hexyloxolan-2-one	2-Decalactone; decanoic acid; gamma-lactone; decanolactone; 4-decanolide; decanolide-1,4; 5-hexyldihydro-2(3H)-furanone; gamma-*n*-hexyl-gamma-butyrolactone	$C_{10}H_{18}O_2$	170.25	706-14-9
Terpenoids	Acoradiene	1,8-Dimethyl-4-prop-1-en-2-yl-spiro[4.5]dec-8-ene	(-)-alpha-Acoradiene; 1,8-dimethyl-4-isopropenylspiro[4.5]dec-7-ene; 1,8-dimethyl-4-(1-methylethenyl)-spiro[4.5]dec-7-ene,(1R,4S,5S)-; spiro[4.5]dec-7-ene, 1-isopropenyl-4,8-dimethyl-,(1S,4R,5S)-(-)-	$C_{15}H_{24}$	204.35	24048-44-0
	β-Bisabolene	6-Methyl-2-(4-methyl-1-cyclohex-3-enyl)-hepta-1,5-diene	(-)-beta-Bisabolene; 1,5-heptadiene, 6-methyl-2-(4-methyl-3-cyclohexen-1-yl)-, (S)-(-)-; cyclohexene, 1-methyl-4-(5-methyl-1-methylene-4-hexenyl)-, (S)-; (S)-1-methyl-4-(5-methyl-1-methylene-4-hexenyl)-1-cyclohexene	$C_{15}H_{24}$	204.35	495-61-4
	Cadinene	1,6-Dimethyl-4-propan-2-yl-1,2,3,4,4a,5,6,8a-octahydronaphthalene	b-Cadinene; [1S-(1alpha,4alpha,4aalpha,6alpha, 8alphabeta)]-decahydro-1,6-dimethyl-4-(1-methylethyl)naphthalene	$C_{15}H_{26}$	206.37	29350-73-0
	Δ3-Carene	3,7,7-Trimethyl-bicyclo[4.1.0]hept-3-ene	3-Carene; car-3-ene; delta-3-carene; S-3–carene; isodiprene; 3,7,7-trimethyl bicyclohept-3-ene; 3,7,7-trimethylbicyclo[4.1.0]-3-heptene; 3-norcarene, 3,7,7-trimethyl-; 4,7,7-trimethyl-3-norcarene	$C_{10}H_{16}$	136.24	13466-78-9

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Category	Common name or name used in review	IUPAC-name	Synonyms (selected)	Chemical formula	Molecular weight	CAS-number
	Camphene	2,2-Dimethyl-3-methylidene-norbornane	(+/−)-Camphene; 2,2-dimethyl-3-methylene-bicyclo[2.2.1]heptane; 2,2-dimethyl-3-methylene norbornane; 3,3-dimethyl-2-methylene-norcamphane; 3,3-dimethyl-2-methylene norcamphone	$C_{10}H_{16}$	136.24	79-92-5
	β-Caryophyllene	4,11,11-Trimethyl-8-methylidene-bicyclo [7.2.0]undec-4-ene	(−)-beta-Caryophyllene; l-caryophyllene; (−)-*trans*-caryophyllene; (−)-E-caryophyllene; [1R-(1R*,4E,9S*)]-8-methylene-4,11,11-trimethylbicyclo[7.2.0]-4-undecane; [1R-(1R*,4E,9S*)]-4,11,11-trimethyl-8-methylene-bicyclo[7.2.0]-4-undecene; 4,11,11-trimethyl-8-methylene-bicyclo[7.2.0]undec-4-ene; bicyclo[7.2.0]undec-4-ene, 4,11,11-trimethyl-8-methylene-, (E)-(1R,9S)-(-)-	$C_{15}H_{24}$	204.35	87-44-5
	β-Chamigrene	1,1,9-Trimethyl-5-methylidene-spiro[5.5]undec-9-ene	Spiro[5.5]undec-2-ene, 3,7,7-trimethyl-11-methylene, (6R)-; (-)-3,7,7-trimethyl-11-methylenespiro[5.5]undec-2-ene	$C_{15}H_{24}$	204.35	18431-82-8
	α-Curcumene	2-Methyl-6-(4-methyl-phenyl)-hept-2-ene	a-Curcumene; 2-Heptene, 2-methyl-6-*p*-tolyl-; 1-(1,5-dimethyl-4-hexenyl)-4-methylbenzene; 1-methyl-4-(6-methylhept-5-en-2-yl)benzene	$C_{15}H_{22}$	202.34	644-30-4
	β-Elemene	1-Ethenyl-1-methyl-2,4-diprop-1-en-2-yl-cyclohexane	Cyclohexane, 1-ethenyl-1-methyl-2,4-bis(1-methylethenyl)-, (1alpha,2beta,4beta)-; 2,4-diisopropenyl-1-methyl-1-vinylcyclohexane, stereoisomer	$C_{15}H_{24}$	204.35	33880-83-0
	α-Farnesene	(3E,6E)-3,7,11-Trimethyldodeca-1,3,6,10-tetraene	*trans*-alpha-Farnesene; (3E, 6E)-alpha-farnesene; 2,6,10-trimethyl-2,6,9,11-dodecatetraene; 3,7,11-trimethyl-1,3,6,10-dodecatetraene	$C_{15}H_{24}$	204.35	502-61-4
	β-Farnesene	(6E)-7,11-Dimethyl-3-methylidene-dodeca-1,6,10-triene	*trans*-beta-Farnesene; E-beta-farnesene; 7,11-dimethyl-3-methylene-1,6,10-dodecatriene	$C_{15}H_{24}$	204.35	18794-84-8

Geosmin	4,8a-Dimethyldecalin-4a-ol	1-α,10-β-Dimethyl-9α-decalol, 2,6-dimethyl bicyclo[4.4.0]decan-1-ol; octahydro-4,8a-dimethyl-4a(2H)-naphthalenol; *trans*-1,10-dimethyl-trans-9-decalol	$C_{12}H_{22}O$	182.31	23333-91-7 and 19700-21-1
α-Gurjunene	No IUPAC name	(-)-α-Gurjunene; 1H-cycloprop[e]azulene, 1a,2,3,4,4a,5,6,7b-octahydro-1,1,4,7-tetramethyl-, (1aR, 4R, 4aR, 7bS)-; 1H-cycloprop[e]azulene, 1a.beta.,2,3,4,4a.alpha.,5,6,7b.beta.-octahydro-1,1,4.beta.,7-tetramethyl-	$C_{15}H_{24}$	204.35	489-40-7
Limonene	1-Methyl-4-prop-1-en-2-yl-cyclohexene	DL-Limonene; eulimen; DL-*p*-mentha-1,8-diene; acintene DP dipentene; cajeputene; ciene; cinene; cyclil decene; nesol; terpodiene; 1-methyl-4-(1-methylethenyl)-cyclohexene; 4-(1-methylethenyl)-1-methyl-cyclohexene; 4-isopropenyl-1-methyl-1-cyclohexene; 4-isopropenyl-1-methyl-cyclohexene; methyl-4-(1-methylethenyl)cyclohexene; methyl-4-isopropenyl-1-cyclohexene; methyl-4-isopropenylcyclohexene	$C_{10}H_{16}$	136.24	138-86-3
Longifolene	No IUPAC name	Kuromatsuene; junipene; d-longifolene; (+)-longifolene; (+)-longofolene; [1S-(1alpha,3abeta,4alpha,8abeta)]-decahydro-4,8,8-trimethyl-9-methylene-1,4-methanoazulene; decahydro-4,8,8-trimethyl-9-methylene-1,4-methanoazulene	$C_{15}H_{24}$	204.35	475-20-7
2-Methyli-soborneol	1,2,7,7-Tetramethyl-norbornan-2-ol	Bicyclo [2.2.1] heptan-2-ol; 1,2,7,7-tetramethyl-, (1R, 2R, 4R)-rel-; bicyclo [2.2.1] heptan-2-ol, 1,2,7,7,tetramethyl-, exo-; 2-norbornanol, 1,2,7,7-tetramethyl-, exo-; 2-endo-methyl-2-exo-bornanol exo-1,2,7,7-tetramethylbicyclo[2.2.1]heptan-2-ol	$C_{11}H_{20}O$	168.28	2371-42-8

(Continued on next page)

TABLE 2
Chemical identification, based on laboratory studies, of the compounds frequently reported as microbial volatile organic compounds (MVOCs) of fungi and bacteria common in the environment. The 15 substances selected for further investigation are in bold face type (ChemBioFinder, 2005; CHEMINFO, 2005; The Physical and Theoretical Chemistry Laboratory, Oxford University, 2005) *(Continued)*

Category	Common name or name used in review	IUPAC-name	Synonyms (selected)	Chemical formula	Molecular weight	CAS-number
	β-Phellandrene	3-Methylidene-6-propan-2-yl-cyclohexene	1(7)-2-*p*-Menthadiene; 3-methylene-6-(1-methylethyl)-cyclohexene	$C_{10}H_{16}$	136.24	555-10-2
	α-Pinene	4,7,7-Trimethyl-bicyclo[3.1.1]hept-3-ene	2-Pinene; pin-2(3)-ene; acintene A; cyclic dexadiene; 2,6,6-trimethylbicyclo[3.1.1]hept-2-ene	$C_{10}H_{16}$	136.24	80-56-8
	β-Pinene	7,7-dimethyl-4-methylidene-bicyclo[3.1.1]-heptane	2(10)-Pinene; nopinene; pseudopinene; terebenthene; bicyclo[3.1.1]heptane, 6,6-dimethyl-2-methylene-	$C_{10}H_{16}$	136.24	127-91-3
	Thujopsene	No IUPAC name	(-)-Thujopsene; sesquichamene; widdrene; cyclopropa[d]naphthalene, 1,1a,4,4a,5,6,7,8-octahydro-2,4a,8,8-tetramethyl-, (1aS, 4aS, 8aS)-	$C_{15}H_{24}$	204.35	470-40-6
	Trichodiene	1,4-Dimethyl-4-(1-methyl-2-methylidene-cyclopentyl)-cyclohexene	Cyclohexene, 1,4-dimethyl-4-[(1S)-1-methyl-2-methylenecyclopentyl]-; cyclohexene, 1,4-dimethyl-4-(1-metyl-2-methylenecyclopentyl)-, [S-(R*, R*)]-	$C_{15}H_{24}$	204.35	28624-60-4
Sulphur and nitrogen compounds	**Dimethyl disulphide**	Methyldisulfanyl-methane	Methyl disulphide; 2,3-dithiabutane; (methyldithio)methane	$C_2H_6S_2$	94.19	624-92-0
	Dimethyltrisulphide	Methylsulfanyldisul-fanyl-methane	Methyl trisulphide; trisulphide, dimethyl; 2,3,4-trithiapentane	$C_2H_6S_3$	126.27	3658-80-8
	2-Isopropyl-3-methoxy-pyrazine	2-Methoxy-3-propan-2-yl-pyrazine	2-Isopropyl-3,5 (or 6)-methoxypyrazine; 2-methoxy-3,5(6)-isopropyl pyrazine; 2-methoxy-3-isopropyl-pyrazine; 2-methoxy-3-(1-methylethyl)-pyrazine	$C_8H_{12}N_2O$	152.20	25773-40-4
	2-Methoxy pyrazine	2-Methoxypyrazine	Methoxy pyrazine	$C_5H_6N_2O$	110.12	3149-28-8

irrelevant in the context of MVOCs. However, some MVOCs are also industrial chemicals, and some health-effect data can be obtained from such exposures. As industrial exposure levels are generally much higher than those encountered in the MVOC context, the lowest available doses are high when compared with levels of microbial origin. Most of the concern raised regarding MVOC exposure has been about home environments. In the present review, the focus is on the non-industrial working population rather than the general public, although the majority of the available data originates from dwellings.

This review is an updated version of a criteria document from the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals originally published in the serial Arbete och Hälsa (Korpi et al., 2006).

SUBSTANCE IDENTIFICATION

MVOCs are formed during both the primary and the secondary metabolism of micro-organisms as side-products, mainly in the metabolic oxidation of glucose, from various precursors, such as acetate, amino acids, fatty acids, and keto acids (Berry, 1988). The primary metabolism of micro-organisms comprises the synthesis of DNA and amino and fatty acids, whereas the secondary metabolism consists of reactions following the primary metabolism. As the primary metabolism involves an inter-related series of enzyme-catalysed chemical reactions, it is basically the same for all living systems (Korpi, 2001). Thus, for several MVOCs other sources, such as vegetation and even mammalian breath, sweat, and skin emanations, have been identified (Helmig et al., 1999; Phillips et al., 1999; Takken and Knols, 1999). The identified MVOCs are alcohols, ketones, terpenes, esters, lactones, hydrocarbons, aldehydes, sulphur and nitrogen compounds (Larsen and Frisvad, 1995a; Wilkins and Larsen, 1995b; Jelen and Wasowicz, 1998). The complex metabolic pathways for MVOC formation are depicted in Figure 1 and the precursors of some common MVOCs are presented in Table 3.

For convenience, it is often stated that MVOCs are side-products of the primary metabolism of micro-organisms, and

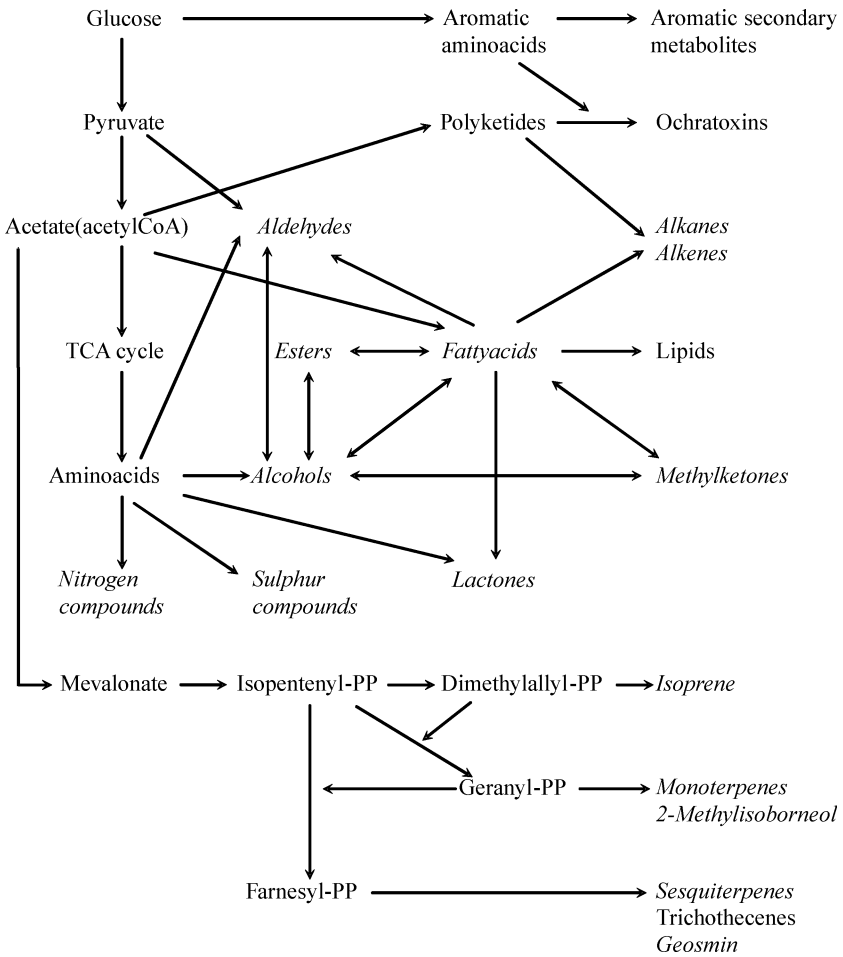

FIG. 1. Main metabolic pathways for the production of some microbial volatile organic compounds (MVOCs) and mycotoxins (Turner, 1971; Gadd, 1988; Sunesson, 1995; Wessen et al., 1995; Korpi, 2001). Volatile compounds are in italics. Abbreviations: Co A = coenzyme A, PP = pyrophosphate, TCA = tricarboxylic acid.

TABLE 3
Some common microbial volatile organic compounds (MVOCs) and their precursors in the microbial metabolism

Precursor	Volatile product(s)	Reference
Amino acids		
Alanine	Acetaldehyde	Hawke (1966)
α-Amino acids	Alkyl methoxy pyrazine	Sunesson (1995)
Glycine	Formaldehyde	Hawke (1966)
Leucine	3-methyl-1-butanol	Berry (1988), Slaughter (1988), Bjurman (1999)
Methionine, cysteine	Dimethyl disulphide	Sunesson (1995), Bjurman (1999)
Valine	2-methyl-1-propanol	Berry (1988), Slaughter (1988), Bjurman (1999)
Phenylalanine	Phenyl acetaldehyde, styrene	Hawke (1966), Berry (1988), Slaughter (1988), Larsen and Frisvad (1995a), Bjurman (1999)
Organic acids		
Fatty acids	Alkenes and alkadienes, aldehydes, methylketones with one carbon less than the original fatty acid (e.g. 2-butanone, 2-pentanone, 2-hexanone, 2-heptanone, 2-undecanone)	Hawke (1966), Sunesson (1995), Wilkins and Larsen (1995b)
Medium-chain fatty acids	Acetates	Berry (1988)
γ- or δ-Hydroxy acids, keto acids, long-chain fatty acids	4-hexanolide, 6-pentyl-α-pyrone	Fessenden and Fessenden (1990), Chalier and Crouzet (1992), Sunesson (1995)
Linoleic acid, linolenic acid	1-octen-3-ol, 3-octanol, 3-octanone, hexanal, heptanal, nonanal	Wurzenberger and Grosch (1984), Chalier and Crouzet (1993), Larsen and Frisvad (1995a), Bjurman (1999)
Others		
Isopentenyl pyrophosphate	Terpenoid compounds: monoterpenes, sesquiterpenes and their alcohols, geosmin	Turner (1971), Bentley and Meganathan (1981), Turner and Aldridge (1983), Sunesson (1995), Bjurman (1999)

that mycotoxins are end-products of the secondary metabolism. However, since the division between primary and secondary metabolism is not absolute (Bentley and Bennett, 1988), it can only be stated that MVOCs are formed during both (Berry, 1988). As nutritional imbalances and disorders (e.g. a lack of primary carbon and nitrogen sources) lead to expression of the secondary metabolism, changes in the nutritional state may often promote or trigger the production of several MVOCs (Turner, 1971; Berry, 1988; Bjurman, 1999; Korpi, 2001). On the other hand, it has been suggested that secondary metabolites may be inhibitors of the primary metabolism (Sunesson, 1995), and volatile metabolites of certain bacteria may stimulate mycotoxin production (Barr, 1976). The production of certain fungal MVOCs has also been suggested to be associated with mycotoxin production. Evidence of such relationships has been reported between the sesquiterpenes and aflatoxins, between monoterpenes, sesquiterpenes and trichothecenes, and between ketones and ochratoxins (Zeringue et al., 1993; Jelen et al., 1995; Pasanen et al., 1996; Demyttenaere et al., 2003, 2004; Wilkins et al., 2003).

Chemical reactions in the environment may further convert the produced MVOCs into other compounds. For example, alcohols are easily oxidised to aldehydes and further to carboxylic acids (Wilkins et al., 1997), and ketones may react with hydroxyl radicals in the air to form aldehydes (Atkinson et al., 2000).

Chemical reactions may also produce MVOCs in the atmosphere; the reactions between ozone (and other oxidants) and unsaturated hydrocarbons (isoprenes/terpenes) have recently been investigated experimentally. The main products in

these reactions are aldehydes, ketones, and organic acids, but the intermediate products formed during the reactions have been suggested to be much more irritating than the corresponding original reactants and end-products (Wolkoff et al., 1999, 2000; Weschler, 2000). For example, under humid conditions, the reaction between ozone and isoprene produces hydrogen peroxide, methacrolein, and methylvinyl ketone (Sauer et al., 1999), all of which are known irritants. Another suspected oxidation product of isoprene is 3-methylfuran (Helmig et al., 1999).

Finally, it must not be overlooked that MVOCs may also have other sources in the environment, such as building materials, human activities, traffic, foodstuffs, and smoking (Sunesson, 1995; Helmig et al., 1999; Schleibinger et al., 2002).

So far, more than 200 individual compounds have been recognised as MVOCs in laboratory studies (Larsen and Frisvad, 1995a; Wilkins and Larsen, 1995b; Jelen and Wasowicz, 1998). The majority of the experimental studies have been carried out with pure cultures of selected, individual microbial species, often grown on agar, cereals and other foodstuffs, bedding materials (e.g. straw, peat, shavings) or building materials (e.g. wood, wall paper, gypsum, chipboard, cardboard and plasterboard, insulation materials like glass and mineral wool), degradable household waste, and house dust (Kaminski et al., 1972, 1974; Seifert and King, 1982; Harris et al., 1986; Börjesson et al., 1989, 1990, 1993; Zeringue et al., 1993; Jelen et al., 1995; Sunesson, 1995, 1996; Wilkins and Larsen, 1995a, 1995b; Pasanen et al., 1996; Sunesson et al., 1996, 1997; Wessén and Schoeps, 1996b; Bjurman et al., 1997; Korpi et al., 1997, 1999c; Lappalainen et al., 1997; Pasanen et al., 1997; Wheatley et al., 1997; Wilkins et al., 1997, 2000, 2003; Fischer et al., 1998, 1999; Schleibinger and Rüden, 1999; Fiedler et al., 2001; Gao et al., 2002; Gao and Martin, 2002; Menetrez and Foarde, 2002; Schleibinger et al., 2003; Meruva et al., 2004; Claeson and Sunesson, 2005; Claeson, 2006). MVOCs produced by mixed cultures on building materials have been investigated in a few studies (Ezeonu et al., 1994; Wessén et al., 1995; Korpi et al., 1998; Braathen et al., 2002; Claeson et al., 2002a, 2002b). In these studies, MVOCs were produced by species or strains of microbial genera common in the environment, such as *Absidia, Acremonium, Alternaria, Aspergillus, Botrytis, Candida, Chetomium, Cladosporium, Coniophora*, *Fusarium, Paecilomyces, Penicillium, Phialophora, Poria, Pseudomonas, Rhizopus, Saccharomyces, Serpula, Stachybotrys, Streptomyces*, *Trichoderma, Ulocladium* and *Wallemia*.

The 15 MVOCs that were selected for closer examination in the present document are listed in Table 1 and represent compounds analysed and reported in laboratory or field studies. In these studies, the selection of compounds identified was often limited to 10–15 because of study-design and analytical restraints, and the whole range of MVOCs has not been monitored. For example, acetaldehyde, nonanal, 2-pentanone, limonene, and sesquiterpenes are among the most commonly identified microbial metabolites in laboratory experiments, yet they have not been reported in field samples, probably because of non-microbial sources in the field, and analytical limitations (sesquiterpenes).

A more comprehensive list, covering 96 frequently reported MVOCs and including substance identification data, is given in Table 2. For additional lists of compounds, the reader is referred to the publications by Larsen and Frisvad (1995a) and Jelen and Wasowics (1998).

Thus, based on present knowledge, it is difficult to make a reliable list of relevant MVOCs. This is because, in the majority of experimental studies, controlled experiments are lacking, as respective sterile materials and their qualitative and quantitative emissions have seldom been reported. Therefore, the concepts of VOC and MVOC overlap inasmuch as the origin of a compound reported as an MVOC may well be the emission of a substrate as well. This hampers the interpretation of the data in field settings. For example, Wilkins and Larsen (1995b) have suspected that toluene, xylenes, and ethyl benzene might not result from microbial metabolism, even though these compounds are often reported as MVOCs. Furthermore, an individual MVOC cannot be related to a certain microbial species, because the same MVOC may be produced by different microorganisms; that is, bacterial and fungal species share the same MVOCs. This is natural because of the similarities in metabolism and growth conditions that are key factors for MVOC production in any microbial species. Finally, the methodology used for MVOC analyses varies between studies and affects the MVOC profiles reported in the literature considerably. Attempts have been made to apply principal-component analysis in order to identify areas of microbial contamination relying on the VOC profiles of environmental samples (Wilkins et al., 1997).

PHYSICAL AND CHEMICAL PROPERTIES

Some physical and chemical properties of MVOCs are listed in Table 4. An indication of the volatility of a compound can be deduced from the number of carbon atoms, the molecular weight, boiling point, and the vapour pressure (Sunesson, 1995). The interpretation of vapour pressures of the MVOCs presented in Table 4 is as follows: 0.00001–0.00100 kPa = moderately volatile compound; 0.001–0.100 kPa = volatile compound; and >0.1 kPa = very volatile compound (Nikunen et al., 2000).

OCCURENCE

As MVOCs are a result of microbial metabolism, factors that control microbial growth also influence MVOC production: (a) microbial species and strains (this is the basis for approaches for species identification based on MVOC profile); (b) substrates and nutrients (e.g. lack of certain nutrients leads to terpene emissions, and presence of certain amino acids in the substrate results in sulphur and nitrogen compounds); (c) moisture conditions (water activity and relative humidity, which affect growth and thereby MVOC production); (d) ergosterol content of the growth substrate; (e) ambient VOCs in the air or in the growth substrate; and (f) temperature (Sprecher and Hanssen, 1982; Börjesson et al., 1989, 1990, 1992, 1993; Bjurman and

TABLE 4
Some physical and chemical properties of compounds reported as MVOCs. Data are partly based on calculated or predicted coefficients (International Programme on Chemical Safety/WHO, 1989; CAS, 2005; ChemBioFinder, 2005; CHEMINFO, 2005; US National Library of Medicine, 2005; International Programme on Chemical Safety, 2005; The Physical and Theoretical Chemistry Laboratory, Oxford University, 2005; Syracuse Research Corporation, 2005). Substances selected for closer examination are in bold face type

Category	Compound	Boiling point (°C)[a] at 101.3 kPa	Vapour pressure (kPa) at 25°C	Octanol:water partition coefficient, log K_{ow}	
				Experimental	Calculated
Alcohols	1-Butanol	117.7	0.587–0.73[c]	0.88	—
	4-Decanol	210.5	0.0049	—	3.71
	Ethanol	78.5	5.9[c]	−0.32	—
	2-Ethyl-1-hexanol	183.5	0.007[c]; 0.048[c]	—	2.73
	2-Heptanol	159.2	0.164	2.31	—
	1-Hexanol	157.1–157.5	0.124	2.03	—
	2-Methyl-1-propanol	108	1.33	0.65; 0.83	—
	2-Methyl-1-butanol	128	0.416	1.29	—
	3-Methyl-1-butanol	130.5	0.316	1.16	—
	3-Methyl-2-butanol	111.5	1.22	1.28	—
	1-Octanol	194.5–195.0	0.0106	3.00	—
	3-Octanol	169.0	0.068	—	2.73
	1-Octen-3-ol	180	0.071	—	2.60
	2-Octen-1-ol	195.8 ± 8.0	0.014	—	2.59
	1-Pentanol	137.8	0.218[c]	1.42; 1.48; 1.51	—
	2-Pentanol	119.0–119.3	0.815	1.19	—
	1-Propanol	97.2– 97.8	1.9–2.0[c]	0.25; 0.34	—
Aldehydes	Acetaldehyde	20.2	100[c]	−0.34	—
	Acrolein	52.5	28.5[c]	—	−0.01
	Benzaldehyde	178–179	0.133[d]	—	1.48
	Decanal	208	0.028	—	3.76
	Formaldehyde	–19.0 to –19.5	519; 462	0.35	—
	Heptanal	152.8	0.469	—	—
	Hexanal	131	1.507	—	1.78
	Nonanal	191	0.049	—	3.27
	Octanal	163.4	0.28	—	2.78
	Phenylacetaldehyde	200	0.049	—	—
Hydrocarbons	Benzene	80	12.7	1.18–1.90; 2.13; 2.15	—
	Ethylbenzene	136.2	1.28	3.15	—
	1-Heptene	94	7.62	—	3.99
	Toluene	110.6	2.93[c]	2.11–2.80	—
	1-Methyl-4-methylethyl benzene	177.10	0.20	—	4.10
	2-Methyl-1,3-butadiene	34.067	73.33	—	2.42
	1-Nonene	146.9	0.720	—	5.15
	1,3-Octadiene	130–131	1.79	—	—
	1-Octene	121.2	2.32	—	4.57
	Styrene	145.2	0.81	2.95	—
	Xylenes	129–150[b]	0.800–0.867[c]	3.12–3.20	—
Acids	Acetic acid	117.9	1.52[c]	–0.31	—
	Octanoic acid	237; 239.7	0.133[e]	0.63	—

TABLE 4
Some physical and chemical properties of compounds reported as MVOCs. Data are partly based on calculated or predicted coefficients (International Programme on Chemical Safety/WHO, 1989; CAS, 2005; ChemBioFinder, 2005; CHEMINFO, 2005; US National Library of Medicine, 2005; International Programme on Chemical Safety, 2005; The Physical and Theoretical Chemistry Laboratory, Oxford University, 2005; Syracuse Research Corporation, 2005). Substances selected for closer examination are in bold face type *(Continued)*

Category	Compound	Boiling point (°C)[a] at 101.3 kPa	Vapour pressure (kPa) at 25°C	Octanol:water partition coefficient, log K_{ow}	
				Experimental	Calculated
Ethers	Anisole	155.5	0.472	—	2.11
	1,3-Dimethoxybenzene	217.5	0.026	—	2.21
	2,5-Dimethylfuran	93.1 ± 9.0	7.61	—	2.24
	1-Methoxy- 3-methylbenzene	177	0.24	—	2.66
	1-Methoxy- 3-methylbutane	90	11.06	—	1.96
	2-Methylfuran	65	23.48	—	1.85
	3-Methylfuran	65–66	21.46	—	1.91
	2,3,5-Trimethylfuran	121–122	1.92	—	—
Esters	Ethyl acetate	76.5–77.5	9.73[c]	0.66; 0.73	—
	Ethyl-2-methyl propionate	110.1	2.88	—	1.77
	Ethyl propionate	99.1	5.0	1.21	—
	Methyl acetate	56.9	23.1[c]; 21.7[c]	0.18	—
	3-Methyl-1-butyl acetate	142.5	0.75	2.26	—
	Methyl-2-methyl-propionate	93–95	6.72	—	1.28
	Propyl acetate	101.6	4.67	1.39; 1.60	—
Ketones	Acetone	56.2	24.0–24.7[c]	–0.24	—
	2-Butanone	79.6	10.33[c]	0.26; 0.29	—
	Cyclopentanone	130.6	1.52	—	0.24
	2-Heptanone	150.6; 151.5	0.213; 0.28	2.03	—
	2-Hexanone	126–128	1.47[c]; 0.36[c]	1.38	—
	3-Hydroxy-2-butanone	148	0.256	—	–0.36
	3-Methyl-2-butanone	93	8.6[c]	—	0.84
	3-Methyl-2-pentanone	117.3–117.5	2.42	—	1.16
	4-Methyl-3-hexanone	135–138	1.075	—	1.66
	2-Nonanone	194	0.086	—	3.14
	2-Octanone	173	0.23	—	2.37
	3-Octanone	157–162	0.267	—	2.22
	2-Pentanone	102	3.59[c]	0.91	–
	3-Pentanone	102	4.7	0.99	—
	2-Undecanone	231.5	0.013	—	4.09
Lactones	γ-Decalactone	266.7 ± 8.0	0.00113	—	—
Terpenoids	Acoradiene	273.1 ± 15.0	0.0013	—	6.99
	β-Bisabolene	275.4 ± 15.0	0.0011	—	7.12
	Cadinene	120[f]	5.33[g]	—	6.19
	Δ3-Carene	167–170	0.248	—	4.61
	Camphene	158.5	0.333	—	4.22
	β-Caryophyllene	268.4 ± 10.0	0.0017	—	6.30
	β-Chamigrene	273.2 ± 15.0	0.0013	—	7.02
	α-Curcumene	276.3 ±15.0	0.0011	—	6.29
	β-Elemene	252.1 ± 15.0	0.0042	—	7.04
	α-Farnesene	279.6 ± 15.0	0.00090	—	7.10
	β-Farnesene	272.5 ± 15.0	0.0013	—	7.17

(Continued on next page)

TABLE 4
Some physical and chemical properties of compounds reported as MVOCs. Data are partly based on calculated or predicted coefficients (International Programme on Chemical Safety/WHO, 1989; CAS, 2005; ChemBioFinder, 2005; CHEMINFO, 2005; US National Library of Medicine, 2005; International Programme on Chemical Safety, 2005; The Physical and Theoretical Chemistry Laboratory, Oxford University, 2005; Syracuse Research Corporation, 2005). Substances selected for closer examination are in bold face type *(Continued)*

Category	Compound	Boiling point (°C)[a] at 101.3 kPa	Vapour pressure (kPa) at 25°C	Octanol:water partition coefficient, log K_{ow}	
				Experimental	Calculated
	Geosmin	252.4 ± 8.0	0.00041	—	3.57
	α-Gurjunene	263.9 ± 7.0	0.0022	–	6.18
	Limonene	170	0.280[c]	—	4.57
	Longifolene	250–255	0.0042	—	5.48
	2-Methylisoborneol	208.7 ± 8.0	0.0065	–	3.31
	β-Phellandrene	171.5	0.210	—	4.70
	α-Pinene	155	0.47	—	4.83
	β-Pinene	166.0	0.32	—	4.35
	Thujopsene	256.5 ± 7.0	0.0033	—	6.12
	Trichodiene	256.7 ± 15.0	0.0033	—	—
Sulphur and nitrogen compounds	**Dimethyl disulphide**	109.8	3.83	1.77	—
	Dimethyl trisulphide	183.1 ± 23.0	0.142	—	1.87
	2-Isopropyl-3-methoxy-pyrazine	210.8 ± 30.0	0.036	—	2.37
	2-Methoxy pyrazine	153.6 ± 0.0	0.56	—	0.73

[a] ± indicates that the value was obtained with an extrapolation model providing a range.
[b] Variable depending on isomer composition.
[c] 20°C.
[d] 26°C.
[e] 92.3°C, extremely low at room temperature.
[f] 9 mmHg (1.2 kPa).
[g] 180°C.

Kristensson, 1992a, 1992b; Rivers et al., 1992; Zeringue et al., 1993; Dionigi and Ingram, 1994; Jelen et al., 1995; Larsen and Frisvad, 1995b, 1995c; Sunesson et al., 1995b, 1996, 1997; Pasanen et al., 1996; Whillans and Lamont, 1996; Bjurman et al., 1997; Korpi et al., 1997, 1998, 1999c; Lappalainen et al., 1997; Bjurman, 1999; Horner et al., 1999; Wilkins et al., 1999, 2000, 2003; Fiedler et al., 2001; Braathen et al., 2002; Claeson et al., 2002a, 2002b; Gao and Martin, 2002; Schleibinger et al., 2002, 2003, 2005). On the other hand, sporulation intensity (the concentration of culturable spores) has not been shown to affect MVOC production (Börjesson et al., 1990, 1992; Wilkins et al., 2000). Contradictory results on the influences of some factors (e.g. production of metabolic CO_2, oxygen concentration, and growth phase or age of the colony) on MVOC profiles have also been reported. One explanation for this may be defects in sampling techniques and differences in study design (Korpi et al., 1997). Though MVOCs mainly originate from fresh and metabolically active microbial contamination, certain MVOCs have been suggested to reflect emissions from an aged, perhaps even previous, microbial contamination, because of their high absorption affinity to building materials (Wessén et al., 1995). MVOC levels indoors are a balance between production rates, absorption to and desorption from building materials and furniture, and ventilation.

In minor scale, MVOCs were initially analysed in order to detect undesirable or spoilage processes during the storage or processing of foodstuffs (Miller et al., 1973; Lee et al., 1979; Dainty et al., 1984, 1989; Börjesson et al., 1989, 1992; Wilkins and Scholl, 1989). More recently, MVOC analysis was applied to recognise indoor odour sources and hidden microbial growth behind interior surfaces without opening building structures (Bayer and Crow, 1994; Ström et al., 1994; Wessén and Schoeps, 1996a, 1996b; Morey et al., 1997; Wilkins et al., 1997), because it was assumed that, being gases, MVOCs may enter indoor air through water-vapour barriers more easily than spores (Ström et al., 1994; Wessén and Hall, 1999).

However, it is not possible to conclude whether a compound derives from microbial metabolism or from the emission of substrates or environmental pollutants. This hampers the specificity

and interpretation of MVOC analyses and limits the use of MVOCs for identifying contaminated areas in a building. For example, terpenes are commonly emitted from wood products, but are also reported as MVOCs in laboratory studies. Likewise, 2-ethyl-1-hexanol, which has been named as an MVOC, is a degradation product of phthalates in polyvinyl chloride (PVC) floorings under humid and alkaline conditions (Gustafsson, 1990). Korpi et al. (1998) reported that moist building materials not microbiologically contaminated emitted compounds that, when deriving from microbial metabolism, would be called MVOCs. Kuske et al. (2005) suggested that MVOC evaporation from humid materials could actually be used to indicate moisture problems anticipating fungal growth. In favourable conditions, microbial germination and growth can occur in one day (Pasanen et al., 1992). Still, the concentrations of MVOCs cannot unequivocally be related to mould grade. According to Laussmann et al. (2004), the sum of eight MVOCs failed to discriminate between rooms according to their mould status. Schleibinger et al. (2005, 2008) concluded similarly that MVOCs could not be used as predictors for mould damage in indoor environments. In a study of 40 dwellings with and 44 dwellings without mould damage, the occurrence of 2-methylfuran and 3-methylfuran correlated with smoking rather than with mould infestation. Even though 2-methyl-1-butanol and 1-octen-3-ol were weakly correlated with fungal state, the sensitivity and specificity of these compounds were concluded to be too low to make them useful indicators (Schleibinger et al., 2004, 2008).

MEASUREMENT AND ANALYSIS OF MVOCs

As there are no standards, consensus, or even recommendations regarding the sampling and analysis of MVOCs, the methodology presented in the literature varies greatly and comparative data on different methods are scarce. MVOCs can be collected from ambient air with either active or passive sorbent sampling. Several sorbents or their combinations, like activated charcoal (e.g. Anasorb® 747), graphitised carbon blacks (e.g. Carbotrap C, Carbopack B), silica gels (e.g. Porasil C), and polymers (e.g. Tenax® TA or GR, Anasorb® 727, Chromosorb 102, XAD-4) have been used for both sampling techniques in indoor environments (Batterman, 1995; Sunesson, 1995; Sunesson et al., 1995a; Elke et al., 1999; Claeson et al., 2002b; Schleibinger et al., 2008). In addition, carbonyl compounds have been collected separately with 2,4-dinitrophenylhydrazine-silica Sep-Pak® cartridges in some cases (Korpi et al., 1998; Schleibinger and Rüden, 1999). Tenax® TA has been widely used because of favourable properties regarding recovery, breakthrough, and precision during sampling and analysis (Sunesson et al., 1995a). On the other hand, activated charcoal enables longer sampling periods and the collection of very volatile MVOCs (Ström et al., 1994).

Nowadays, MVOCs from environmental samples are mainly analysed with high-resolution gas chromatograph and mass spectrometry and identified according to their mass spectra. Another applicable detector is the flame ionisation detector (Batterman, 1995; Sunesson, 1995; Korpi et al., 1998; Claeson et al., 2002b). The sample preparation depends on the sorbent used; for example, for Tenax® polymers, the sample is led from the adsorbent to the gas-chromatography column by a thermal desorption cold trap injector (Sunesson, 1995), whereas for charcoal sorbents (such as Anasorb®), desorption with solvent (e.g. methylene chloride) is required before leading the sample into the gas chromatograph (Ström et al., 1994). Carbonyl compounds collected in 2,4-dinitrophenylhydrazine-silica Sep-Pak cartridges are analysed by high-performance liquid chromatography after extraction with acetonitrile (Korpi et al., 1998; Schleibinger and Rüden, 1999; Claeson et al., 2002b).

Recently, a solid-phase microextraction (SPME)–gas-chromatography–mass-spectrometry technique has been applied to analyse MVOCs qualitatively from microbial cultures or contaminated building materials (Fiedler et al., 2001; Wady et al., 2003). In SPME, a short fused silica fibre coated with a polymeric organic material (e.g. polyacrylate and polydimethylsiloxane) is used as a secondary phase. Nilsson et al. (1996) reported comparable results between SPME and Tenax® adsorption. The SPME method has been applied by several research teams to qualitatively characterise fungal emissions (Nilsson et al., 1996; Fiedler et al., 2001; Demyttenaere et al., 2003, 2004; Jelen et al., 2003; Wady et al., 2003).

Attempts have been made to establish evaluation criteria for indoor environments (Lorenz et al., 2002). The principal component analysis is one approach for interpreting chromatograms of house-dust samples collected from areas with various grades of microbial contamination (Wilkins et al., 1997). The use of an electronic nose to detect fungal contamination in indoor environments has also been recently reviewed. The electronic nose is meant to recognise the patterns of compounds related to the occurrence of fungi. The authors concluded that at present, despite promising implications, the low MVOC concentrations and presence of interfering substances restrict the use of the electronic nose in indoor settings (Kuske et al., 2005).

EXPOSURE DATA

Measurements of MVOCs in field settings have focused on indoor environments, especially buildings with water and microbial damage or unspecified indoor-air problems. Published data on MVOC measurements in problem buildings are available mainly from Sweden, Germany, and the US (Ström et al., 1994; Wessén et al., 1995, 1999, 2000; Smedje et al., 1996; Wessén and Schoeps, 1996a, 2000; Morey et al., 1997, 2000; Carlson and Quraishi, 1999; Fedoruk et al., 1999; Keller et al., 1999; Lorenz et al., 2002; Wieslander et al., 2007). The aim has not been to get exposure data, but rather to reveal contaminated areas or buildings. The data are, however, far too limited for the evaluation of global or even local exposure to MVOCs. Also, the lack of standardised and validated analytical methods for MVOCs makes comparison between studies difficult (Keller et al., 1999). Even though the number of determined MVOCs and analytical methods have been the same in different studies,

the sum of MVOCs in problem buildings may differ by three orders of magnitude (Ström et al., 1994; Morey et al., 1997; Fedoruk et al., 1999; Wessén et al., 1999, 2000).

The available data regarding concentrations of MVOCs in problem and normal buildings or areas and outdoor air are summarised in Table 5. The indoor-air concentrations have been measured in residences or in non-industrial work sites such as schools. In some of these studies, the study design and the presentation of the data have not allowed a satisfactory differentiation between problem and reference buildings or areas (Smedje et al., 1996; Morey et al., 2000; Lorenz et al., 2002). The concentrations of individual compounds in problem buildings have varied from a few ng/m^3 to 1 mg/m^3, and the same compounds have also been identified in reference buildings or areas and even outdoor air. Generally, the maximum reported levels of individual MVOCs are 0.1–10 μg/m^3 in problem buildings. However, levels of approximately 100 μg/m^3 of 2-heptanone (Morey et al., 2000) and 270 μg/m^{3}of 3-methyl-1-butanol (Morey et al., 2000) and 2-octen-1-ol (Morey et al., 1997) have been reported. The highest individual MVOC concentration (approximately 900 μg/m^3) is reported for 1-octen-3-ol (Morey et al., 1997).

When it comes to the use of the sum of certain MVOCs—or total MVOCs, as they are sometimes called—investigators have included different MVOCs. In fact, different research groups have included between 7 and 23 compounds in total MVOCs. The decision on which MVOCs to include has differed significantly even if the number of compounds was the same. Bearing in mind the great variation in the number of compounds, some ranges for total MVOC levels can still be indicated. In problem buildings or areas, total MVOCs have been reported as 0.05–85.7 μg/m^3 (although there is one case report in which a total MVOC concentration of 1,800 μg/m^3 is reported), in reference areas as n.d. to 30.1 μg/m^3, and in outdoor air as n.d. to 9.5 μg/m^3 (Ström et al., 1994; Wessén et al., 1995, 1999, 2000; Wessén and Schoeps, 1996a; Morey et al., 1997; Carlson and Quraishi, 1999; Fedoruk et al., 1999; Keller et al., 1999; Lorenz et al., 2002; Norbäck et al., 2003; Kim et al., 2007; Wieslander et al., 2007).

Because of overlapping concentrations of both individual compounds and the sum of selected MVOCs in problem and reference buildings, it is difficult to recognise problem buildings on the basis of MVOC measurements, or to establish reference values for MVOCs, though some suggestions have recently been presented. Based on the presented data, concentrations $\geq$15 μg/m^{3}of 2-octen-1-ol, $\geq$10 μg/m^3 of 1-octen-3-ol and 3-methyl-1-butanol, $\geq$1.5 μg/m^{3}of 2-methyl-1-propanol and 2-methylisoborneol, $\geq$0.4 μg/m^3 of 2-isopropyl-3-methoxypyrazine, $\geq$0.2 μg/m^{3}of 3-methylfuran, 3-methyl-2-butanol and 3-octanol, and $\geq$0.05 μg/m^{3}of geosmin could be assumed to indicate an abnormal level (Table 5). However, according to Lorenz et al. (2002), the detection of main indicators (i.e. 3-methylfuran, 1-octen-3-ol, and dimethyl disulphide) at concentrations above 0.05 μg/m^3 would clearly indicate a microbial source. In addition, the presence of at least one of the main indicators and the sum of eight MVOCs exceeding 0.6 μg/m^3 or 1.0 μg/m^3 would indicate a probable or very probable microbial source, respectively. To avoid false-positive results, new buildings (<6 months), rooms with flower pots, waste, and pet cages, and interference from smoking, cooking and baking should be excluded (Lorenz et al., 2002). At present, the concentration limits suggested by Lorenz et al. are difficult to apply universally, since different research groups are measuring different MVOCs. Differences in methods of sampling and analysis add additional variability.

In some studies (Fedoruk et al., 1999; Wessén and Schoeps, 2000), increased levels of some MVOCs (3-methylfuran, 3-methyl-1-butanol, dimethyl disulphide, 2-hexanone, 2-heptanone, 1-octen-3-ol, and 3-octanone) were detected before remedial actions and moisture or microbial-contamination control measures in buildings. A decrease in the levels was observed after the mitigation, though measurements in some cases provided contradictory results (Fedoruk et al., 1999). Again, the selection of compounds (which has never been justified in the MVOC literature) and the analysis methods affect the results.

Little attention has been paid to MVOCs in work environments with productive microbial sources or high levels of contamination (Fischer and Dott, 2003). MVOCs like 3-methyl-1-butanol, 2-methyl-1-butanol, ketones, furans, sulphur compounds, geosmin, and terpenes have been identified in the air of compost facilities (Fischer et al., 1998, 1999, 2000; Li et al., 2004; Muller et al., 2004a). Individual MVOC concentrations have varied from 0.1 μg/m^3 to 1,000 μg/m^3 (Muller et al., 2004a). In a laboratory study, typical VOCs in composts included carbonyl derivatives, organosulphur compounds, pyrazines, pyridines, and oxygenated monoterpenes. Concentrations of organic sulphur compounds (thioethers, disulphides, and trisulphides) in garden waste were concluded to be sufficiently high (10–50 mg/m^3) to cause irritation and other symptoms of toxicity among waste-handling personnel (Wilkins and Larsen, 1995a). Herr et al. (2002) reported gradually decreasing concentrations of 11 MVOCs (in the range 0.005–6.0 μg/m^3) measured at different distances (200–550 m) from a large-scale composting site. The authors demonstrated an association between concentrations of residential bioaerosol pollution including MVOCs (<200 m from the plant) and complaints of airway irritation (Herr et al., 2002). In a similar study, compost-derived MVOCs (especially terpenes) were registered by measurements at distances up to 800 m from the composting facilities. Dispersal of volatile contaminants from the composting plant was associated with odour complaints and irritation symptoms (Muller et al., 2004b). The compounds most often detected at different distances (70–1,445 m) in the surroundings of three composting facilities were 3-methyl-1-butanol, 2-heptanone, 1-octen-3-ol, and dimethylsulphide. The maximum concentration detected was approximately 0.55 μg/m^3 for 3-methyl-1-butanol. These authors noticed, however, that MVOC concentrations did not necessarily decrease with increasing distance from the facility. Nor did the MVOC concentrations coincide with odour dispersal,

TABLE 5
Reported concentrations of individual microbial volatile organic compounds (MVOCs) in buildings and outdoor air

	Range of reported MVOC concentrations ($\mu g/m^3$)				
Compound	Problem buildings/ complaint areas	Reference buildings/ non-complaint areas	Building/area with unspecified identification	Outdoor air	References
2-Methyl-1-propanol	nd–1.740	0.340–1.380	na	nd–0.210	Ström et al. (1994), Kim et al. (2007), Wieslander et al. (2007)
3-Methyl-1-butanol	0.175–260	nd–8.700	nd–110	nd–3.800	Ström et al. (1994), Smedje et al. (1996), Morey et al. (1997, 2000), Fedoruk et al. (1999), Lorenz et al. (2002), Mehrer and Lorenz (2005), Kim et al. (2007)
3-Methyl-2-butanol	0.190–1.190	nd–0.160	na	nd–0.070	Ström et al. (1994), Fedoruk et al. (1999)
2-Pentanol	nd–1.400	nd–1.700	nd–0.450	nd–0.630	Ström et al. (1994), Smedje et al. (1996), Fedoruk et al. (1999), Lorenz et al. (2002), Mehrer and Lorenz (2005), Kim et al. (2007), Wieslander et al. (2007)
3-Octanol	nd–8.86	nd	nd–0.040	nd–0.140	Ström et al. (1994), Smedje et al. (1996), Carlson and Quraishi (1999), Fedoruk et al. (1999)
1-Octen-3-ol	nd–904	nd–7	nd–1.540	nd–1.900	Ström et al. (1994), Smedje et al. (1996), Morey et al. (1997), Carlson and Quraishi (1999), Fedoruk et al. (1999), Lorenz et al. (2002), Norbäck et al. (2003), Mehrer and Lorenz (2005), Kim et al. (2007), Wieslander et al. (2007)
2-Octen-1-ol	1.560–266	nd–13.100	nd–14	nd–6.820	Ström et al. (1994), Smedje et al. (1996), Morey et al. (1997, 2000), Carlson and Quraishi (1999), Fedoruk et al. (1999)
3-Methylfuran	nd–1.800	nd–0.1600	nd–0.024	nd–0.110	Ström et al. (1994), Smedje et al. (1996), Morey et al. (1997), Fedoruk et al. (1999), Lorenz et al. (2002), Norbäck et al. (2003), Mehrer and Lorenz (2005), Kim et al. (2007), Wieslander et al. (2007)

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TABLE 5
Reported concentrations of individual microbial volatile organic compounds (MVOCs) in buildings and outdoor air *(Continued)*

Compound	Range of reported MVOC concentrations ($\mu g/m^3$)				References
	Problem buildings/ complaint areas	Reference buildings/ non-complaint areas	Building/area with unspecified identification	Outdoor air	
2-Hexanone	0.025–8.800	0.007–2.900	traces–0.190	nd–0.800	Ström et al. (1994), Fedoruk et al. (1999), Lorenz et al. (2002), Kim et al. (2007), Wieslander et al. (2007)
2-Heptanone	nd–97	nd–1.200	nd–44	nd–1.100	Ström et al. (1994), Smedje et al. (1996), Morey et al. (1997, 2000), Fedoruk et al. (1999), Lorenz et al. (2002), Kim et al. (2007), Wieslander et al. (2007)
3-Octanone	nd–3.020	nd–3	nd–0.410	nd–2	Ström et al. (1994), Smedje et al. (1996), Fedoruk et al. (1999), Lorenz et al. (2002), Mehrer and Lorenz (2005), Kim et al. (2007), Wieslander et al. (2007)
2-Methylisoborneol	nd–2.8	nd–0.56	nd–0.020	nd–1.180	Ström et al. (1994), Smedje et al. (1996), Fedoruk et al. (1999)
2-Isopropyl-3-methoxy-pyrazine	nd–9.5	nd	nd–0.003	nd–0.340	Ström et al. (1994), Smedje et al. (1996), Fedoruk et al. (1999)
Geosmin	nd–0.55	nd	nd–0.050	nd–0.010	Ström et al. (1994), Smedje et al. (1996), Fedoruk et al. (1999)
Dimethyl disulphide	0.016–0.09	nd–0.71	nd–0.050	nd–0.260	Lorenz et al. (2002), Mehrer and Lorenz (2005), Kim et al. (2007), Wieslander et al. (2007)

Abbreviations: nd, not detected, na, not analysed.

indicating, as the authors pointed out, that even compounds not analysed in the study or those occurring in concentrations below the detection limit can contribute to specific compost odour (Fischer et al., 2008). Lappalainen et al. (1997) measured MVOCs in a horse stable. The concentrations were $\leq$0.5 $\mu g/m^3$ for 2-hexanone, $\leq$4.6 $\mu g/m^3$ for 2-heptanone, and $\leq$1.5 $\mu g/m^3$for 3-octanone. These authors estimated that the concentrations of potential MVOCs were only approximately 0.07–0.31% of the concentrations of total VOCs in the horse stable. The emission rates for single VOCs from bedding materials in the stable varied between 0.2 $\mu g/kg/h$ and 2 $\mu g/kg/h$, being about 10 times higher than the corresponding rates in the laboratory experiments.

To conclude, reported individual and total MVOC levels are quite low and barely exceed 1 mg/m^3, even in fairly contaminated areas.

TOXICOKINETICS

The body burden of MVOCs, as of any chemical substance, is influenced by the rate of absorption, distribution, biotransformation, and excretion. MVOCs are by definition volatile, hence the dominating route of exposure is via inhalation. On the basis of experiences with organic solvents, some of which may also be considered MVOCs, it can safely be assumed that the respiratory uptake of MVOCs is in general considerable and that the dermal uptake of vapour is not more than a few

percent of the respiratory uptake. Since MVOCs are small and mostly uncharged molecules, they easily diffuse across cellular membranes. Hence, they are readily transported between alveolar air and blood and between blood and other tissues. The distribution of MVOCs in the body depends on their tissue:blood partition coefficients. The log octanol:water partition coefficients of MVOCs are listed in Table 4. Substances with high octanol:water partition coefficients tend to have high tissue:blood and especially fat:blood partition coefficients (Poulin and Krishnan, 1995). Examples of such substances are long-chained alcohols (e.g. octanol and decanol), hydrocarbons (e.g. heptene) and ketones (e.g. undecanone), aromatic hydrocarbons, and terpenoids (Table 2). For example, the high solubility of terpenes in blood and other tissues suggests high respiratory uptake and thus accumulation in adipose tissue (Falk et al., 1990).

Aliphatic and aromatic alcohols and carboxylic acids undergo conjugation with glucuronic acid in the liver, kidney, intestine, skin, brain, and spleen. Glucuronides are excreted from the body via urine or bile. Another important conjugation reaction for hydroxyl groups (present in aliphatic alcohols) is sulphation, yielding conjugates that are excreted mainly in urine. Oxidation-reduction systems prevail in the body for the biotransformation of aldehydes, ketones, and alcohols. Aldehydes and ketones can be reduced to alcohols by aldehyde/ketone reductases, alcohols can be oxidised to aldehydes by alcohol dehydrogenase, and then further oxidised to acids by aldehyde dehydrogenase (Sipes and Gandolfi, 1991). Ketones may also undergo an omega-minus-1 oxidation process to form hydroxyketones and be further metabolised to the corresponding diones (Wibowo, 1990; ATSDR, 1992a, 1992b). One example is 2-hexanone, which undergoes biotransformation to the neurotoxic γ-diketone 2,5-hexanedione (Bos et al., 1991).

The aromatic ether 3-methylfuran is metabolically activated via microsomal oxidation, cleaving the furan ring to a highly reactive unsaturated dialdehyde (methyl butenedial) that binds covalently to tissue macromolecules (Ravindranath et al., 1984).

For sulphur-containing compounds, the oxidation of sulphur or desulphuration occurs by the addition of oxygen via cytochrome P450. Alkene epoxidation and oxidative *N*-dealkylation, *O*-dealkylation, or *S*-dealkylation proceed via cytochrome P450-mediated reactions to form epoxide and hydroxyalkyl moieties, respectively. The formed aliphatic epoxides are then hydrolysed to dihydrodiol products, and the hydroxyalkyl part decomposes into an aldehyde or ketone and a metabolite containing a free amino, hydroxyl, or sulphhydryl group (Sipes and Gandolfi, 1991).

BIOLOGICAL MONITORING

Methods for biological exposure monitoring are available for many organic solvents that also appear as MVOCs, such as acetone, benzene, 1-butanol, 2-butanone, ethylbenzene, 2-hexanone, toluene, terpenes, and xylenes or their metabolites (DFG, 2005; American Conference of Government Industrial Hygienists, 2006). However, these methods have been developed and are applicable for much higher exposure levels than those typically encountered in the MVOC setting. For the 15 MVOCs listed in Table 1, no such methods are routinely available. Moreover, although background levels in human blood or breath are found for only a few of the typical MVOCs in the scientific literature (e.g. acetone, ethanol, isoprene, and methanol; Smith et al., 1999; Diskin et al., 2003), most MVOCs are likely to be present in small amounts in human tissues, as a result of endogenous or microbial metabolism, or both. Thus, a number of the alcohols, aldehydes, ethers, and esters listed in Tables 2 and 4 have been detected in the exhaled breath of humans (Mathews et al., 1997). The endogenous production and the resulting background levels for these compounds are not known exactly, although some VOC measurements have been taken from the exhaled breath of humans (Fenske and Paulson, 1999; Phillips et al., 1999). Obviously, endogenous background exposure may invalidate biomonitoring of MVOCs at low exposure levels. High metabolism rates and low exposure levels restrict the application of biomonitoring for the exposure assessment of MVOCs. In addition, two or more exposing agents may produce the same metabolites, as is the case with 2-hexanone and *n*-hexane, thus hampering the selection of a specific biomarker for exposure to 2-hexanone.

MECHANISM OF TOXICITY

MVOCs can elicit a variety of toxic systemic effects at concentrations far higher than is relevant in this context. Such toxicity is not discussed in this section. Sensory irritation is a known effect of exposure to VOCs; this effect thus also applies to MVOCs.

Irritation of the eyes and upper airways (i.e. sensory irritation, also called pungent sensation), is because of stimulation of the trigeminal nerve (Cometto-Muñiz and Cain, 1996). It has been suggested that the strength of the response depends on the number of occupied receptors. Only limited knowledge exists about such receptors (Nielsen et al., 1992, 2007; Wolkoff et al., 2006), which have been identified only in a few cases (Nielsen et al., 2007). It has also been proposed that the magnitude of the response in turn depends on the chemical structure of the compounds (Nielsen et al., 1992). Even small differences in the chemical structure, such as different enantiomers of the same compounds, may affect the potency (Kasanen et al., 1998; Nielsen et al., 2005).

Wolkoff et al. (2006) have recently proposed that it is possible to distinguish between four types of different organic compounds in the indoor environment that could provoke sensory irritation in the airways. The groups of the proposed compounds are as follows: (a) chemically non-reactive, stable organic compounds (i.e. octane, toluene, butanol, and alike); (b) chemically reactive organic compounds like alkenes that react with ozone alone or with nitrogen dioxide in the presence of light to produce new oxygenated products; (c) organic compounds that form chemical bonds to receptor sites in the mucous membranes; and (d) organic compounds with (known) toxic properties—these

compounds are characterised by effects developed over long duration of exposure. Receptors, if any, that mediate the effects of MVOCs have yet to be elucidated and characterised. However, it is likely that at least some of the MVOC-mediated effects are due to activation of receptors in the airways (Alarie, 1973).

It has been proposed that sensory-irritation receptors can be activated in different ways. Physical binding to the receptor is typical for non-reactive VOCs, including most MVOCs. Chemicals with high water solubility and high reactivity, such as ammonia, formaldehyde, and acrolein, would lead to receptor activation through modification of the receptor structure or adjacent structures important for receptor activation (Alarie, 1973, 1998a). Other mechanisms that activate receptors associated with sensory irritation include chemical reactions of amines and nucleophilic addition of isocyanates (Alarie et al., 1998b).

It has also been suggested that irritation may arise through activation of polymorphonuclear neutrophils (PMNs), alveolar macrophages or other professional phagocytes in the lung tissue (Alarie, 1973; Nielsen et al., 1995; Wolkoff et al., 2006). These effects are thought to be due to proinflammatory and other bioactive mediators released from the phagocytic cells upon their activation (Nielsen et al., 2005). It should be noted that irritations due to an inflammatory reaction and due to stimulation of nerve endings are not related. Finally, pulmonary irritation may be due to stimulation of vagal nerve endings at the alveolar level. Direct compound-stimulation of vagal nerve endings occurs rapidly in relation to the onset of exposure, and disappears when exposure is terminated. However, these nerve endings can also be stimulated because of oedema. As oedema develops and dissipates slowly, the onset of such an irritative process is slow.

EFFECTS IN ANIMALS AND *IN VITRO* STUDIES

Irritation and Sensitisation

The most apparent effect following acute MVOC exposure is irritation. In this article, only irritation from vapours is considered. Skin-irritation studies with application of concentrated solutions of the test substance were regarded irrelevant in the context of MVOCs.

Alarie (1966) introduced the so-called mouse bioassay, which was later established as a standard test method for estimating sensory irritancy of airborne chemicals by the American Society for Testing and Materials (1984). This method has been widely used to assess the sensory-irritation potency of aerosols, gases, and vapours. Thus, the method is also applicable for estimation of airway irritation due to inhalation of MVOCs. The sensory-irritation potency can be quantified by the changes in breathing patterns and respiratory functions at a given exposure level (airborne concentrations of a chemical used in the experiments). From these relationships, the concentration causing a 50% decrease in the respiratory rate (RD_{50}) can be estimated (Alarie, 1966, 1973).

Schaper (1993) compiled a large database of results obtained by this bioassay. The data since 1993 until 2006 have been gathered in Nielsen et al. (2007). In addition to the bioassay, the sensory-irritation potencies of non-reactive volatile compounds, such as alkylbenzenes, saturated alcohols, and ketones, can be estimated on the basis of physicochemical descriptors (e.g. molecular weight, vapour pressure, or Ostwald gas–liquid partition coefficients). This is possible because the effect of the compounds is probably induced via physical adsorption to the biological receptors (Abraham et al., 1994; Alarie et al., 1995, 1996, 1998a, 1998b). Since most MVOCs are non-reactive (towards SH or OH groups in proteins), their RD_{50}s can be calculated theoretically by means of the physicochemical variables. RD_{50}s calculated or determined by the mouse bioassay for some MVOCs are presented in Table 6.

TABLE 6
The RD_{50}s for some microbial volatile organic compounds (MVOCs) (Schaper, 1993; Pasanen et al., 1998; Korpi et al., 1999b)

	RD_{50}	
Compound	mg/m^3	ppm
2-Methyl-1-propanol	5,499	1,815
3-Methyl-1-butanol	9,325	2,583
3-Methyl-2-butanol	9,645	2,672
2-Pentanol	9,907	2,744
3-Octanol	1,359	255
1-Octen-3-ol	182	35
2-Octen-1-ol	–[a]	–[a]
3-Methylfuran	–[a]	–[a]
2-Hexanone	10,449	2,550
2-Heptanone	4,163	891
3-Octanone	17,586	3,359
2-Methylisoborneol	811	118
2-Isopropyl-3-methoxy-pyrazine	–[a]	–[a]
Geosmin	216	29
Dimethyl disulphide	37,330[b]	9,700[b]

[a]Fundamental understanding or data about the substance's potency as a sensory irritant is missing.

[b]Estimated by document authors by using the following formula (Alarie et al., 1998b): $\log RD_{50}$ (ppm) = 2.693 + (0.887 $\log P^{\circ}$) (P°, mmHg).

In the case of exposure to MVOCs, low exposure concentrations of several MVOCs frequently occur (in the range of ng/m^3–$\mu g/m^3$). Effects of exposure to chemical mixtures can be additive, antagonistic, or synergistic. If we assume that additivity prevails at low exposure levels to VOC mixtures, the total sensory-irritation potency would be the sum of the effects that each compound would elicit alone (Nielsen et al., 1995). The estimation is based on the sum of ratios of the fractional concentration (c) and the RD_{50} of each compound:

$$1 / RD_{50mixture} = \Sigma\ (c_n/RD_{50n})$$

It has been proposed that effects at higher exposure concentrations might show synergistic interactions (Nielsen et al., 1995). This was verified by Korpi et al. (1999b), who investigated the sensory-irritation potency of 1-octen-3-ol, 3-octanol, and 3-octanone, separately, and the potency of an MVOC mixture including 2-methyl-1-propanol, 3-methyl-1-butanol, 1-octen-3-ol, 2-heptanone, and 3-octanone by the mouse bioassay. The RD_{50}s for these MVOCs are presented in Table 6. The RD_{50} for the mixture was 3.6 times lower than estimated from the sum of fractional concentrations and the RD_{50}s of individual compounds (the estimated $RD_{50}$was 504 mg/m^3 and the observed RD_{50} 142 mg/m^3). As expected, if a particular compound in the mixture is much more potent than the other ones, it may dominate the effect.

Korpi et al. (1999a) also investigated the effect of repeated exposures (30 min per day during four consecutive days) to 3-octanone (3,531 mg/m^3), 1-octen-3-ol (36 mg/m^3), or to a mixture of 2-methyl-1-propanol ($\sim$6 mg/m^3), 3-methyl-1-butanol ($\sim$6 mg/m^3), 1-octen-3-ol ($\sim$19 mg/m^3), 2-heptanone ($\sim$19 mg/m^3) and 3-octanone ($\sim$6 mg/m^3) by the mouse bioassay. The levels for the two individual MVOC experiments were chosen to produce a clear respiratory rate decrease (11–20% for 1-octen-3-ol with a very steep dose–response curve and 32% for 3-octanone). The proportions of the MVOCs in the mixture were chosen to reflect those measured in mouldy buildings or mouldy building materials, and test concentrations were chosen to maximally yield a 32% decrease in the respiratory frequency. For single MVOCs, no changes in the responses were observed between the exposures, and only a very slight adaptation in respiratory function occurred along with the exposures to the MVOC mixture. The authors concluded that MVOCs seem to act as 'pure' sensory irritants and the effects of a short-term, repeated exposure at levels ranging from $<0.001 \cdot RD_{50}$ to $0.2 \cdot RD_{50}$ seem non-cumulative and transient.

Histamine induces inflammation and, in an *in vitro* study, human bronchoalveolar lavage cells were incubated with MVOCs of *Trichoderma viride* (e.g. 2-methyl-1-propanol, 3-methyl-1-butanol, 2-methyl-1-butanol, 1-pentanol) with the result of evoked histamine release from the cells. The histamine release was statistically significant when it increased from approximately 12% to 20% at VOC concentrations ranging from 0.04% to 10% (v/v; Larsen et al., 1998). Hypothetically, exposure to MVOCs, especially to reactive oxygen metabolites (after reactions with ozone and other oxidants) may then function as adjuvants by inducing non-specific airway hyperresponsiveness and inflammation (Nielsen et al., 1995).

In the reactions between oxidants and unsaturated hydrocarbons, intermediates formed may be much more irritating than the original reactants and end-products (Sauer et al., 1999; Wolkoff et al., 1999, 2000; Weschler, 2000).

In summary, irritation is the most probable effect of MVOC exposure and RD_{50}s for a number of MVOCs have been estimated by the mouse bioassay. Assuming additivity at low exposure concentrations, the total sensory potency of an MVOC mixture can be calculated. However, at higher concentrations, synergy may occur. Effects of short-term, repeated exposures at levels high enough to produce a clear respiratory rate decrease seem to be non-cumulative and transient.

Effects of Single Exposure

The most apparent effect following acute MVOC exposure is irritation. However, acute high-level vapour exposure to MVOCs generally has the potential to cause narcosis, central-nervous-system disturbance and death (Andrews and Snyder, 1991).

The lethal dose for 50% of the exposed animals at single administration (LD_{50}) and the corresponding lethal concentration for 50% of the animals at single inhalation exposure (LC_{50}) are measures of the general acute toxic potency of a chemical (Andrews and Snyder, 1991) for comparison with other substances. LC_{50}s, lowest observed lethal concentrations (LC_{Lo}), and dermal LD_{50}s for some of the 15 selected MVOCs are presented in Table 7. However, for several of those MVOCs, such values have not been determined. According to the Hodge and Sterner scale, the substances listed in Table 7, with the possible exception of dimethyl disulphide, would be classified as slightly toxic (i.e. having an LC_{50} in the range 1,000–10,000 ppm in rats (CCOHS, 2006). Also the dermal LD_{50}s indicate a low acute toxicity termed as slightly (350–2,810 mg/kg) or practically non-toxic (2,820–22,590 mg/kg) according to the same toxicity scale. The concentrations of MVOCs need to be thousands of mg/m^3 in order to produce lethal effects in animals (Table 7), whereas the concentrations of individual MVOCs indoors in general are in the range of 100 ng up to 1 mg/m^3 (Table 5).

The cytotoxicity of 13 so-called MVOCs, including 1-octen-3-ol, 3-octanol, 3-methyl-1-butanol, 2-methyl-1-propanol, 3-octanone, 2-heptanone, and 2-hexanone, was studied using a human lung carcinoma epithelial cell line A549 in a colony formation assay and two colorimetric assays. 1-Octen-3-ol and 3-octanol were approximately 10–100 times more cytotoxic than the other MVOCs. However, all tested MVOCs were more than 1,000-fold less toxic than the known cytotoxic substance gliotoxin measured as the concentration resulting in 50% inhibition of colony growth or absorbance (Kreja and Seidel, 2002b).

Other toxicological data of relevance on the 15 selected substances are presented below.

2-Methyl-1-propanol

Signs of toxicity reported in acute inhalation studies (>19,000 mg/m^3) in several species include narcosis, irritant effects on the mucous membranes, and effects on the liver and kidneys (BG Chemie, 1999).

3-Methylfuran

Acute inhalation studies of 3-methylfuran have revealed damage to the epithelium lining the small airways at high doses. Mice seem to be more sensitive than rats and hamsters with extensive necrosis of the bronchiolar epithelium within 1 day following a 1-h exposure to initial concentrations of 343–906 ppm

TABLE 7
LC_{50}s, LC_{Lo}s and LD_{50}s for some MVOCs most often reported in field studies

Compound	Species	LC_{50}^a Concentration mg/m^3	LC_{50}^a Concentration ppm	LC_{50}^a Duration (h)	LC_{Lo}^b Concentration mg/m^3	LC_{Lo}^b Concentration ppm	LC_{Lo}^b Duration (h)	Dermal LD_{50}^c mg/kg	Reference
2-Methyl-1-propanol	Rat	19,200–24,200	6,300–8,000	4	24,200 8,000	8,000 2,600	4 4	—	US National Library of Medicine (US NLM; 2005), Registry of Toxic Effects of Chemical Substances (RTECS; 2005)
	Guinea pig	19,900	6,600	4	—	—	—	—	US NLM (2005), RTECS (2005)
	Mouse	15,500	5,100	2	—	—	—	—	RTECS (2005)
	Rabbit	26,200 2,600	8,600 860	— 4	—	—	—	3,400	US NLM (2005), RTECS (2005)
	Rabbit, male	—	—	—	—	—	—	>2,000	BG Chemie (1999)
	Rabbit, female	—	—	—	—	—	—	2,460 (1,790–3,390)	BG Chemie (1999)
	Rabbit	—	—	—	—	—	—	3,400	BG Chemie (1999)
	Rabbit, occlusive	—	—	—	—	—	—	4,240 (2,520–7,120)	BG Chemie (1999)
3-Methyl-1-butanol	Rabbit	—	—	—	—	—	—	3,240	American Conference of Government Industrial Hygienists (2001)
3-Octanol	Rabbit	—	—	—	—	—	—	>5,000	Bevan (2001)
1-Octen-3-ol	Rabbit	—	—	—	—	—	—	3,300	Birmingham (1976)
3-Methylfuran	Mouse	3,000	900	1	—	—	—	—	Haschek, et al. (1984)
	Rat	6,700	2,000	1	—	—	—	—	Haschek, et al. (1983)
	Hamster	>26,400	>7,900	2	—	—	—	—	Haschek, et al. (1983)
2-Hexanone	Rat	32,700	8,000	4	—	—	—	—	National Institute for Occupational Safety and Health (NIOSH; 2005), RTECS (2005)
	Guinea pig	—	—	—	82,000 40,000	20,000 9,800	1.2 0.5	—	NIOSH (2005), RTECS (2005)
	Rabbit	—	—	—	—	—	—	4,800	RTECS (2005)
2-Heptanone	Rat	—	—	—	18,600	4,000	4	—	US NLM (2005), RTECS (2005)
	Guinea pig	—	—	—	22,400	4,800	4	—	RTECS (2005)
	Rabbit	—	—	—	—	—	—	10,200[e] 13,000	RTECS (2005), US NLM (2005)
3-Octanone	Rabbit, occlusive	—	—	—	—	—	—	>5,000	Shelanski (1973)
Dimethyl disulphide	Rat	15.8[d]	4.1[d]	2	—	—	—	—	CHEMINFO (2005), RTECS (2005)
	Mouse	12.3[d]	3.2[d]	2	—	—	—	—	CHEMINFO (2005), RTECS (2005)
	Rat	3,100	800	4	—	—	—	—	CHEMINFO (2005), Arkema (2005)
	Rat	4,800	1,200	4	—	—	—	—	CHEMINFO (2005)
	Rabbit	—	—	—	—	—	–	>2,000	Arkema (2005)

[a]Lethal concentration for 50% of the animals at single exposure.
[b]Lowest observed lethal concentration.
[c]Lethal doses for 50% of the animals at single administration.
[d]The validity of the value has been questioned (CHEMINFO, 2005). The rat data are not supported by data on developmental toxicity.
[e]Conversion from 12,600 μL/kg (density 0.811 g/ml).

(1,149–3,038 mg/m^3). Virtually complete regeneration of the epithelium was observed within 21 days. 3-Methylfuran-induced injury also occurred in the liver, lymphoid system, and nasal mucosa, although species differences were present (Haschek et al., 1983, 1984; Morse et al., 1984).

Conclusion

Single-exposure data are lacking or very scarce for all of the 15 selected substances. Available data on the alcohols, ketones, and 3-methylfuran suggest a slight, and those on dimethyl disulphide a slight to moderate, acute toxicity. Reported effect levels

are more than three orders of magnitude higher than reported MVOC indoor air levels.

Effects of Short-Term and Long-Term Exposure

Repeated exposure data, available for 7 of the 15 selected MVOCs, are presented below. Focus is on inhalation and the lowest administered doses. If inhalation data are lacking or scarce, however, oral data have been included.

3-Methyl-1-butanol

No compound-related, toxicologically relevant effects were found in rats exposed in drinking water to doses up to 1,068 (males) or 1,431 (females) mg/kg body weight for 90 days (Health Council of the Netherlands, 2005). Oral exposure of rats to doses up to 1,000 mg/kg body weight/day, 7 days/week for 17 weeks, was not accompanied by adverse effects. However, a decreased body weight gain, which was ascribed a reduced food intake was reported at the highest dose (Health Council of the Netherlands, 2005).

2-Methyl-1-propanol

A comprehensive set of neurotoxicity tests, including an assessment of complex behaviour dependent on learning and memory, full histopathology, and blood-chemistry evaluations were conducted following the exposure of rats to 0 ppm, 250 ppm, 1,000 ppm, and 2,500 ppm (0 mg/m^3, 760 mg/m^3, 3,030 mg/m^3, and 7,600 mg/m^3) for 90 days. A slight decrease in response to external stimuli was observed during the actual exposures at all concentrations. There were no morphological or behavioural effects indicative of a specific, persistent, or progressive effect on the nervous system at any exposure level (Li et al., 1999).

In two 90-day studies in male and female rats and according to OECD guidelines, no-effect levels of approximately 316 and 1,450 mg/kg body weight per day were determined following administration by gavage and in drinking water, respectively (Schilling et al., 1997; BG Chemie, 1999).

3-Octanol

In a recent subchronic oral toxicity study, no effects were observed in rats dosed with 25 mg/kg body weight. Treatment-related lesions in the kidney (100 mg/kg body weight) and liver (400 mg/kg body weight) were observed at higher dose levels (Lindecrona et al., 2003).

3-Methylfuran

In male and female hamsters and mice exposed for a total of 2 h to an initial concentration of 8,400 ppm (28,200 mg/m^3) and a final ditto of 1,900 ppm (6,400 mg/m^3), and for 1 h to an initial concentration of 700 ppm and a final concentration of 400 ppm (2,400 mg/m^3 and 1,300 mg/m^3), respectively, once a week for 10 consecutive weeks, the results of respiratory-function tests and the histopathologic evaluation of the lungs did not reveal any major long-lasting changes 10 months later. In mice, the tumour incidence in exposed animals was not increased when compared with controls 2 years after exposure (Witschi et al., 1985).

2-Hexanone

The target tissue in 2-hexanone toxicity is the nervous system. Neurotoxic effects, expressed as peripheral neuropathy, and weight loss or retarded weight gain, have been observed in several species after repeated exposures and different modes of administration (Bos, 1990; Bos et al., 1991; Lundberg, 1992a).

Exposure to 40 ppm (164 mg/m^3) of 2-hexanone vapour 8 h/day, 5 days/week for 22–88 days did not result in any clinical or pathological signs of neuropathy in rats, whereas 3/20 rats showed demyelination of the sciatic nerve after 13 weeks of exposure to 50 ppm (205 mg/m^3) of 2-hexanone vapour under similar conditions (LOEL). In rats exposed for 6 months a reduced nerve conduction velocity was observed within 17 weeks. Even after 6 months of exposure no clinical signs of neuropathy were observed, but widespread demyelination of the sciatic nerve was seen in 32/40 rats. It cannot be ruled out that prolongation of the 40 ppm exposure would have revealed signs of neuropathy at a later time.

In another study, exposure to 100 ppm (410 mg/m^3) of 2-hexanone vapour for 6 h/day, 5 days/week resulted in a reduced motor conduction velocity of the sciatic-tibial nerve in male rats within 29 weeks ($n = 30$) as well as in male monkeys (within 9 months) ($n = 24$). Complete recovery occurred in monkeys within 2 months post-exposure.

Rats exposed to 200 ppm (820 mg/m^3) of 2-hexanone vapours for 6 weeks (8 h/day, 5 days/week) showed several signs of neuropathy (axonal hypertrophy and segmental breakdown of myelin). Continuous inhalatory exposure of 12 rats to 225 ppm (920 mg/m^3) resulted in clinical paralysis after 66 days.

Chicken continuously exposed to 100 ppm (410 mg/m^3) 2-hexanone vapour developed leg dragging after 4–5 weeks.

The neurotoxicity of 2-hexanone is enhanced by co-exposure to other chemicals, especially other ketones like 2-butanone. 2-Hexanone can also potentiate the toxicity of other compounds, such as chloroform and carbon tetrachloride.

2-Heptanone

Repeated ($n = 19$) inhalation exposures of 115–1,500 ppm (540–7,000 mg/m^3) for 6–8 h did not cause behavioural changes in rats, but some reduction in response rate occurred at exposure to 1,575–1,900 ppm (7,400–8,900 mg/m^3). Tolerance developed over the course of the study (Anger et al., 1979).

No adverse effects on cardiopulmonary function or clinical chemistry, or signs of neurotoxicity were noted in male rats and monkeys after inhalation exposures up to approximately 1,000 ppm (4,700 mg/m^3) for 9–10 months, 6 h/day, 5 days/week (Johnson et al., 1978, 1979; Lynch et al., 1981). 2-Heptanone has

been shown to increase the chloroform induced nephrotoxicity and hepatotoxicity in rats (Hewitt and Brown, 1984).

Dimethyl Disulphide

No toxic effects were noted in rats after inhalation of 100 ppm (390 mg/m^3), 6 hours/day for 20 days (Lundberg, 1987).

Two other inhalation studies of rats exposed to dimethyl disulphide 6 h/day, 5 days/week for 13 weeks, and according to OECD guidelines, have been performed. In the first study, reduced body weight and food intake, and changes in some serum biochemical parameters were observed at 25 ppm (96 mg/m^3) in the males. At 125 ppm (480 mg/m^3) the same effects and in addition an increase in some organ weights were seen in both genders. No treatment-related effects were observed at the lowest exposure level of 5 ppm (19 mg/m^3; Kim et al., 2006). In the other study, hypoactivity, reduced body weight and food consumption, and changes in organ weights and in white-blood-cell counts were reported. Reversible microscopic changes in the nasal mucosa were noted at all exposure levels (10 ppm, 50 ppm, 150 ppm, and 250 ppm; 38 mg/m^3, 190 mg/m^3, 580 mg/m^3, and 960 mg/m^3). The NOEL was judged to be slightly lower than 10 ppm (Arkema, 2005).

Conclusion

The animal short-term and long-term toxicity database is poor for most of the 15 selected substances. Virtually no data exist for 2-octen-1-ol, 2-pentanol, 3-octanone, geosmin, 2-methylisoborneol, and 2-isopropyl-3-methoxy-pyrazine. For some of the alcohols, and for 2-heptanone, the available data indicate a slight toxicity. Two 13-week inhalation studies on dimethyl disulphide in rats suggest a NOEL below 10 ppm (38 mg/m^3). In rats, peripheral neuropathy has been observed after exposure to 50 ppm (205 mg/m^3) 2-hexanone (LOEL). Thus, adverse effects from some of the selected substances have been reported only at doses far higher than what can be obtained when their main source is microbial.

Mutagenicity and Genotoxicity

Genotoxicity tests on the 15 substances selected for further investigation are summarised in Table 8. With few exceptions results are negative. Data are lacking for some of the substances.

In an example of recent studies on MVOCs, Kreja and Seidel (2002a) investigated genotoxic, clastogenic, and mutagenic potential of 16 MVOCs *in vitro* (Table 8). Each compound induced DNA damage only under cytotoxic conditions. Clastogenic (causing chromosomal breaks) and mutagenic effects were not detected.

By contrast, SOS-inducing activity was reported for 15 out of 20 MVOCs including 2-methyl-1-propanol, 3-methyl-1-butanol, 3-methyl-2-butanol, 2-pentanol, 3-octanol, 1-octen-3-ol, 2-hexanone, 2-heptanone, and 3-octanone in the luminescent umu test. (The SOS response in bacteria describes changes in gene expression in response to DNA damage). 3-Methyl-2-butanone and 3-methyl-2-butanol were the only MVOCs that were tested positive also in the less sensitive conventional light absorption umu test. These two MVOCs were subsequently tested also in the Ames test and were reported positive (Nakajima et al., 2006).

Carcinogenicity

The International Agency for Research on Cancer (IARC, 2005) has not evaluated the carcinogenicity of any of the 15 MVOCs listed in Table 1. The US National Toxicology Program (NTP) has not listed those chemicals in its report on carcinogens. In the broader list of identified MVOCs (Table 2), some substances (such as formaldehyde) are classified as human carcinogens or as possible human carcinogens (such as acetaldehyde, ethylbenzene, isoprene, and styrene). Considering the low concentrations encountered in the MVOC context, cancer is not likely to be a concern. The very few studies that were retrieved from the literature are described below.

3-Methyl-1-butanol

Oral administration of approximately 81 mg/kg body weight, twice a week for 135 weeks, or subcutaneous injection of approximately 32 mg/kg body weight, once a week for 95 weeks, induced an increase in the incidence of malignant tumours in rats (4 and 10, respectively). No malignant tumours were found in the controls (Health Council of the Netherlands, 2005). The study design and documentation of reported findings have several flaws that hamper the interpretation of the data; for example, a low number of animals, unknown sex ratios, lack of information on tumour incidences in historical controls, and the exceeding of the maximum tolerated dose evidenced by chronic toxic effects on the liver and haematopoietic system.

2-Methyl-1-propanol

In rats, oral administration of approximately 160 mg/kg body weight, twice a week for 72 weeks, or subcutaneous injection of approximately 41 mg/kg body weight, twice a week for 90 weeks, led to an increase in the number of malignant tumours. No malignant tumours were seen in the controls (BG Chemie, 1999). The study does not comply with current standards (see text on 3-methyl-1-butanol).

Reproductive and Developmental Studies

Studies on reproductive and developmental effects of MVOC exposure are rare. Of the selected 15 MVOCs, data exist for four compounds.

3-Methyl-1-butanol

The substance was tested for developmental toxicity in pregnant Wistar rats and Himalayan rabbits. In total, 25 female rats

TABLE 8
Genotoxicity tests with some microbial volatile organic compounds (MVOCs) often reported in field studies

Compound	Test system	Endpoint	Concentration	Metabolic activation[a]	Result	Reference
2-Methyl-1-propanol	Ames test/*S. typhimurium* TA98, 100, 1535, 1537, 1538	Gene mutation	5–5,000 μg/plate	No/Yes	Negative/Negative	Chemical Carcinogenesis Research Information System (CCRIS; 2006)
	Ames test/*S. typhimurium* TA97, 98, 100, 1535, 1537, 1538	Gene mutation	100–10,000 μg/plate	No/Yes	Negative/Negative	
	Light absorption *umu* test/ *S. typhimurium* TA1535/pSK1002	DNA damage (SOS-induction)	Not given	No	Negative	Nakajima et al. (2006)
	Luminescent *umu* test/*S. typhimurium* TA1535/pTL210	DNA damage (SOS-induction)	Not given	No	Positive	
	E. coli/ WP2 uvrA	Gene mutation	5–5,000 μg/plate	No/Yes	Negative/Negative	CCRIS (2006)
	Chinese hamster V-79 / HPRT assay	Gene mutation	107 mM	No/Yes	Negative/Negative	
	Human lung carcinoma epithelial A549 cells/ Alkaline comet assay	DNA damage	53 and 270 mM	No	Negative/Positive[b]	Kreja and Seidel (2002a)
	V-79 Chinese hamster fibroblasts/ Alkaline comet assay	DNA damage	53 and 270 mM	No	Negative/Positive[b]	
	Human peripheral blood cells/Alkaline comet assay	DNA damage	53 and 270 mM	No	Negative/Positive[b]	

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TABLE 8
Genotoxicity tests with some microbial volatile organic compounds (MVOCs) often reported in field studies *(Continued)*

Compound	Test system	Endpoint	Concentration	Metabolic activation[a]	Result	Reference
	V-79 Chinese hamster fibroblasts: micronucleus test, HPRT assay	Micronuclei	11 and 53 mM	No	Negative	
		Gene mutation	0–107 mM	No/Yes	Negative/Negative	
3-Methyl-1-butanol	Ames test/*S. typhimurium* TA98, 100, 1535, 1537	Gene mutation	Not given	No/Yes	Negative/Negative	Health Council of the Netherlands (2005)
	Light absorption *umu* test/*S. typhimurium* TA1535/pSK1002	DNA damage (SOS-induction)	Not given	No	Negative	Nakajima et al. (2006)
	Luminescent *umu* test/*S. typhimurium* TA1535/pTL210	DNA damage (SOS-induction)	Not given	No	Positive	
	Chinese hamster V-79/HPRT assay	Gene mutation	51.5 mM	No/Yes	Negative/Negative	CCRIS (2006)
	Human blood cells/Comet assay	DNA damage (strand breaks, alkali-labile sites)	—	—	Negative	Health Council of the Netherlands (2005)
	Human lung carcinoma epithelial A549 cells/ Alkaline comet assay	DNA damage	23, 46, and 91 mM	No	Negative	Kreja and Seidel (2002a)
	V-79 Chinese hamster fibroblasts/Alkaline comet assay	DNA damage	46 and 91 mM	No	Negative	
	Human peripheral blood cells/Alkaline comet assay	DNA damage	23 and 91 mM	No	Negative/Positive[b]	

	V-79 Chinese hamster fibroblasts: micronucleus test, HPRT assay	Micronuclei	5, 9, and 23 mM	No/Yes	Negative/Negative	
		Gene mutation	0–51.5 mM	No/Yes	Negative/Negative	
	Rat bone marrow *in vivo*	Chromosomal aberration	1/5 LD_{50}	—	Positive	Health Council of the Netherlands (2005)
		Polyploid cells			Negative	
		Chromosome gaps			Negative	
3-Methyl-2-butanol	Ames test/*S. typhimurium* TA98, 100	Gene mutation	0–2.5 μl/plate	No/Yes	Positive/Positive	Nakajima et al. (2006)
	Light absorption *umu* test/*S. typhimurium* TA1535/pSK1002	DNA damage (SOS-induction)	Not given	No	Positive	
	Luminescent *umu* test/*S. typhimurium* TA1535/pTL210	DNA damage (SOS-induction)	Not given	No	Positive	
	Human lung carcinoma epithelial A549 cells/ Alkaline comet assay	DNA damage	45 and 90 mM	No	Negative	Kreja and Seidel (2002a)
	V-79 Chinese hamster fibroblasts: micronucleus test	Micronuclei	45 and 90 mM	No	Negative	
2-Pentanol	Light absorption *umu* test/*S. typhimurium* TA1535/pSK1002	DNA damage (SOS-induction)	Not given	No	Negative	Nakajima et al. (2006)
	Luminescent *umu* test/*S. typhimurium* TA1535/pTL210	DNA damage (SOS-induction)	Not given	No	Positive	

(Continued on next page)

TABLE 8
Genotoxicity tests with some microbial volatile organic compounds (MVOCs) often reported in field studies *(Continued)*

Compound	Test system	Endpoint	Concentration	Metabolic activation[a]	Result	Reference
3-Octanol	Light absorption *umu* test/*S. typhimurium* TA1535 / pSK1002	DNA damage (SOS-induction)	Not given	No	Negative	
	Luminescent umu test/S. typhimurium TA1535 / pTL210	DNA damage (SOS-induction)	Not given	No	Positive	
	Human lung carcinoma epithelial A549 cells/ Alkaline comet assay	DNA damage	6.2 and 31 mM	No	Negative/Positive[b]	Kreja and Seidel (2002a)
	V-79 Chinese hamster fibroblasts/Alkaline comet assay	DNA damage	6.2 and 31 mM	No	Negative/Negative	
	V-79 Chinese hamster fibroblasts	Micronuclei	3.1 and 6.2 mM	No	Negative	
1-Octen-3-ol	Light absorption *umu* test/*S. typhimurium* TA1535/pSK1002	DNA damage (SOS-induction)	Not given	No	Negative	Nakajima et al. (2006)
	Luminescent *umu* test/*S. typhimurium* TA1535/pTL210	DNA damage (SOS-induction)	Not given	No	Positive[c]	
	Chinese hamster V-79/HPRT assay	Gene mutation	5 mM	No/Yes	Negative/Negative	CCRIS (2006)
	Human lung carcinoma epithelial A549 cells/ Alkaline comet assay	DNA damage	0.6 and 6.4 mM	No	Negative	Kreja and Seidel (2002a)

	V-79 Chinese hamster fibroblasts/Alkaline comet assay	DNA damage	0.6 and 6.4 mM	No	Negative/Positive[b]	
	Human peripheral blood cells / Alkaline comet assay	DNA damage	0.6 and 6.4 mM	No	Negative/Positive[b]	
	V-79 Chinese hamster fibroblasts: micronucleus test,	Micronuclei	0.6, 3.2, and 6.4 mM	NoYes	Negative/Negative	
	HPRT test	Gene mutation	0–5 mM	No/Yes	Negative/Negative	
2-Hexanone	Light absorption *umu* test/*S. typhimurium* TA1535 / pSK1002	DNA damage (SOS-induction)	Not given	No	Negative	Nakajima et al. (2006)
	Luminescent *umu* test/*S. typhimurium* TA1535/pTL210	DNA damage (SOS-induction)	Not given	No	Positive	
	Chinese hamster V-79/HPRT assay	Gene mutation	40 mM	No/Yes	Negative/Negative	CCRIS (2006)
	Saccharomyces cerevisiae	Chromosome loss	48 mM	No	Weakly positive[d]	Mayer and Goin (1994)
	Human lung carcinoma epithelial A549 cells/ Alkaline comet assay	DNA damage	40 and 80 mM	No	Negative/Positive[b]	Kreja and Seidel (2002a)
	V-79 Chinese hamster fibroblasts/Alkaline comet assay	DNA damage	40 and 80 mM	No	Negative	

(Continued on next page)

TABLE 8
Genotoxicity tests with some microbial volatile organic compounds (MVOCs) often reported in field studies *(Continued)*

Compound	Test system	Endpoint	Concentration	Metabolic activation[a]	Result	Reference
	Human peripheral blood cells / Alkaline comet assay	DNA damage	40 and 80 mM	No	Negative/Positive[b]	
	V-79 Chinese hamster fibroblasts: micronucleus test, HPRT assay	Micronuclei	40 and 80 mM	No/Yes	Negative/Negative	
		Gene mutation	0–40 mM	No/Yes	Negative/Negative	
2-Heptanone	Light absorption *umu* test /*S. typhimurium* TA1535/pSK1002	DNA damage (SOS-induction)	Not given	No	Negative	Nakajima et al. (2006)
	Luminescent *umu* test /*S. typhimurium* TA1535 / pTL210	DNA damage (SOS-induction)	Not given	No	Positive	
	Chinese hamster V-79/HPRT assay	Gene mutation	18.2 mM	No/Yes	Negative/Negative	CCRIS (2006)
	Human lung carcinoma epithelial A549 cells/ Alkaline comet assay	DNA damage	7, 35, and 70 mM	No	Negative/Negative/Positive[b]	Kreja and Seidel (2002a)
	V-79 Chinese hamster fibroblasts /Alkaline comet assay	DNA damage	7, 35, and 70 mM	No	Negative/Negative/Positive[b]	
	Human peripheral blood cells/Alkaline comet assay	DNA damage	7 and 35 mM	No	Negative/Positive[b]	
	V-79 Chinese hamster fibroblasts: micronucleus test, HPRT test	Micronuclei	17 and 35 mM	No	Negative	
		Gene mutation	18.2 mM	No/Yes	Negative/Negative	

3-Octanone	Light absorption *umu* test /*S. typhimurium* TA1535 / pSK1002	DNA damage (SOS-induction)	Not given	No	Negative	Nakajima et al. (2006)
	Luminescent *umu* test /*S. typhimurium* TA1535 / pTL210	DNA damage (SOS-induction)	Not given	No	Positive	
	Chinese hamster V-79 / HPRT assay	Gene mutation	14.4 mM	No/Yes	Negative/Negative	CCRIS (2006)
	Human lung carcinoma epithelial A549 cells / Alkaline comet assay	DNA damage	6, 31, and 62 mM	No	Negative/Negative/Positive[b]	Kreja and Seidel (2002a)
	V-79 Chinese hamster fibroblasts / Alkaline comet assay	DNA damage	6, 31, and 62 mM	No	Negative/Negative/Negative	
	Human peripheral blood cells / Alkaline comet assay	DNA damage	6 and 62 mM	No	Negative/Positive[b]	
	V-79 Chinese hamster fibroblasts: micronucleus test, HPRT test	Micronuclei	16 and 31 mM	No	Negative	
		Gene mutation	0–14.4 mM	No/Yes	Negative/Negative	

(Continued on next page)

TABLE 8
Genotoxicity tests with some microbial volatile organic compounds (MVOCs) often reported in field studies *(Continued)*

Compound	Test system	Endpoint	Concentration	Metabolic activation[a]	Result	Reference
Geosmin	Ames test/ *S. typhimurium* TA98, 100	Gene mutation	3.93–2,000 μg/plate	No/Yes	Negative/Negative	CCRIS (2006)
	Ames test/ *S. typhimurium* TA98, 100, 1535, 1537, 1538	Gene mutation	Not given		Negative	Kier et al. (1986)
	Ames test/ *S. typhimurium* TA98, 100, 102, 1535, 1537, 1538	Gene mutation	Not given	No/Yes	Negative/Negative	Nakamura et al. (1987)
	Umu test/ *S. typhimurium* TA1535/pSK1002	DNA damage (SOS-induction)	0–400 μg/ml	No/Yes	Negative/Negative	
	Chinese hamster lung fibroplast cell line CHL	Chromosome abberation	0–0.15 mg/ml	No/Yes	Negative/Negative	Matsuoka et al. (1998)
2-Methylisoborneol	Ames test/ *S. typhimurium* TA98, 100	Gene mutation	9.85–5,000 μg/plate	No/Yes	Negative/Negative	CCRIS (2006)
	Ames test/ *S. typhimurium* TA98, 100, 102, 1535, 1537, 1538	Gene mutation	Not given	No/Yes	Negative/Negative	Nakamura et al. (1987)
	Umu test/ *S. typhimurium* TA1535/pSK1002	DNA damage (SOS-induction)	0–400 μg/ml	No/Yes	Negative/Negative	
	Chinese hamster lung fibroplast cell line CHL	Chromosome abberation	0–0.2 mg/ml	No/Yes	Negative/Negative	Matsuoka et al. (1998)

Dimethyl disulphide	Ames test/ *S. typhimurium* TA98, 100, 102	Gene mutation	0.011–1,100 μg/plate	No/Yes	Negative/Negative	CCRIS (2006)
	Ames test/*S. typhimurium* TA98, 100, 1535, 1537, 1538	Gene mutation	50–5,000 μg/plate	No/Yes	Negative/Negative	Arkema (2005)
	Chinese hamster ovary / HPRT assay	Gene mutation	0.46–1,000 μg/ml	No/Yes	Negative/Negative	
	Rat hepatocytes in primary culture	DNA damage and repair assay	1–300 μg/ml	No	Negative	
	Human lymphocytes	Chromosome aberration	3.7–300 μg/ml	No/Yes	Ambiguous/ Ambiguous	
	Mouse bone marrow *in vivo*	Micronuclei	0, 250, and 500 ppm	–	Negative	
	Rat hepatocytes *in vivo*	Unscheduled DNA synthesis	0 and 500 ppm	–	Negative	

[a] Addition of a metabolising system, usually the microsomal fraction of an Aroclor 1254-induced rat liver, a so-called S9-mix.
[b] At cytotoxic concentrations.
[c] A result where the number of revertant colonies was 1.5–2.0 times that of spontaneous colonies.
[d] Combined treatment with methyl ethyl ketone potentiated the effect. 2,5-Hexanedione was strongly positive alone and in combination with acetone or methyl ethyl ketone.

and 15 female rabbits per group were exposed to 3-methyl-1-butanol vapour at concentrations of 510, 2 500, or 9 800 mg/m^3, 6 h/day. The rats were exposed on days 6–15 post-coitum and the rabbits were exposed on days 7–19 after insemination. The rat and rabbit dams were sacrificed on day 20 and day 29, respectively. The foetuses were removed from the uterus and examined for malformations and variations externally, in soft and skeletal tissue. Exposure to 9,800 mg/m^3 caused eye irritation in dams of either species during the exposure. Pregnancy and litter data were similar in all groups, and no signs of embryotoxicity or foetotoxicity were observed in foetuses of either species. The overall incidence of variations was significantly increased in rabbit offspring in the highest exposure group; however, the number of malformations did not differ between groups (Klimisch and Hellwig, 1995).

2-Methyl-1-propanol

This was tested for developmental toxicity in a study of similar design as described above for 3-methyl-1-butanol, with exposure concentrations of 510, 2,500, or 9,800 mg/m^3. Pregnancy and litter data were similar in all groups, and no signs of embryotoxicity or foetotoxicity were observed in foetuses of either species. The overall incidence of variations was significantly increased in rabbit offspring in the highest exposure group, whereas the number of foetuses with retarded ossification was lowest in this group. The number of malformations exhibited no differences between groups (Klimisch and Hellwig, 1995).

2-Hexanone

Male rats (strain not specified) were exposed to 700 ppm (2,870 mg/m^3) 2-hexanone for 72 h weekly (two 20 h and two 16-h exposure periods) for 11 weeks. Exposure was associated with a marked reduction in body weight. Generally, organ weight changes reflected the reduction in body weight; however, both absolute and relative weights of testes were significantly reduced. Microscopically, atrophy of the testicular germinal epithelium was observed (Katz et al., 1980).

Peters et al. (1981) exposed groups of 25 pregnant Fisher 344 rats by inhalation to 0, 500, 1,000, or 2,000 ppm (2,050, 4,100, or 8,200 mg/m^3) 2-hexanone for 6 h/day throughout gestation. Five male and female pups per group (one from a litter) were examined for developmental landmarks and tested for simple reflexes, activity in open field and running wheel, food maze behaviour, a swimming stress test, and shock avoidance. Tests were performed at puberty, adulthood, and old age; however, all exposure groups were not tested in all tests at all ages. Additional animals were tested for pentobarbital-induced sleeping time, clinical chemistry, and haematology. Offspring from the 500 ppm group had to be discarded because of non-treatment related circumstances. Maternal weight gain was non-significantly reduced at the two higher concentrations, and a detectable change in neurological function was observed in 2,000 ppm dams. These females produced smaller litters of lower weight pups, the latter persisting in male offspring throughout life.

Behavioural alterations were detected in most tests. In the food maze, offspring from exposed animals performed better at puberty but poorer as adults. Treated offspring exhibited reduced activity in the open field early in life (2,000 ppm) and increased activity in the running wheel until adulthood. Performance in avoidance conditioning was poorer in puberty females, and the treated animals generally exhibited increased random movement during the intertrial interval (1,000 ppm). A few sporadic changes were also noted in clinical chemistry values, however consistency lacked. Haematology revealed no differences between exposed and control groups (Peters et al., 1981).

Dimethyl Disulphide

Rats were exposed to 0, 5, 15 and 50 ppm (0, 19, 58 and 190 mg/m^3) dimethyl disulphide for 6 hours/day from day 6 to day 15 of gestation. Exposure to 50 ppm caused marked maternal toxicity and foetal growth retardation. At 15 ppm, there were less marked maternal toxicity and no foetal effects. No maternal or foetal effects were observed at 5 ppm (Arkema, 2005).

Smotherman and Robinson (1992) examined the behavioural responses of near term rat foetuses to a range of potential chemosensory fluids, including milk and dimethyl disulphide, a constituent of pup saliva promoting postnatal nipple attachment. On day 21 of gestation, the uteri of pregnant females were externalised and individual foetuses delivered. Only milk and dimethyl disulphide altered foetal motor activity and foetal responsiveness to perioral cutaneous stimulation, suggesting dimethyl disulphide acts as a chemical messenger during the neonatal period. Furthermore, the opiod antagonist naloxone reversed the pup behavioural response to dimethyl disulphide, indicating that this chemical is capable of promoting opiod activity, as is milk.

Conclusion

Studies are lacking for most of the 15 selected substances. Some effects on postnatal development and behaviour have been reported after 2-hexanone exposure of pregnant rats. However, considering the low levels encountered in MVOC settings reproductive and developmental effects caused by MVOCs are unlikely.

OBSERVATIONS IN MAN

Odour Sensation, Irritation, and Inflammation

Complaints of unpleasant odours are often presented in damp buildings with microbial contamination (Ström et al., 1994; Smedje et al., 1996; Putus, 2005). Because many MVOCs have musty, earthy, mushroom-like, sweet, and/or fruity smell (Ruth, 1986; Keller et al., 1999), MVOCs have been assumed to be responsible for odour sensations in problem buildings. However, the occurrence of MVOCs or odours is not a direct measure

TABLE 9
Odour and sensory irritation thresholds/irritating concentrations for some microbial volatile organic compounds (MVOCs) most frequently searched for in problem buildings

Compound	Odour characterisation	Odour threshold[a]		Irritation threshold[b] or irritating concentration[c]	
		ppm	mg/m^3	ppm	mg/m^3
2-Methyl-1-propanol	Mild, musty, fungus-like	0.001–74	0.003–225	99	300
3-Methyl-1-butanol	Sour, sharp, malty	0.010–35	0.045–126	100	360
1-Octen-3-ol	Raw mushroom	—	—	—	—
2-Hexanone	Acetone-like	0.076	0.31	—	—
2-Heptanone	Fungus-like, musty	0.02–0.35	0.094–1.6	281	1310
3-Octanone	Mild, fruity, fresh, herbal, lavender, sweet, fungus-like	6	31.2	50	260
2-Methylisoborneol	Musty, earthy	0.000001	0.000007	—	—
2-Isopropyl-3-methoxy-pyrazine	Musty, mouldy	0.0000002	0.000001	—	—
Geosmin	Musty, earthy	0.0009	0.0076	—	—
Dimethyl disulphide	Uncomfortable	0.00003–0.09	0.0001–0.3465	—	—

[a] Amoore and Hautala, 1983; Ruth, 1986; Hau and Connell, 1998; Keller et al., 1999; Wilkins, 2002; CHEMINFO, 2005; US National Library of Medicine, 2005.
[b] Nasal pungency threshold from human anosmics; available for 2-heptanone (Cometto-Muñiz and Cain, 1994).
[c] Ruth, 1986.

of the extent of microbial growth in a building (Ström et al., 1994; Johansson, 2000) because many factors affect MVOC levels indoors as well as the human sensation of odours (the odour threshold of an MVOC, occupants' susceptibility to odour). The odour thresholds may vary at least by a factor of 10^8 (from 10^{-7} to 10^1 ppm) between individual MVOCs and by a factor of 10^1–10^4 within the same compound between different studies. In one study, odour complaints in problem buildings were reported at the sum concentration of 13 MVOCs of 15 μg/m^3, while in the same study, odour was not noticed even at concentrations up to 40 μg/m^3 (Ström et al., 1994). The authors stated that odour complaints are related to the occurrence of individual compounds or their combinations, rather than to the sum of selected MVOCs.

Despite the lack of studies on concentration-response relationships, MVOCs have been associated with general discomfort (i.e. headache, dizziness, and fatigue) in buildings when occurring in concentrations above the odour thresholds. In addition, in epidemiological and case studies, the presence of MVOCs or musty, earthy odours has been related to the prevalence of eye, nose, and throat irritation, wheezing, and other asthma-like symptoms (Tobin et al., 1987; Jaakkola et al., 1993; Ruotsalainen et al., 1995; Knasko, 1996; Elke et al., 1999; Wessén and Schoeps, 2000; Kim et al., 2007). Perceived mould odour was found to be a risk indicator for occurrence of nasal congestion, secretion, cough, phlegm, wheeze, and the occurrence of symptoms was related to the frequency of the days with mould odour expressed (Jaakkola et al., 1993). In this study, the data on symptoms and causes were obtained by questionnaires, and no measurements (on, for example, MVOC levels) were performed. In general, when the concentration of a non-reactive MVOC exceeds a certain limit, it begins to evoke the odour sensation, and if the concentration is high enough, the symptoms of irritation appear. Available odour and irritation thresholds for some MVOCs are presented in Table 9. Irritation thresholds and irritating concentrations are in the range of 50–280 ppm, but are available only for 4 of the 15 selected compounds.

Some MVOCs, like 3-methylfuran, 2-heptanone, 1-octen-3-ol, and 2-methylisoborneol, were observed to be related to asthma among subjects working in schools with elevated levels of airborne fungi (Smedje et al., 1996). The authors point out, however, that the occurrence of MVOCs is an indication of active growth of micro-organisms and not a signal that MVOCs cause asthma.

In the recent study by Kim et al. (2007), an association between respiratory symptoms and indoor MVOC concentration was found in pupils of non-water damaged schools. At higher (not specified) indoor total MVOC concentrations, nocturnal breathlessness and doctor-diagnosed asthma were reported more often in the questionnaire. In addition, 3-methylfuran, 3-methyl-1-butanol, dimethyl disulphide, 2-heptanone, 1-octen-3-ol, and 3-octanone measured in the classrooms were associated with nocturnal breathlessness, whereas 3-octanone was associated with wheeze as well.

There are few studies on MVOCs and irritation or inflammatory responses (Table 10). In human experimental studies by Wålinder et al. (1999, 2005), some signs of inflammatory

TABLE 10
Dose-effect relationships in man after single or short-term inhalation exposure to VOCs, single or in combination

Compound	Exposure level	Duration	No. of subjects	Effects	Reference
3–Methyl-1-butanol	25 ppm (90 mg/m^3)	10 min	4 healthy, male volunteers	Throat irritation.	Health Council of the Netherlands (2005)
	100 ppm (360 mg/m^3)	3–5 min	Ca 10 male and female subjects	Slight throat irritation.	
	150 ppm (540 mg/m^3)	3–5 min	Ca 10 male and female subjects	Throat, eye and nose irritation.	
1-Octen-3-ol	19 ppm (10 mg/m^3)	2 h	30 healthy subjects serving as their own controls	Increases in eye, nose, throat irritation, headache, dizziness, nausea, intoxication, blinking rate, and in the amounts of lysozyme, myeloperoxidase and eosinophilic cationic protein in the nasal lavage fluid.	Wålinder et al. (1999)
3-Methylfuran	0.30 ppm (1 mg/m^3)	2 h	1 volunteer with previous occupational fungal exposure and presence of mould allergy	An immediate (during the last 30 min of exposure) obstructive reaction and a delayed pulmonary reaction with flu-like symptoms.	Wålinder et al. (1998)
	0.30 ppm (1 mg/m^3)	2 h	29 healthy volunteers serving as their own controls	No increase in subjective symptom ratings (discomfort in eyes, nose, and throat, dyspnoea, headache, fatigue, dizziness, nausea, and feeling of intoxication). However, blinking frequency, tear film break-up time and the nasal lavage biomarkers myeloperoxidase and lysozyme were increased and forced vital capacity was decreased.	Wålinder et al. (2005)
2-Hexanone	50 ppm (205 mg/m^3)	7.5 h	3 healthy volunteers	Symptoms not mentioned.	Bos (1990)
	100 ppm (410 mg/m^3)	4 h	3 healthy volunteers	Symptoms not mentioned.	
VOC mixtures, total concentrations	22 VOCs at 25 mg/m^3	4 h	14 subjects	A two-fold increase in PMNs in nasal lavage immediately after exposure.	Koren et al. (1992)
	21 VOCs at 25 mg/m^3 and 50 mg/m^3	4 h	15 subjects	No significant difference in nasal lavage cellularity or differential cell counts. Increases in lower and upper respiratory symptoms both	Pappas et al. (2000)

TABLE 10
Dose-effect relationships in man after single or short-term inhalation exposure to VOCs, single or in combination *(Continued)*

Compound	Exposure level	Duration	No. of subjects	Effects	Reference
				immediately and 2 hours after exposure to 50 mg/m^3. Increases in upper respiratory symptoms immediately after exposure to 25 mg/m^3. No changes in lung function (FEV_1, FVC, or FEF_{25-75}), cellularity or cell differentials, biomarkers of airway inflammation including interleukin-8, leukotriene B_4, or albumin in nasal lavage or induced sputum samples.	
	23 VOCs at 2.5, 25, and 25 mg/m^3+40 ppb ozone, respectively	3 × 135 min	130 healthy women	No significant differences in nasal irritation symptoms or nasal lavage PMNs between VOC + ozone, VOC alone, or masked air (clean air with a maximum of 2.5 mg/m^3 of VOCs) conditions.	Laumbach et al. (2005)
	Emissions from 5 mould species grown on particle board and pine wood: Emissions included 1-butanol, 2-methyl-1-propanol, 3-methyl-1-butanol, 2-hexanone and 2-heptanone at individual MVOC concentrations in the range 0.56–3.4 μg/m^3	60 min	17 women and 10 men	No effects on perceived air quality or skin symptoms. No effects on the cornea reflected by self-reported[a] tear film break-up time or on attention and processing speed.	Claeson (2006)
	Emissions as above, at individual MVOC concentrations in the range 13.2–214 μg/m^3	10 min	13 women and 11 men with or with out nose-clip	In exposure without nose-clip, increased ratings of perceived poor air quality (stuffy air, smell) and increased reporting of skin irritation. No effects on the self-reported[a] corneal tear film break-up time or on attention and processing speed.	

[a]Self-reported tear-film break-up time measures the length of time the subject can keep the eyes open without pain when watching a fixed point on the wall.

FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; FEF_{25-75} = forced expiratory flow between 25 and 75% of FVC; PMN = polymorphonuclear neutrophil.

responses and respiratory reactions were reported after MVOC exposure. Human subjects ($n = 30$) were exposed to 10 mg/m^3 of 1-octen-3-ol for 2 h. Increases in eye, nose, and throat irritation, headache, dizziness, nausea, intoxication, and blinking frequency, and in the amounts of lysozyme, myeloperoxidase, and eosinophilic cationic protein in the nasal lavage fluid were reported (Wålinder et al., 1999). In another study, 29 healthy volunteers were randomly exposed to sham or 1 mg/m^3 3-methylfuran for 2 h. No subjective symptom ratings (related to smell, irritative, and general symptoms) were increased during exposure. However, blinking frequency, tear film break-up time, and the lavage biomarkers myeloperoxidase and lysozyme were increased and forced vital capacity was decreased during exposure to 3-methylfuran compared with ambient air exposure (Wålinder et al., 2005). The exposure to 3-methylfuran caused an immediate obstructive (during the last 30 min of exposure) and late (3 days after exposure) pulmonary reaction in a subject with previous occupational fungal exposure and presence of mould allergy (Wålinder et al., 1998). These experimental exposures were performed with 10 and 500 times higher concentrations of 1-octen-3-ol and 3-methylfuran, respectively, than measured in field samples (Table 5).

Koren et al. (1992) reported a twofold increase in PMNs in nasal lavage of 14 subjects immediately after a 4-h exposure to a mixture of 22 VOCs at a total of 25 mg/m^3, whereas Pappas et al. (2000) observed no significant increase in PMNs in 15 subjects after a for the most part compositionally similar exposure of 21 VOCs at 25 mg/m^3 and 50 mg/m^3. However, increases in lower and upper respiratory symptoms were reported both immediately and 2 h after exposure to VOCs at 50 mg/m^3 and increases in upper respiratory symptoms immediately after exposure to VOCs at 25 mg/m^3. No changes were observed in lung function (forced expiratory flow in 1 second, forced vital capacity, forced expiratory flow between 25% and 75% of forced vital capacity), epithelial and immune cells as well as other biomarkers of airway inflammation including interleukin-8, leukotriene B_4, or albumin in nasal lavage or induced sputum samples (Pappas et al., 2000). The VOC mixtures of Koren et al. and Pappas et al., respectively, were designed to mimic the levels and types of VOCs found in homes in the US, excluding suspected carcinogens and very irritating compounds. However, none of the 15 substances evaluated in the present document were included but the mixture contained e.g. *p*-xylene (8.25 mg/m^3), 1-butanol, ethylbenzene, hexanal, α-pinene (825 μg/m^3 each), 2-butanone, and 3-methyl-2-butanone (75 μg/m^3 each), which can be regarded as MVOCs.

Laumbach et al. (2005) exposed 130 healthy women three times for 135 min each to odour masked clean air, or to a mixture of 23 VOCs at 25 mg/m^3 with and without the addition of 40 ppb ozone. Their VOC mixture did not contain any of the 15 substances evaluated in the present document, whereas other MVOCs such as *p*-xylene (measured concentration was 9.5 mg/m^3), 1-butanol, ethylbenzene, hexanal, α-pinene ($\sim$1 mg/m^3 each), limonene (0.7 mg/m^3), 2-butanone (0.09 mg/m^3), 1-octene (0.01 mg/m^3), and 3-methyl-2-butanone (calculated concentration 0.08 mg/m^3) were included (Fan et al., 2003). No significant differences in nasal irritation symptoms or nasal lavage PMNs between VOC + ozone, VOC alone, or clean air conditions were reported, and the authors concluded that MVOCs appear an unlikely cause of acute upper respiratory irritation or inflammation (Laumbach et al., 2005).

In a study reported by Claeson (2006), 17 women and 10 men were exposed to low-level emissions from 5 mould species grown on particle board and pine wood for 60 min. In a second-exposure set-up, 13 women and 11 men with or without nose-clip were exposed to moderate level emissions from mouldy building materials for 10 min. The emissions included 1-butanol, 2-methyl-1-propanol, 3-methyl-1-butanol, 2-hexanone and 2-heptanone at individual MVOC concentrations in the range 0.56–3.4 μg/m^3 and 13.2–214 μg/m^3 representing low and medium (moderate) level exposures, respectively. Exposure to moderate MVOC levels in the condition without nose-clip increased the reports of perceived poor air quality (stuffy air, smell), and skin irritation. No such outcome was observed when participants were exposed to low MVOC levels or to moderate MVOC levels with nose-clip. Irrespective of exposure level or duration, no effects on the cornea reflected by self-reported tear film break-up time or on attention and processing speed were found (Claeson, 2006).

Certain pathophysiological effects, such as the production of inflammatory mediators, cell influx into the airways, antibody responses, and cell desquamation, have been more intensively studied after exposure to other compounds related to microbial exposure than the MVOCs. These microbial particulate or non-volatile fractions include for example, fungal and actinomycete spores, cell-wall components, proteins, glycoproteins, polysaccharides, mycotoxins, and bacterial-derived polypeptides and endotoxins. The immune responses may be noticed as the activation of PMNs and/or alveolar macrophages resulting in secretion of inflammatory mediators like cytokines (Nielsen et al., 1995; Ammann, 2005; Putus, 2005).

Conclusion

Microbial VOCs have been related to complaints of general symptoms, as well as eye, nose, and throat irritation, and even asthma-like symptoms. However, there is a general lack of studies on dose–effect or dose–response relationships regarding irritation from single MVOC exposures and from MVOC mixtures. Human irritation thresholds, determined as nasal pungency thresholds by human anosmics or reported irritating concentrations, are available for 4/15 selected compounds and are considerably higher than measured indoor air levels for these compounds. Inflammatory responses have not been definitely confirmed although a few experimental studies indicate inflammatory responses and pulmonary reactions after exposure to 1-octen-3-ol and 3-methylfuran,

respectively, at exposure levels 10 and 500 times higher than measured in field. The very few experimental studies on exposure to MVOC mixtures and inflammatory effects are inconclusive.

Extrapolation of Animal Data on Sensory-Irritation Responses to Humans

At the levels relevant in this context, the effects from MVOC exposure are those related to irritation in the eyes and upper airways. At higher exposure levels, MVOCs may also cause other effects. Thus, the evaluation of human health risks caused by MVOC exposure focuses on the sensory irritation. Sensory-irritation potency is assessed by determining the RD_{50} in mice. However, the question of the application of RD_{50}s to human responses is a critical issue. Cometto-Muñiz and Cain (1994) showed that the sensory-irritation potencies of 21 VOCs (for example, alcohols, acetates, ketones, alkylbenzenes) estimated in the mouse bioassay were well correlated ($r = 0.85$) with the human potencies, measured as the nasal pungency thresholds. The extrapolation of the mouse bioassay to human exposures predicted that, in general, slight but tolerable irritation would occur at $0.1 \cdot RD_{50}$ and minimal or no effect at $0.01 \cdot RD_{50}$ (Kane et al., 1979). Further, regression analyses suggest that RD_{50}s correlate with the threshold limit values elaborated by American Conference of Governmental Industrial Hygienists ($r = 0.88$) with a slope factor (regression coefficient) of 0.03 (the mid-point between 0.10 and 0.01 on a logarithmic scale) (Schaper, 1993). As a pragmatic approach, such levels ($0.03 \cdot RD_{50}$) could constitute an acceptable level of human exposure to prevent sensory irritation in work environments. The RD_{50}s and corresponding $0.03 \cdot RD_{50}$s for the selected MVOCs are presented in Table 11. For the tabulated MVOCs, the $0.03 \cdot RD_{50}$s are in the range 5–530 mg/m^3 (approximately 0.9–100 ppm).

The levels of the compounds usually measured in water-damaged or mould-problem buildings (Table 5) are generally several orders of magnitude lower than the $0.03 \cdot RD_{50}$s given in Table 11. For such low-concentration mixtures of MVOCs, it seems prudent to apply the additivity rule (Alarie et al., 1996). The underlying assumption is that all the compounds act on the same biological site and individual compounds act as dilutions (depending on their relative potencies) of the same toxic compound (Könemann and Pieters, 1996). For the occupational setting the additive effect could be calculated as follows:

$$\text{Additive effect} = \sum (c_n / 0.03 \cdot RD_{50n}),$$

where c = measured concentration of a chemical

If the additive effect exceeds the value 1, sensory irritation may be expected, whereas levels below 1 should be of no concern (Alarie et al., 1996).

The interest in the indoor environment is to protect the general, rather than the working, population. This includes sensitive individuals (e.g. asthmatics and children) and continuous exposure for 24 h per day. On this basis, Nielsen et al. (1995) proposed

TABLE 11
The RD_{50}s (Schaper, 1993; Pasanen et al., 1998; Korpi et al., 1999b) and $0.03 \cdot RD_{50}$s for some microbial volatile organic compounds (MVOCs). The values for acrolein and formaldehyde were added for comparison

Compound	RD_{50} (mg/m^3)	$0.03 \cdot RD_{50}$ (mg/m^3)
2-Methyl-1-propanol	5,499	165
3-Methyl-1-butanol	9,325	280
3-Methyl-2-butanol	9,645	289
2-Pentanol	9,907	297
3-Octanol	1,359	41
1-Octen-3-ol	182	5.5
2-Hexanone	10,449	313[a]
2-Heptanone	4,163	125
3-Octanone	17,586	528
2-Methylisoborneol	811	24
Geosmin	216	6.5
Acrolein	4	0.12
Formaldehyde	5	0.15

[a]Neurotoxicity appears at lower exposure levels.

that the $0.03 \cdot RD_{50}$ should be divided by 40 when calculating a recommended indoor air level (RIL) for individual non-reactive VOCs outside occupational settings. The factor 40 includes a duration of indoor air exposure four times longer than occupational exposure and a safety factor of 10 for potential risk groups (Nielsen et al., 1995), which can be considered a conservative approach (Nielsen et al., 2007). The assumption of additivity and thus the same procedure for calculating the additive effect applies also for RILs.

However, it should be pointed out that the approach to calculate 'acceptable' levels is applicable only for sensory-irritation effects. For reactive substances or substances with effects other than sensory irritation as the primary concern, other extrapolations to protect humans should be applied.

Pasanen et al. (1998) calculated RILs for 27 MVOCs in a theoretical setting and for 3–14 MVOCs with reported concentrations in some problem buildings. Individual RILs for single MVOCs approach hundreds of μg/m^3 (e.g. 1-octen-3-ol, 2-methylisoborneol, geosmin) or thousands of μg/m^3(e.g. 2-methyl-1-butanol, 3-methyl-1-butanol, 3-methyl-2-butanol, 2-pentanol, 3-octanol, 2-hexanone, 2-heptanone). Such high MVOC concentrations rarely occur in indoor environments. Laumbach et al. (2005) and Sigsgaard and Bornehag (2005) recently reached the same conclusion. Similarly, Böck (2001) concluded that, on the basis of the data in the literature, the indoor concentrations of single MVOCs are 4–6 orders of magnitude below their RD_{50}s.

Both in theoretical calculations and on the basis of MVOC concentrations measured in some problem buildings, when

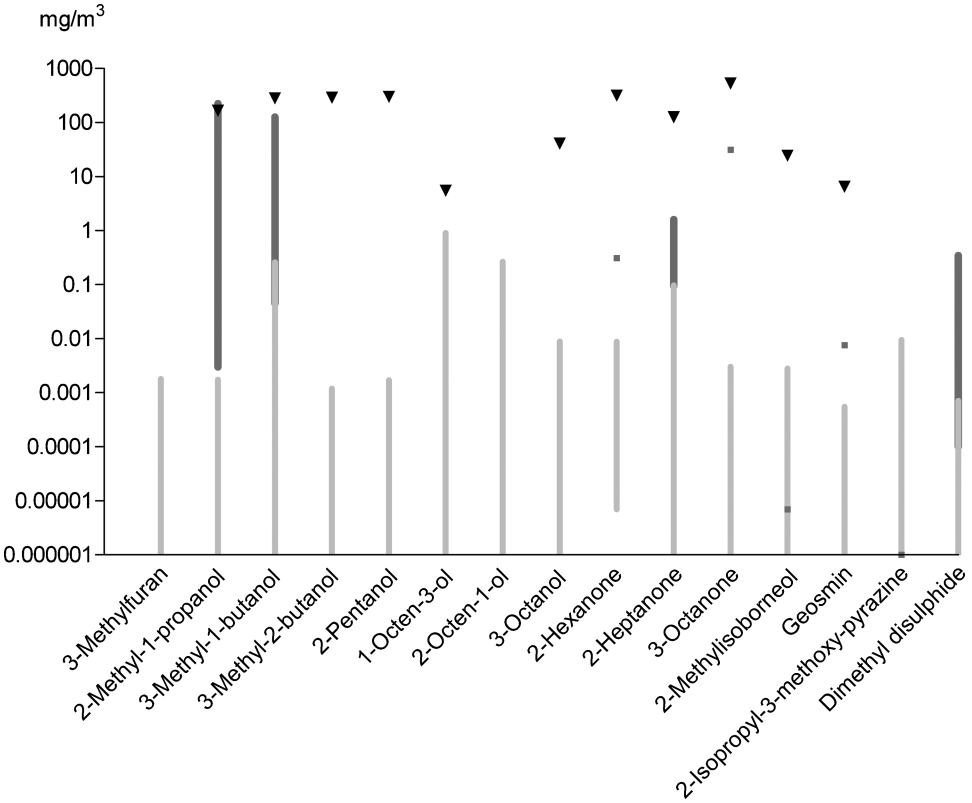

FIG. 2. The $0.03 \cdot RD_{50}$s (▼), odour thresholds as ranges or single values (dark grey lines) and indoor air concentrations (light grey lines) of selected microbial volatile organic compounds (MVOCs), when available. The indoor air concentrations were measured in residences or in non-industrial work sites, such as schools.

assuming additivity the total effect has remained below unity even when using RILs instead of $0.03 \cdot RD_{50}$s as acceptable limits (see the above-mentioned formula), indicating that irritation symptoms due to MVOCs should not be expected. These authors also estimated that microbial growth seems to have only marginal effects on the total VOC load in the room (Pasanen et al., 1998). Odour thresholds, indoor air concentrations, and the $0.03 \cdot RD_{50}$s are combined and presented in Figure 2.

Effects of Single and Short-Term Exposure

Experimental single-exposure studies have been conducted for 5 of the 15 substances selected for further investigation. In the text below, the focus is on inhalation and the lowest administered doses (Table 10). However, if inhalation data are lacking or scarce, oral data have been included.

2-Methyl-1-propanol

Human toxicological data are virtually missing. In a drinking study in which 10 volunteers were given ethanol in orange juice with or without the addition of 2-methyl-1-propanol, a clear increase in the frequency of errors and subjective hangover symptoms in the post-alcoholic phase was recorded with the addition of 2-methyl-1-propanol. No data on ingested amounts were given. In another report, it was stated that 2-methyl-propanol vapours cause narcosis and irritation of the upper airways. No further details were given (BG Chemie, 1999).

3-Methyl-1-butanol

Throat irritation was reported in a respiratory uptake study in which four healthy male volunteers were exposed through a mouthpiece to 25 ppm (90 mg/m^3) for 10 min. In another study, slight throat irritation was reported in human volunteers after exposure to 100 ppm (360 mg/m^3) 3-methyl-1-butanol for 3–5 min. Following exposure to 150 ppm (540 mg/m^3), eye and nose irritation were also noted (Health Council of the Netherlands, 2005).

1-Octen-3-ol

Mucosal irritation and weak general symptoms were reported in human subjects ($n = 30$) exposed to 10 mg/m^3 of 1-octen-3-ol for 2 h. Subjective ratings of smell, eye, nose and throat irritation, dizziness, headache, intoxication, and nausea were increased, as were some of the results from objective measurements (blinking frequency and levels of the nasal lavage fluid biomarkers eosinophilic cationic protein, lysozyme, and myeloperoxidase; Wålinder et al., 1999).

3-Methylfuran

In one study, 29 healthy volunteers were randomly exposed to sham or 1 mg/m^3 3-methylfuran for 2 h. No subjective symptom ratings (discomfort in the eyes, nose, and throat, dyspnoea, headache, fatigue, dizziness, nausea, and feeling of intoxication) were increased during exposure. However, blinking frequency, tear film break-up time, and the lavage biomarkers myeloperoxidase and lysozyme were increased and forced vital capacity was decreased during exposure to 3-methylfuran compared with sham exposure. In conclusion, the acute effects from eyes, nose, and airways indicate mucosal reactive properties of 3-methylfuran (Wålinder et al., 2005). One subject was removed from the study because of a two-phased pulmonary reaction. This suspected adverse reaction was described separately in a case report. The subject suffered an acute obstructive reaction and a delayed pulmonary reaction with flu-like symptoms. Previous occupational exposure to fungi and presence of mould allergy may have contributed to the reaction (Wålinder et al., 1998).

2-Hexanone

Human subjects exposed to 1,000 ppm (4,100 mg/m^3) of 2-hexanone for a few minutes reported transient moderate eye and nasal irritation (Bos, 1990).

In a toxicokinetic study in which three healthy volunteers were exposed to 50 ppm (205 mg/m^3) of 2-hexanone vapours for 7.5 h or to 100 ppm (410 mg/m^3) for 4 h, symptoms were not mentioned (Bos, 1990).

Conclusion

In conclusion, for all of the 15 selected substances, data are either totally lacking or very scanty. In most of the reported studies, doses are high when compared with actual MVOC levels in houses. However, acute effects from eyes, nose, and airways following exposure to 1 mg/m^3 of 3-methylfuran, and 10 mg/m^3 of 1-octen-3-ol, respectively, have been reported. Still, such exposure levels are 10 and 500 times higher than levels reported indoors.

Effects of Long-Term Exposure

Relevant long-term studies were found for 2 of the 15 selected substances, all from work environments where the source of exposure was not microbial metabolism.

2-Hexanone

Occupational exposure to 2-hexanone, mostly as a paint thinner (usually at least 4 months), has resulted in changes in both motor and sensory nerves with symptoms such as muscular weakness or trembling of the extremities, and difficulty in walking and handling objects. Also weight reduction has been reported in many cases. Medical examination has shown a reduced nerve conduction velocity and electromyographic changes. Nerve biopsies have shown neurotoxic effects such as axonodal swelling and demyelination. Recovery after termination of exposure has been slow and not always complete. In most cases, nerve function gradually improved but some cases even showed a slight worsening. In many cases, exposure was both dermal and inhalatory.

In an epidemiological study, peripheral neuropathy was reported in workers in a coated fabrics plant. Four months before the onset of symptoms 2-hexanone had been introduced in the solvents in the printing department. Measurements indicated 2-hexanone levels in the range 1–156 ppm (4–640 mg/m^3) and on average 9.2 ppm in front of the printers. However, the air samples were collected after the problem had arisen and only 9/17 printing machines were in operation during the 2-day sampling period. The true exposure levels could therefore not be estimated and data were insufficient to correlate 2-hexanone air levels with neurotoxic effects. In addition, percutaneous uptake could not be excluded, and also 2-butanone (methyl-ethyl ketone) was present in the area (highest measured concentration approximately 500 ppm; Bos, 1990; Bos et al., 1991; Lundberg 1992a). It can therefore not be ruled out that severe neuropathy has developed at exposure concentrations down to one or a few ppm. Such 2-hexanone levels would still be more than 400 times higher than those encountered in indoor air (below 9 μg/m^3).

Dimethyl Disulphide

Some 81 pulp-mill workers exposed to dimethyl disulphide (0–1.5 ppm, 0–5.8 mg/m^3), dimethyl sulphide (0–14 ppm), hydrogen sulphide (0–6 ppm), and methyl mercaptan (0–15 ppm) complained of inability to concentrate, headaches, restlessness, and lack of vigour. However, only the increased frequency of headache reached statistical significance compared with controls (Kangas et al., 1984). The highest reported concentration of dimethyl disulphide in buildings is approximately 0.7 μg/m^3.

The relationship between exposure to organic sulphides and disturbances in iron metabolism was investigated in 18 workers at a pulp and paper plant. Measured mean exposure levels were low, generally below the detection limits; that is, <0.2 ppm for methylmercaptan, <0.05 ppm for dimethyl sulphide, and <0.05 ppm (<0.19 mg/m^3) for dimethyl disulphide. However, peak concentrations of one or two orders of magnitude higher were registered. Five subjects experiencing such peaks within 2 months before blood sampling had significantly elevated concentrations of serum iron and transferrin, and lower ferritin concentrations than referents. As an incidental finding, six workers who were not participants of the study, but were involved in the clean-up following a minor explosion that had led to leakage of substantial amounts of sulphides, had significantly increased serum iron levels at 2 days post-exposure compared with 10 days post-exposure (Klingberg et al., 1988).

Conclusion

In conclusion, long-term exposure studies are virtually missing, except for 2-hexanone, which is an established neurotoxicant. It cannot be ruled out that peripheral neuropathy may develop in workers exposed to only a few mg/m^3 of 2-hexanone. For comparison, reported levels in non-industrial settings are <9 μg/m^3 (i.e. about three orders of magnitude lower). A disturbed iron metabolism among workers exposed to organic sulphides has been reported. Levels of dimethyl disulphide were several orders of magnitude above those reported in indoor air.

Genotoxic Effects

No studies on genotoxic effects in humans were found for the 15 substances selected for further investigation.

Carcinogenic Effects

No studies assessing the carcinogenic potential in humans were found following exposure to any of the 15 substances selected for further investigation.

Reproductive and Developmental Effects

No studies on reproductive and developmental effects in humans were found for the 15 substances selected for further investigation.

PREVIOUS EVALUATIONS BY NATIONAL AND INTERNATIONAL BODIES

No evaluations of the health risks of MVOCs in general were found in the literature. For the 15 selected compounds, health risks have been evaluated for five of them, as presented in Table 12. However, it should be noted that the purpose of these evaluations has been to estimate the health risks in industrial work environments and processes where workers are exposed to much higher concentrations of one or a few of these chemicals. This contrasts with exposure to chemicals of microbial origin (e.g. in buildings with moisture and microbial damage) where people are exposed to a wide range of MVOCs, albeit at much lower concentrations.

EVALUATION OF HUMAN-HEALTH RISKS

Assessment of Health Risks

It is difficult to evaluate human-health risks because of the lack of sufficient knowledge of the specific MVOCs, exposure to MVOCs (in particular mixtures) especially in work environments, and of the mechanisms of possible health effects of MVOCs. Furthermore, if there are MVOCs in the air, there will certainly be other agents (e.g. fungal components) present as well. The toxicological database is poor, at least for the 15 typically analysed MVOCs. Considering typical MVOCs—as reported qualitatively and quantitatively in the field so far—it seems evident that eye and upper-respiratory-tract (sensory) irritation is the most probable response to MVOC exposure, and no long-term or more toxic effects are expected. Inflammatory responses (e.g. increase in the count of inflammatory cells or other mediators) after single or repeated MVOC exposures have not been unequivocally confirmed in controlled human exposure studies. Thus, sensory irritation by the stimulation of the trigeminal nerves seems to be the most likely mechanism of toxicity of typical MVOCs. Occupational exposure limits (OELs) based on irritation as the critical effect have been shown to correlate roughly to 3% of their respective RD_{50}s. This would correspond to 5–530 mg/m^3 (0.9–100 ppm) for the 15 typical MVOCs, with geosmin and 1-octen-3-ol in the lower, and 3-octanone in the higher range. A further reduction by a factor of 40 has been proposed to protect the general population, including sensitive groups, which would correspond to 0.1–13 mg/m^3 for the individual MVOCs evaluated in this document.

Groups at Higher Risk

There are no scientific data available suggesting that any particular group is at higher risk.

Scientific Basis for an Occupational Exposure Limit

There are insufficient data to establish OELs for MVOC mixtures. There is no clear definition, but several hundred substances may be considered MVOCs. With few exceptions, little is known about the concentrations of these substances in indoor air, and even less is known about their health hazards. Measurements in indoor air have generally focused on a relatively small number of substances.

It should be pointed out, however, that some of the substances considered MVOCs are also used in industry or occur at relatively high levels in the work environment. For these substances, more is known about exposure levels in work places and health effects, and some have established OELs.

Sensory irritation seems to be the critical effect for many of the individual substances. Considering the low levels generally occurring in indoor air, it seems prudent to apply the additivity rule to calculate the risk for sensory irritation. Such calculations based on the RD_{50}s determined in mice suggest that the MVOC concentrations measured so far in indoor environments are well below the levels expected to cause sensory irritation. However, such exercises must be executed and interpreted with care and cannot be applied to reactive substances, and substances with other endpoints than irritation as the major concern (2-hexanone).

RESEARCH NEEDS

In the past, MVOCs have been a focus of research in two ways: as indicators of microbial growth in a substrate (foodstuffs, building constructions) or as possible causative agents for adverse health effects in buildings with moisture and microbial damage. However, among the compounds identified so far, none has been verified as a ‘pure’, MVOC (i.e. of solely microbial origin). Possible candidate groups for such specific MVOCs could include sesquiterpenes, furans, and very volatile

TABLE 12
Previous evaluations of some individual volatile organic compounds (VOCs) used in industrial processes

Compound	Organisation (Year)	Summary of conclusion/assessment	Reference
2-Methyl-1-propanol	Swedish Criteria Group for Occupational Standards (1984)	Reported effects of long-term exposure are primarily irritation of eyes and mucous membranes and some dizziness. In experimental animals central nervous system effects have been shown after relatively high doses.	Lundberg (1984)
	International Programme on Chemical Safety and World Health Organization (1987)	The available data are inadequate to set an OEL. In line with good manufacturing practice, exposure to isobutanol should be minimised. Isobutanol is severely irritating to the eyes and moderately irritating to the skin. From the animal studies available, it is not possible to determine a no-observed-adverse-effect-level for long-term exposure. No adequate data are available to assess mutagenicity or teratogenicity of isobutanol or effects on reproduction.	(IPCS/WHO) (1987)
	American Conference of Governmental Industrial Hygienists (ACGIH; 2001)	A TLV-TWA of 50 ppm is recommended for occupational exposure to isobutanol to minimise the potential for skin and ocular irritation. Sufficient data were not available to recommend skin, sensitiser or carcinogenicity notations or a STEL.	ACGIH (2001)
3-Methyl-1-butanol	ACGIH (2001)	A TLV-TWA of 100 ppm and a TLV-STEL of 125 ppm are recommended for occupational exposure to isoamyl alcohol, in part by analogy with the irritation data for *n*-butanol. This value is intended to minimise the potential for upper respiratory tract, and ocular irritation, with possible corneal damage. Sufficient data were not available to recommend skin, sensitiser or carcinogenicity notations.	ACGIH (2001)
2-Hexanone	German Research Foundation (DFG; 1975)	Concentrations down to 6 ppm lead to occurrence of polyneuritis in chronically exposed humans. Long-term studies in animals have also shown neurotoxic effects at 100–200 ppm. The MAK value is therefore established at 5 ppm.	DFG (1975)

(Continued on next page)

TABLE 12
Previous evaluations of some individual volatile organic compounds (VOCs) used in industrial processes *(Continued)*

Compound	Organisation (Year)	Summary of conclusion/assessment	Reference
	US National Institute for Occupational Safety and Health (NIOSH) (1978)	Studies on a variety of animals have conclusively demonstrated that repeated exposure to methyl *n*-butyl ketone produced peripheral neuropathy and data indicated that the no effect concentration in animals was probably less than 100 ppm. Human data indicate that apparently 2.3 ppm cannot be ruled out as causing neuropathy. Because of the severity of the toxic effects and the incomplete reversibility of the lesions in workers a cautious approach is needed. The ketone has the ability to penetrate skin as well as to cause local skin effects. It is recommended that methyl *n*-butyl ketone concentrations in workplace air not exceed 1 ppm (10 h TWA).	NIOSH (1978)
	Dutch Expert Committee on Occupational Standards (DECOS) and the Swedish Criteria Group for Occupational Standards (1990)	The primary target organ for 2-hexanone is the nervous system. It cannot be ruled out that severe neurotoxic effects that are not always completely reversible may develop in man at exposure levels as low as 2 ppm. Percutaneous absorption may contribute significantly to the occupational 2-hexanone exposure. Attention should be paid to the potentiation of 2-hexanone neurotoxicity by other chemicals. DECOS recommends (DECOS, 1990a) a health-based OEL for 2-hexanone of 0.5 ppm as an 8 h TWA concentration.	Bos (1990), DECOS (1990a)
	Swedish Criteria Group for Occupational Standards (1992)	The critical effect of occupational exposure to 2-hexanone is its effect on the nervous system. It should be noted that 2-hexanone is readily absorbed by the skin.	Lundberg (1992a)
	Agency for Toxic Substances and Disease Registry (ATSDR; 1992)	The most important health effect from exposure to 2-hexanone is its harmful effect on the nervous system. These effects were seen in workers who were exposed to 2-hexanone for almost a year. The major effects were weakness, numbness, and tingling in the skin of the hands and feet. Similar effects were seen in animals that ate or breathed high levels of 2-hexanone, these effects included weakness, clumsiness, and paralysis.	ATSDR (1992a)
	ACGIH (2001)	A TLV-TWA of 5 ppm and a STEL of 10 ppm are recommended. These values are intended to minimise the potential for distal peripheral neuropathy primarily nerve fibre conduction, with weakness in the hands and feet and loss of coordination. A STEL is recommended to control exposure concentrations, which have the potential to induce testicular toxicity. A skin notation is assigned based on data reporting skin uptake in humans contributing substantially to the total body burden. Sufficient data were not available to recommend sensitiser or carcinogenicity notations.	ACGIH (2001)

TABLE 12
Previous evaluations of some individual volatile organic compounds (VOCs) used in industrial processes *(Continued)*

Compound	Organisation (Year)	Summary of conclusion/assessment	Reference
2-Heptanone	DECOS and the Nordic Expert Group for Documentation of Occupational Exposure Limits (NEG; 1990)	The target organs for exposure to 2-heptanone are the upper respiratory tract for its irritation properties, the central nervous system, the liver and kidneys. On the basis of animal inhalation data, 1,000 ppm was considered an overall no adverse effect level. DECOS therefore recommended (DECOS, 1990b) a health-based OEL of 50 ppm as an 8 h TWA concentration.	Wibowo (1990), DECOS (1990b)
	Swedish Criteria Group for Occupational Standards (1992)	Judging from animal data, the critical effect of 2-heptanone is irritation of the upper respiratory tract.	Lundberg (1992b)
	American Conference of Governmental Industrial Hygienists (ACGIH; 2001)	Although based on limited toxicity data a TLV-TWA of 50 ppm is recommended to minimise the potential for eye and skin irritation. The lack of objective signs of toxicity, including neurotoxicity, in rats and monkeys inhaling 131 ppm of 2-heptanone on a daily basis for 9 months provide the basis for the recommended TLV.	ACGIH (2001)
Dimethyl disulphide	Swedish Criteria Group for Occupational Standards (1987)	There are no data on which to base dose-response or dose-effect relationships for occupational exposure. The critical effect of dimethyl disulphide is the discomfort caused by the smell.	Lundberg (1987)

Abbreviations: MAK, Maximale Arbeitsplatz-Konzentration (maximum workplace concentration); OEL, occupational exposure limit; STEL, short-term exposure limit; TLV®, threshold limit value; TWA, time weighted average.

compounds. The search requires further development of analytical methods. The other approach to increase the reliable interpretation of MVOC results might be to focus on statistical data handling of chromatograms. Some attempts on application of the principal component analyses have been made, but this area needs more research. On the other hand, statistical analyses require large databases on MVOC concentrations (exposure data) in different environments and occasions collected with the identical methodology. Before databases can be gathered, consensus on recommended sampling and analytical methods should be reached among researchers. These measures are necessary if MVOC analysis is intended to be used further either in the research or in field settings, although according to the present knowledge, the use of MVOC concentrations for both the above mentioned purposes appears to be questionable.

Considering health effects of MVOCs, more *in vitro* and *in vivo* data on the inflammatory and other immunological responses to MVOCs are needed. Furthermore, information on co-effects of several microbiological agents is still missing, though it is evident that no single agent studied so far is responsible for the health effects observed in subjects exposed to micro-organisms in living and work environments. One possibility is to direct the measurements towards more reactive compounds (such as amines, acids), as they are more likely to affect human health.

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DECLARATION OF INTEREST

The work was done in the course of the authors' regular employment (see authors' affiliations). The authors declare no conflicts of interest.

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