Food Sci. Biotechnol. Vol. 17, No. 3, pp. 447 ~ 456 (2008)

REVIEW

Food Science and Biotechnology

Promises and Risks of Unsaturated Volatile Organic Compounds: Limonene, Pinene, and Isoprene

Kyong-Suk Jin, Mira Jun[1], Min-Ji Park, Seon Ok, Jae-Han Jeong, Hye-Sook Kang, Wan-Keun Jo[2], Ho-Jin Lim[2], and Woo-Sik Jeong*

Food Science Institute, School of Food and Life Science, College of Biomedical Science and Engineering, Inje University, Gimhae, Gyeongnam 621-749, Korea

[1]Division of Food Science, Dong-A University, Busan 604-714, Korea

[2]Department of Environmental Engineering, Kyungpook National University, Daegu 702-701, Korea

Abstract Limonene, pinene, and isoprene are abundant and ubiquitous volatile organic compounds (VOCs) which are found in various natural products and also produced from various manufacture processes. Limonene and pinene are major components of food additives and household products for enrichment of good flavors and elimination of malodors, and isoprene is a basal motif of monoterpenes such as limonene and pinene. They have shown many beneficial effects such as chemopreventive, chemotherapeutic, and antioxidant activities. Upon certain conditions, however, adverse effects of these compounds on human health have also been reported. Although they do not seem to have acute and severe toxicity to human, they can easily generate secondary organic aerosols (SOAs) when they react with oxygen and/or ozone, which have shown certain toxic effects on experimental animal models as well as on humans. Numerous household and scented products containing limonene, pinene, and isoprene are widely used in these days. However, biological consequences upon exposure to these products are largely unknown. The aim of this review is to summarize and analyze the current understanding on the biological effects of VOCs, in particular limonene, pinene, and isoprene, as well as their SOAs.

Keywords: limonene, pinene, isoprene, volatile organic compound (VOC), secondary organic aerosol (SOA), health risk

Introduction

The terpenoid group constitutes the largest family of natural products in number, consisting of over 22,000 identified compounds (1). They are found in almost all plants and are consumed by humans in their normal daily diet (2). Terpenoids are mostly cyclic unsaturated hydrocarbons with the basic isoprene skeleton while non-cyclic terpenoid compounds such as lycopene are also available in nature. Terpenes have the general formula $(C_5H_8)_n$ ($n \geq 2$) and they are classified into mono-, sesquit-, di-, tri-, tetra-, and poly-terpenes, depending on the number of isoprene unit (C_5H_8) (3).

Among terpenes, monoterpenes ($C_{10}H_{16}$) such as limonene and pinene are volatile organic compounds (VOCs) naturally existed in the essential oils of citrus fruits, vegetables, spices, and herbs, etc (2,4-9). Physiological functions of monoterpenes in plant include their ability to act as chemoattractants or chemorepellents (1). Monoterpenes are widely used as fragrance components in foods, fine perfumes, and household products including cleansing products and air fresheners (10-12). Isoprene, the basal motif of terpenes, is one of the most abundant VOCs in the atmosphere and formed in a wide range of plants, bacteria, and mammals including humans (13-15).

Biological properties of monoterpenes and isoprene are well documented in many articles, which include chemopreventive, chemotherapeutic, and antioxidant activities (2,4,16,17). On the other hand, these VOCs may have adverse effects on human health directly or indirectly. Certain VOCs such as limonene, pinene, and isoprene could directly irritate human organs including skin and respiratory systems (18-23). Moreover, these VOCs are emitted from many household products and easily react with ozone in air, resulting in the formation of secondary organic aerosols (SOAs) that may harm human health (24,25).

Since the use of VOCs in particular limonene, pinene, and isoprene as scented products increases in human life, understanding the biological consequences and the underlying molecular mechanisms upon exposure of humans to these VOCs and their SOAs seems necessary. In this review, we discuss the current understanding on VOCs including limonene, pinene, isoprene, and their SOAs, especially on their direct and indirect biological consequences.

Chemical and biochemical properties of limonene, pinene, and isoprene

Limonene consists of over 90% of orange peel oil, explaining its strong odor of orange (4). It is found in different ratios and amounts in essential oils of many other plants, including citrus fruits (lemon, mandarin, lime, and grapefruit, etc), herbs (rosemary, eucalyptus, lavender, caraway, lemongrass, and peppermint), a tea tree, and pine tree (26-29) (Table 1).

Limonene is a chiral compound with two types of enantiomers which are D-limonene (*R*-(+)-limonene; *p*-menta-1,8-diene) and L-limonene (*S*-(-)-limonene; (*S*)-

*Corresponding author: Tel: +82-55-320-3238; Fax: +82-55-321-0691
E-mail: jeongws@inje.ac.kr
Received October 11, 2007; Revised November 12, 2007;
Accepted November 12, 2007

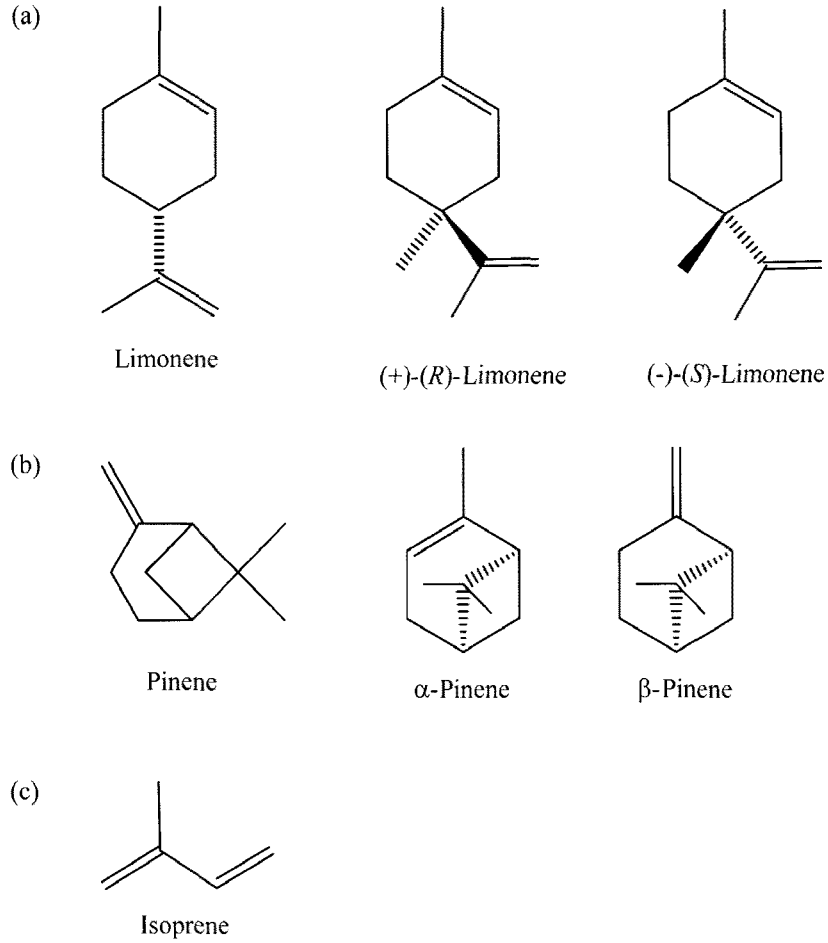

Fig. 1. Structures of limonene, pinene, isoprene, and their subtypes. Limonene has 2 enantiomers, D-limonene [(+)-(*R*)-limonene] and L-limonene [(-)-(*S*)-limonene] (a); pinene has 2 subtypes, α-pinene and β-pinene (b); isoprene is a basic motif of terpenes (c).

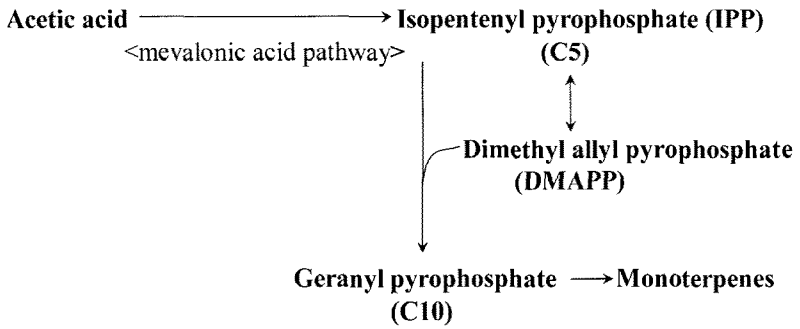

Fig. 2. Biosynthetic pathway of monoterpenes. Monoterpenes are synthesized from neryl pyrophosphate transferred from geranyl pyrophosphate; modified from McGarvey and Croteau (1).

menta-1,8-diene) (30) (Fig. 1). D-Limonene is the major constituent of essential oil in oranges and lemons, whereas L-limonene is mainly present in trees and herbs (30). Limonene is biosynthesized from neryl pyrophosphate formed via cyclization of geranyl pyrophosphate came from acetic acid through mevalonic acid pathway (1) (Fig. 2).

Pinene is a bicyclic monoterpene found in pine oil and is a well-known source of forest fragrance (31). Two structural isomers are found in nature; α-pinene and β-pinene (Fig. 1). α-Pinene is a major component in turpentine and can be found as much amounts in essential oils in pine trees while β-pinene exists with very small amounts (32). As the name suggests, pinenes are important constituents of pine resins; they are also found in resins of many other conifers, and more widely detected in air as it is emitted by a wide variety of plants (33,34). Both α- and β-pinene are also used by many insects in their chemical communication system (e.g., pheromone). On the other hand, α-pinene is a volatile pollutant typically found in waste gases from wood-related industries (35) (Table 1). Pinenes are produced from geranyl pyrophosphate, via cyclization of linaloyl pyrophosphate followed by loss of a proton from the carbocation equivalent (36) (Fig. 2). There are 2 enantiomers of α-pinene found in nature. (+)-α-

Table 1. Common sources of limonene, pinene, and isoprene

	Sources	Ref.
Limonene	Citrus fruits (orange, lemon, mandarin, lime, and grapefruit, etc)	(23)
	Herbs (rosemary, eucalyptus, lavender, caraway, lemongrass, mints, cardamom, dill, celery seed, coriander, and fennel, etc)	(4, 23)
	Tea tree	(23)
Pinene	Pine trees	(33)
	Insect's pheromone	(35)
	Waste gases from wood-related industries	(35)
	Eucalyptus	(4)
	Herbs (caraway, coriander, fennel, juniper berry, rosemary, and thyme, etc)	(4)
Isoprene	Plants (poplar, oak, willow, sycamore, and eucalyptus, etc)	(15)
	Mammals including humans	(13)
	Bacteria and marine algae	(14)
	Petroleum cracking	(15)
	Tobacco smoke	(15)

Table 2. Properties of limonene, pinene, and isoprene

	Limonene	Pinene	Isoprene
Chemical name	*p*-Mentha-1,8-diene	-	2-Methyl-1,3-butadiene
Synonyms	4-Isopropenyl-1-methylcyclohexene	-	Beta-methylbivinyl 2-Methylbutadiene Isopeutadiene
Enantiomer	D-Limonene; (*R*)-enantiomer L-Limonene; (*S*)-enantiomer	α-Pinene β-Pinene	
Racemic	DL-Limonene; dipentene		
Chemical formula	$C_{10}H_{16}$	$C_{10}H_{16}$	C_5H_8
Molecular mass	136.24 g/mol	136.24 g/mol	68.11 g/mol
Appearance	Clear, colorless liquid	Clear, colorless liquid	Clear, colorless liquid
Melting point	-95.2°C	-64°C	-145.95°C
Boiling point	176°C	155°C	34.067°C
Density	0.8411 g/cm^3 at 20°C	0.858 g/cm^3 at 20°C	0.681 g/cm^3 at 20°C
SMILES[1)]	CC_1=CCC(C(=C)(C))CC_1	CC_1(C)C_2CC_1C(C)=CC_2	C=C(C)C=C
CAS No.[2)]	138-86-3	80-56-8	78-79-5
IARC[3)] Class	3	3	2B

[1)]Simplified molecular input line entry system.
[2)]Chemical abstracts service registry numbers.
[3)]International Agency for Research on Cancer, Class 3; not classifiable as to its carcinogenicity to humans, Class 2B; possibly carcinogenic to humans.

Pinene (1*R*, 5*R*-enantiomer) is commoner in North America, whereas (-)-α-pinene (1*S*, 5*S*-enantiomer) is commoner in European pines. The racemic mixture is present in some oils such as eucalyptus oil (37).

Isoprene is the most abundant VOC in the atmosphere. It has a low boiling point (34°C) and high vapor pressure of 66 kPa at 20°C (Fig. 1, Table 2). Isoprene occurs ubiquitously in the environment and is formed in a wide range of plants (15), mammals including humans (13), bacteria, and marine algae (14) (Table 1). Important isoprenoids and terpenes derived from isoprene include rubber, sterols, retinol, tocopherol, vitamin K, carotenoids, coenzyme Q, monoterpenes, chlorophyll, phytol, dolichols, and squalene, etc (22). Isoprene is synthesized by isoprene synthase from dimethyl allyl pyrophosphate (DMAPP) via isopentenyl pyrophosphate (IPP) (15) (Fig. 2). Several studies have indicated that mevalonate, a precursor in cholesterol biosynthesis, is a possible source of the endogenous isoprene (38,39). Isoprene is the second only to acetone in concentration among hydrocarbons easily measured in human breath (40). Plants also produce large amounts of isoprene as much as or more than all of the methane entering the atmosphere on a global scale (41).

Various usages of limonene, pinene, and isoprene in human life

The use of limonene, pinene, and isoprene is summarized in Table 3. They are used as major or minor components of various products in the industries of food, cosmetic, and environment. Naturally occurring limonene is widely used not only as flavorings and fragrances in cosmetics, soaps, and perfumes, but also as a component of organic solvents and insecticides (10,12,18,42-53) (Table 3). During decades, limonene has been introduced as an environmentally acceptable organic solvent originated from plants for industrial cleaning and defatting, especially as a replacing agent of chlorinated hydrocarbons and chlorofluorocarbons

Table 3. Various usages of limonene, pinene, and isoprene in human life

	Usages	Ref.
Limonene	Fragrant compound (in cosmetics, soaps, and perfumes, etc)	(12, 44)
	Food additives	(12, 44)
	Household products (cleaning products, deodorizers, pesticides, and polishes, etc)	(10)
	Organic solvent (as a replacing agent of chlorinated hydrocarbons)	(18)
	Botanical insecticide	(43)
	Inducer of the transdermal absorption of cosmetics and therapheutic drugs	(45-52, 55, 56)
	Solvent for medical dissolution of gallstones	(53)
Pinene	Fragrances and flavorings	(12)
	Household products (cleaning products, deodorizers, and polishes, etc)	(10)
Isoprene	The manufacturing of *cis*-polyisoprene, butyl rubber and a variety of copolymers (thermoplastic and elastomeric co-block polymers, etc)	(58, 59)
	Non-invasive diagnostic biomarker	(60-62)

(18). In these products, the content of limonene ranges from a few % up to 100% (54). In addition, limonene is used in degreasing metals (30% limonene), printing materials (30-100% limonene), paints (43), and insecticides (42). On the other hand, limonene can induce transdermal absorption of cosmetics and therapeutic drugs, such as liqustrazine hydrochloride (55), haloperidol (45), nicorandil (48), nimodipine (47), nicardipine (46), tamoxifen (49), lipophilic and hydrophilic drugs (50), and indomethacin (51), etc (52,56).

Pinene is also one of the major fragrance chemicals in fragrances and flavorings (12,57). It is present in many household products including air freshener, bleach, dishwashing detergent, disinfectant, fabric deodorizer, fabric softener, furniture polish, and general cleaner, etc (10).

The main use of isoprene occurs in two industries; polymer and clinical industries. Isoprene is mainly used for the production of *cis*-polyisoprene and of various copolymers with isobutylene, butadiene, styrene, isobutene, and other monomers (58,59) (Table 3). Isoprene is a major hydrocarbon found in human breath and its level in breath is affected by health condition. There are some trials for measurement of endogenous isoprene level as a non-invasive diagnostic biomarker (60-62). Many evidences show the relationship between endogenous human breath isoprene and blood cholesterol levels (63), lipid disorders and diabetes mellitus (64), oxidant-induced injury to epithelial membrane and fluid linings of the lower respiratory tract by ozone (65). Exercise alone reduces isoprene levels in breath without an additive ozone effect. In fact, there are gender and age specific differences in exhaled isoprene levels (66) and some therapeutic activity can cause the variation of the amount of exhaled or urinary isoprene (67-72). Therefore, breath isoprene measurements could potentially be used for mass screening for lipid disorders (61).

Biological functions of limonene, pinene, and isoprene

Biological functions of limonene, pinene, and isoprene in plants and mammals are summarized in Table 4. The main physiological functions of monoterpenes in plant include their ability to act as chemoattractants or chemorepellents (1). In plants, natural functions of limonene are thought to be prevention of dehydration and microbial infection, especially on fungal growth (30). Evidences on beneficial roles of limonene on human health are elsewhere. The most widely studied biological function of limonene is the chemopreventive and/or chemotherapeutic properties. It has been shown to possess chemopreventive activity against various types of cancer (73-79). In *in vivo* gastric and lung cancer models, limonene inhibited tumor growth and metastasis (77,78). Although the exact mechanism of

Table 4. Biological roles of limonene, pinene, and isoprene

	Function	Ref.
Limonene	Prevention of dehydration and inhibition of microbial growth in natural products (plants and fruits)	(30)
	Antioxidant activity	(123)
	Chemotherapeutic activity	(74, 75)
	Proliferation inhibition	(73, 76)
	Apoptosis induction	(73, 76)
	Chemopreventive activity	(80)
	Modulation of immune responses	(124)
Pinene	Insect's chemical communication system (e.g., pheromone)	(35)
	Antioxidant activity	(84)
	Growth inhibitory activity	(84)
Isoprene	Basic structural motif of important isoprenoids and terpenes (e.g., rubber, sterol, vitamins, coenzyme Q, monoterpenes, chlorophyll, phytol, dolichols, and squalene, etc)	(22)
	Antioxidant activity	(17, 86)
	Stabilization activity of plant cells	(17, 87-90)

chemoprevention by limonene has not been fully understood, there are many studies to elucidate regulatory roles of limonene in molecular level. Limonene has been demonstrated as a chemotherapeutic agent against pancreatic, mammary, and prostatic tumors through its inhibition of posttranslational isoprenylation of cell growth-regulatory proteins such as p21 ras and small GTP-binding proteins, resulting in alteration of their intracellular localization (74,75). Regulation of c-myc oncoprotein by limonene has been reported in a chemically induced hepatocarcinogenesis model (79). Chemoprevention by limonene can be also achieved by the induction of phase 2 detoxifying and antioxidant enzymes such as glutathione-*S*-transferase (GST) and quinine reductase, which blocks the initiation of carcinogenesis (80) (Table 4).

Pinene has been much less studied than limonene especially in the aspect of the health benefit. In fact, there are few studies regarding the biological activity of pinene itself. Rather, it has been reported as a main constituent of essential oils from several plants, which have antioxidant activity. These plants include juniper berry, parsley seed, *Grindelia robusta* Nutt, and *Pistacia lentiscus L* (81-83). Besides antioxidant activity, stress-induced hyperthermia in rats was suppressed after spray treatments with α-pinene (84). In addition, it inhibited nuclear translocation of nuclear factor κB (NF-κB) induced by lipopolysaccharide (LPS) in human monocyte THP-1 cells, partly due to the upregulation of the inhibitor of NF-κB (IκBα) expression (85).

In plant, isoprene is one of the most effective antioxidants (17,86). It stabilizes plant cells, particularly chloroplast thylakoid membranes by quenching ozone (17). Other protective roles of isoprene in plant include its ability to protect plant membrane against thermal shock (87) and environmental stresses, and to decrease nitric oxide concentration (88-90) (Table 4). Studies on the beneficial roles of isoprene in human health are scarce; however, the adverse aspects of isoprene will be discussed later in the review.

Potential health risks of limonene, pinene, and isoprene

In spite of various benefits and usages of monoterpenes such as limonene and pinene and its basal structure unit isoprene, there are increasing concerns on these VOCs due to their potential health risks for human, especially when they are used as consumer products and become sources of indoor air pollutants (10). Many household products are sources of VOCs which are generally found at concentrations several fold higher indoors than outdoors (24). Since on average people spend 85 to 90% of their time indoors in either a home or work environment, these indoor air pollutants are of great concerns (24).

In an animal study with guinea pigs, limonene with high purity gave no significant allergic reactions but it sensitized the animals when they are exposed to air for 2 months (91). The authors found that the content of limonene oxide in limonene increased with prolonged air exposure, suggesting formation of allergenic compounds from the air oxidation of limonene. Larsen *et al.* (92) reported adverse effects of airborne limonene on the respiratory tract. A bronchoconstrictive effect was shown at the concentrations above 1,000 ppm in mice while no-observed-effect level (NOEL) was estimated to be 100 ppm in the animals. Toxicity of limonene might be a gender- or species-specific response. Limonene produced tumors in kidney at high doses only in male rat with the development of hyaline droplet nephropathy (93), but not in humans (54) (Table 5). In fact, International Agency for Research on Cancer (IARC) assorts limonene under Class 3, which is not classifiable as a carcinogen to humans. In human, inhaled limonene was observed in blood for a long time and elimination phase was very slow, indicating possible accumulation of limonene and/or its metabolites in adipose tissues (19).

Limonene is one of the most frequently identified terpenes in indoor settings (94). It is easily oxidized upon exposure to air and/or light, turning non-, or low-sensitizing compounds into mixtures with considerable sensitizing capacity (91,95). Ozone is also commonly found in indoor air during warm weather, which is infiltrated from outdoors and/or produced indoors (94). These high occurrences of limonene and ozone in indoor environment make them easily react and generate harmful oxidation products. Reactions between limonene and ozone can produce hydroperoxides (ROOH) including hydrogen peroxide (H_2O_2) as well as hygroscopic SOAs (96). In addition, air oxidation of limonene can create potent allergens such as (*R*)-(-)-carvone, (+)-limonene oxide (95). These findings

Table 5. Potential health risks of limonene, pinene, and isoprene

	Symptom	Species	Ref.
Limonene	Mild skin irritation	Human	(18)
	Moderate acute toxicity	Rat	(125)
	Sensory irritation	Mice	(92)
	Mild bronchoconstrictive effect	Mice	(92)
	Tumor in kidney	Male rat	(93)
Pinene	Persistent sensory irritation effect on the upper respiratory track	Mice	(20)
	Skin eruption, ataxia, kidney damage, coma, palpitation, dizziness, nervous disturbances, chest pain, bronchitis, nephritis, and benign skin tumor		(126)
	Transient excitement, ataxia, confusion, and stuper		(126)
	Painful urination, albuminuria, and hematuria		(126)
Isoprene	Irritation of the upper respiratory mucosa, larynx, and pharynx	Human	(112)
	Irritation to skin, mucous membranes, and central nervous system depression	Human	(112)
	Catarrhal inflammation, subtrophic and atrophic processes in the upper respiratory tract	Human	(112)

Table 6. Metabolites and secondary organic aerosols (SOAs) of limonene, pinene, and isoprene

	Reactive compound	Products	Properties	Ref.
Limonene	Ozone	Hydroperoxides (ROOH)	Increased H_2O_2 conc.	(127)
	Oxygen (air oxidation)	(*R*)-(-)-Carvones, (+)-Limonene oxide	Potent allergens	(96)
			Bronchoconstrictive airway effects	(18)
			A known skin sensitizer	(18)
Pinene	Oxidation	Verbenone		(107)
	Oxygen or ozone	Acetone, formic acid, pinonaldehyde, pinonic acid, and pinic acid, etc		(107)
Isoprene	Oxidation	Isoprene mono-epoxide (EPOX I)	DNA damage	(128)

suggest that ozone-driven chemistry alters indoor environments, often producing products more irritating than their parent compounds (96). Therefore, the oxidation product of limonene has become a good and frequent indicator of fragrance-related contact allergy (23,95). Recent studies have indicated that limonene-ozone oxidation products cause eye irritation in indoor at the concentrations with part-per-billion levels (97,98). Limonene and its oxidation products are also known as skin irritants. Most reported cases of irritation have involved in long-term industrial exposure to the pure compound, for example during degreasing or the preparation of paints. Limonene-base solvent and oxidized limonene can cause occupational contact dermatitis in a histopathology technician (99,100) and dermatitis patients (23,101). Moreover, limonene can cause contact dermatitis from hand cleansers (102). Besides, acute necrotizing dermatitis and septicemia have been shown in cats after application of a limonene-based insecticidal shampoo (103) (Table 6).

Pinene is known for its growth-inhibitory activity through the induction of oxidative stress in plants (104). In a mice-model study, all forms of pinene enantiomers possessed sensory irritation properties and induce sedation and signs of anaesthesia while they had no pulmonary irritation effects (105). Pinene vapor exhibited a persistent sensory irritation effect on the upper respiratory tract in BALB/c mice while no irritating effect was observed at the alveolar level and no central nervous system effect was shown (20) (Table 5). α- and β-pinenes release into the work environment during sawing of fresh wood (106). They irritate eyes, mucous membranes and skin, and may cause allergic contact dermatitis (106). Verbenols, metabolites from α-pinene, were detected in urine of workers in wood-treating industry exposed to pinene (107) (Table 6). In a human inhalation study, a short-time exposure (20 min) to α-pinene did not cause acute changes in lung function, but a high affinity to adipose tissues was detected (108). One of eight samples of mother's milk collected from 4 urban/industrial areas in the USA was positive for the presence of α-pinene. Moreover, about 79% of the expired air samples were found to contain α-pinene although the compound was detected in all personal air samplers and detected in breath samples from many cities in USA (109). Similar to limonene, reaction of pinene with ozone generates SOAs and many oxidation products such as pinonaldehyde, acetone, formic acid, pinonic acid, and pinic acid, etc (110, 111) (Table 6). However, information on the biological roles of pinene-based SOAs is limited at this moment.

Isoprene is a natural product emitted by plants and endogenously produced by mammals including humans. Therefore, exposure to isoprene is unavoidable and occurs during the entire human life. Isoprene was first evaluated in 1994 by IARC, when it was placed in Group 2B, possibly carcinogenic to humans, on the basis of sufficient evidence for carcinogenicity in experimental animals (112) (Table 5).

Although there is sufficient evidence in experimental animal models for the carcinogenicity of isoprene, no epidemiological data relevant to the carcinogenicity of isoprene are available. There is little information on direct exposure of human to pure isoprene, but there are many reports regarding biological consequences after the occupational exposure of workers in the manufacture processes (113). In the average odor perception of isoprene, human volunteers experienced slight irritation of the upper respiratory mucosa, larynx, and pharynx. Isoprene-driven irritation to skin, mucous membranes, and central nervous system depression were shown in high concentrations. Catarrhal inflammation, subtrophic and atrophic processes in the upper respiratory tract, and deterioration of olfaction were noted in isoprene rubber production workers. The prevalence and degree were correlated with increasing length of service (112). Occupational exposure to isoprene may occur through inhalation and dermal contact with this compound at workplaces where isoprene or synthetic rubber is produced or used. The general population may also be exposed to isoprene by handling consumer products or vegetation that contain this compound and by ingesting foods that contain isoprene.

Isoprene is structurally related to 1,3-butadiene, a major component in synthetic rubber, which has been shown to be carcinogenic in mice and rats and genotoxic in mice (21). Tumorigenicity of isoprene probably originates from the intermediate epoxide metabolites, in particular from the mutagenic 1,2:3,4-diepoxy-2-methyl-butane (114). Isoprene was recently evaluated in the US National Toxicology Programme for carcinogenesis (115). In this study, male and female F344/N rats were exposed to isoprene by whole-body inhalation for 2 years. Under the conditions of study, there was evidence of carcinogenic activity in male F344/N rats based on increased incidences of mammary gland neoplasms, renal tubule adenoma, and testicular adenoma. There was some evidence of carcinogenic activity of isoprene in female F344/N rats based on increased incidences and multiplicity of mammary gland fibroadenoma. Increased incidences of renal tubule hyperplasia and splenic fibrosis were also observed in male rats. Other non-neoplastic effects in mice exposed to

isoprene include spinal cord and sciatic nerve degenerations, skeletal muscle atrophy, degeneration of the olfactory epithelium, epithelial hyperplasia of the forestomach, increased estrous cycle length, testicular atrophy, and decreased epididymal weight, sperm head count, sperm concentration, and sperm motility (116).

The metabolism of isoprene have been investigated in *in vivo* studies (21,117,118). Similar to butadiene metabolism, isoprene metabolizes into mono- and di-epoxides by cytochrome P450 monooxygenases and epoxide hydrolase. Significant sensory irritation was observed by exposing mice to mixtures of isoprene and O_3 or isoprene, O_3, and NO_2 (119). Repeated exposure to isoprene oxidation products by ozone causes enhanced irritations in respiratory tract of multiple murine strains, suggesting increased risks in buildings with high occupant densities where isoprene concentrations can be high (120). Photooxidation is another way to generate cytotoxic isoprene-based SOAs (121). When isoprene releases into the atmosphere, therefore, it can react with ozone to produce SOAs (122).

Conclusion

Limonene, pinene, and isoprene are ubiquitous in daily human life. Although these compounds have various beneficial effects in human life, there are increasing concerns regarding the adverse effects of their oxidation products and SOAs on human health. Unfortunately, we do not have sufficient information on the chemical and biological properties of these SOAs at this moment. Since the use of these VOCs as scented products increases, however, further studies to understand the biological consequences and underlying molecular mechanisms of their oxidation products are necessary.

Acknowledgment

We thank all the members of Dr. Jeong's laboratory for their assistance and critical discussions on this manuscript. This work was supported by grant No. (R01-2006-000-10851-0) from the Basic Research Program of the Korea Science & Engineering Foundation.

References

1. McGarvey DJ, Croteau R. Terpenoid metabolism. Plant Cell 7: 1015-1026 (1995)
2. Wagner KH, Elmadfa I. Biological relevance of terpenoids. Overview focusing on mono-, di-, and tetraterpenes. Ann. Nutr. Metab. 47: 95-106 (2003)
3. Bell SG, Chen X, Sowden RJ, Xu F, Williams JN, Wong LL, Rao Z. Molecular recognition in (+)-alpha-pinene oxidation by cytochrome P450cam. J. Am. Chem. Soc. 125: 705-714 (2003)
4. Jun M, Jeong WS, Ho CT. Health promoting properties of natural flavor substances. Food Sci. Biotechnol. 15: 329-338 (2006)
5. Choi H. Headspace analysis of *Robus coreanus* berry by solid-phase microextraction and its sniffing test by gas chromatopgaphy-olfactometry. Food Sci. Biotechnol. 11: 355-360 (2002)
6. Choi H, Kim M, Sawamura M. Constituents of the essential oil of *Angelica tenuissima*, an aromatic medicinal plant. Food Sci. Biotechnol. 10: 557-561 (2001)
7. Choi H, Sawamura M. Compositions of *Citrus tamurana* Hort. Ex Tanaka (*Hyuganatsu*) cold-pressed oil in different sized fruit. Food Sci. Biotechnol. 11: 71-77 (2002)
8. Wijaya C, Hadiprodjo I, Apriyantono A. Identification of volatile compounds and key aroma compounds of andaliman fruit (*Zanthoxylum acanthopodium* DC). Food Sci. Biotechnol. 11: 680-683 (2002)
9. Choi SI, Chang KM, Lee YS, Kim GH. Antibacterial activity of essential oils from *Zanthoxylum piperitum* A.P. DC. and *Zanthoxylum schinifolium*. Food Sci. Biotechnol. 17: 195-198 (2008)
10. Kwon KD, Jo WK, Lim HJ, Jeong WS. Characterization of emissions composition for selected household products available in Korea. J. Hazard Mater. 148: 192-198 (2007)
11. Marostica M, Mota N, Baudet N, Pastore G. Fungal biotransformation of monoterpenes found in agro-industrial residues from orange and pulp industires into aroma compounds: Screening using solid phase microextraction. Food Sci. Biotechnol. 16: 37-42 (2007)
12. Rastogi SC, Heydorn S, Johansen JD, Basketter DA. Fragrance chemicals in domestic and occupational products. Contact Dermatitis 45: 221-225 (2001)
13. Cailleux A, Cogny M, Allain P. Blood isoprene concentrations in humans and in some animal species. Biochem. Med. Metab. B. 47: 157-160 (1992)
14. Kuzma J, Nemecek-Marshall M, Pollock WH, Fall R. Bacteria produce the volatile hydrocarbon isoprene. Curr. Microbiol. 30: 97-103 (1995)
15. Sharkey TD. Isoprene synthesis by plants and animals. Endeavour 20: 74-78 (1996)
16. Crowell PL. Prevention and therapy of cancer by dietary monoterpenes. J. Nutr. 129: 775S-778S (1999)
17. Loreto F, Mannozzi M, Maris C, Nascetti P, Ferranti F, Pasqualini S. Ozone quenching properties of isoprene and its antioxidant role in leaves. Plant Physiol. 126: 993-1000 (2001)
18. DeWitt C, Bebarta V. Botanical solvents. Clin. Occup. Environ. Med. 4: 445-454, v-vi (2004)
19. Falk-Filipsson A, Lof A, Hagberg M, Hjelm EW, Wang Z. *d*-Limonene exposure to humans by inhalation: Uptake, distribution, elimination, and effects on the pulmonary function. J. Toxicol. Env. Health 38: 77-88 (1993)
20. Nielsen GD, Larsen ST, Hougaard KS, Hammer M, Wolkoff P, Clausen PA, Wilkins CK, Alarie Y. Mechanisms of acute inhalation effects of (+) and (-)-alpha-pinene in BALB/c mice. Basic Clin. Pharmacol. Toxicol. 96: 420-428 (2005)
21. Peter H, Wiegand HJ, Filser JG, Bolt HM, Laib RJ. Inhalation pharmacokinetics of isoprene in rats and mice. Environ. Health Persp. 86: 89-92 (1990)
22. Taalman RD. Isoprene: Background and issues. Toxicology 113: 242-246 (1996)
23. Matura M, Skold M, Borje A, Andersen KE, Bruze M, Frosch P, Goossens A, Johansen JD, Svedman C, White IR, Karlberg AT. Not only oxidized *R*-(+)- but also *S*-(-)-limonene is a common cause of contact allergy in dermatitis patients in Europe. Contact Dermatitis 55: 274-279 (2006)
24. Sunil VR, Laumbach RJ, Patel KJ, Turpin BJ, Lim HJ, Kipen HM, Laskin JD, Laskin DL. Pulmonary effects of inhaled limonene ozone reaction products in elderly rats. Toxicol. Appl. Pharm. 222: 211-220 (2007)
25. Surratt JD, Lewandowski M, Offenberg JH, Jaoui M, Kleindienst TE, Edney EO, Seinfeld JH. Effect of acidity on secondary organic aerosol formation from isoprene. Environ. Sci. Technol. 41: 5363-5369 (2007)
26. Loza-Tavera H. Monoterpenes in essential oils. Biosynthesis and properties. Adv. Exp. Med. Biol. 464: 49-62 (1999)
27. Crowell PL, Gould MN. Chemoprevention and therapy of cancer by *d*-limonene. Crit. Rev. Oncogenesis 5: 1-22 (1994)
28. Choi H, Min K. Headspace-SPME analysis of citrus hybrid, *Hallabong*. Food Sci. Biotechnol. 13: 126-129 (2004)
29. Lee H, Pai T. Chracteristics of cell growth and essential oil accumulation in spearmint cell suspension culture. Food Sci. Biotechnol. 6: 190-192 (1997)
30. Duetz WA, Bouwmeester H, van Beilen JB, Witholt B. Biotransformation of limonene by bacteria, fungi, yeasts, and plants. Appl. Microbiol. Biot. 61: 269-277 (2003)
31. Ishida T. Biotransformation of terpenoids by mammals, microorganisms, and plant-cultured cells. Chem. Biodivers. 2: 569-

590 (2005)
32. Al-Saidan SM, Krishnaiah YS, Chandrasekhar DV, Lalla JK, Rama B, Jayaram B, Bhaskar P. Formulation of an HPMC gel drug reservoir system with ethanol-water as a solvent system and limonene as a penetration enhancer for enhancing *in vitro* transdermal delivery of nicorandil. Skin Pharmacol. Physi. 17: 310-320 (2004)
33. Phillips MA, Savage TJ, Croteau R. Monoterpene synthases of loblolly pine (*Pinus taeda*) produce pinene isomers and enantiomers. Arch. Biochem. Biophys. 372: 197-204 (1999)
34. Lee S, Kim M, Lee S, Ahn Y, Lee H. Inhibitory effects of *Cinnamomun cassia* bark-derived materials on mushroom tyrosinase. Food Sci. Biotechnol. 9: 330-333 (2000)
35. Jin Y, Guo L, Veiga MC, Kennes C. Fungal biofiltration of alpha-pinene: Effects of temperature, relative humidity, and transient loads. Biotechnol. Bioeng. 96: 433-443 (2007)
36. Croteau R, Satterwhite DM, Wheeler CJ, Felton NM. Biosynthesis of monoterpenes. Stereochemistry of the enzymatic cyclizations of geranyl pyrophosphate to (+)-alpha-pinene and (-)-beta-pinene. J. Biol. Chem. 264: 2075-2080 (1989)
37. Liapi C, Anifantis G, Chinou I, Kourounakis AP, Theodosopoulos S, Galanopoulou P. Antinociceptive properties of 1,8-cineole and beta-pinene, from the essential oil of *Eucalyptus camaldulensis* leaves, in rodents. Planta Med. 73: 1247-1254 (2007)
38. Stone BG, Besse TJ, Duane WC, Evans CD, DeMaster EG. Effect of regulating cholesterol biosynthesis on breath isoprene excretion in men. Lipids 28: 705-708 (1993)
39. Cailleux A, Moreau X, Delhumeau A, Allain P. Decrease of isoprene concentrations in blood during general anesthesia. Biochem. Med. Metab. B. 49: 321-325 (1993)
40. Mukhopadhyay R. Measuring isoprene in breath. Anal. Chem. 79: 2610 (2007)
41. Singh AP, Varshney CK, Singh UK. Seasonal variations in isoprene emission from tropical deciduous tree species. Environ. Monit. Assess. 131: 231-235 (2007)
42. Hollingsworth RG. Limonene, a citrus extract, for control of mealybugs and scale insects. J. Econ. Entomol. 98: 772-779 (2005)
43. Lavoue J, Begin D, Geerin M. Technical, occupational health, and environmental aspects of metal degreasing with aqueous cleaners. Ann. Occup. Hyg. 47: 441-459 (2003)
44. Evans DL, Miller DM, Jacobsen KL, Bush PB. Modulation of immune responses in mice by d-limonene. J. Toxicol. Environ. Health 20: 51-66 (1987)
45. Lim PF, Liu XY, Kang L, Ho PC, Chan YW, Chan SY. Limonene GP1/PG organogel as a vehicle in transdermal delivery of haloperidol. Int. J. Pharm. 311: 157-164 (2006)
46. Krishnaiah YS, Satyanarayana V, Bhaskar P. Influence of limonene on the bioavailability of nicardipine hydrochloride from membrane-moderated transdermal therapeutic systems in human volunteers. Int. J. Pharm. 247: 91-102 (2002)
47. Krishnaiah YS, Bhaskar P, Satyanarayana V. Formulation and evaluation of limonene-based membrane-moderated transdermal therapeutic system of nimodipine. Drug Deliv. 11: 1-9 (2004)
48. Krishnaiah YS, Chandrasekhar DV, Rama B, Jayaram B, Satyanarayana V, Al-Saidan SM. *In vivo* evaluation of limonene-based transdermal therapeutic system of nicorandil in healthy human volunteers. Skin Pharmacol. Physiol. 18: 263-272 (2005)
49. Zhao K, Singh J. Mechanisms of percutaneous absorption of tamoxifen by terpenes: Eugenol, d-limonene, and menthone. J. Control Release 55: 253-260 (1998)
50. Ohara N, Takayama K, Nagai T. Combined effect of d-limonene pretreatment and temperature on the rat skin permeation of lipophilic and hydrophilic drugs. Biol. Pharm. Bull. 18: 439-442 (1995)
51. Okabe H, Takayama K, Ogura A, Nagai T. Effect of limonene and related compounds on the percutaneous absorption of indomethacin. Drug Des. Deliv. 4: 313-321 (1989)
52. Koyama Y, Bando H, Yamashita F, Takakura Y, Sezaki H, Hashida M. Comparative analysis of percutaneous absorption enhancement by d-limonene and oleic acid based on a skin diffusion model. Pharm. Res. 11: 377-383 (1994)
53. Igimi H, Tamura R, Toraishi K, Yamamoto F, Kataoka A, Ikejiri Y, Hisatsugu T, Shimura H. Medical dissolution of gallstones. Clinical experience of d-limonene as a simple, safe, and effective solvent. Dig. Dis. Sci. 36: 200-208 (1991)
54. Whysner J, Williams GM. d-Limonene mechanistic data and risk assessment: Absolute species-specific cytotoxicity, enhanced cell proliferation, and tumor promotion. Pharmacol. Therapeut. 71: 127-136 (1996)
55. Zhang CF, Yang ZL, Luo JB. Effects of enantiomer and isomer permeation enhancers on transdermal delivery of ligustrazine hydrochloride. Pharm. Dev. Technol. 11: 417-424 (2006)
56. Crowell PL, Lin S, Vedejs E, Gould MN. Identification of metabolites of the antitumor agent d-limonene capable of inhibiting protein isoprenylation and cell growth. Cancer Chemoth. Pharm. 31: 205-212 (1992)
57. Rastogi SC, Lepoittevin JP, Johansen JD, Frosch PJ, Menne T, Bruze M, Dreier B, Andersen KE, White IR. Fragrances and other materials in deodorants: Search for potentially sensitizing molecules using combined GC-MS and structure activity relationship (SAR) analysis. Contact Dermatitis 39: 293-303 (1998)
58. IARC. Re-evaluation of some organic chemicals, hydrazine, and hydrogen peroxide. Pt 1, pp. 1-315. In: Proceedings of the Working Group on the Evaluation of Carcinogenic Risks to Humans. February 17-24, Lyon, France. International Agency for Research on Cancer, Lyon, France (1998)
59. Leber AP. Overview of isoprene monomer and polyisoprene production processes. Chem. Biol. Interact 135-136: 169-173 (2001)
60. Turner C, Spanel P, Smith D. A longitudinal study of breath isoprene in healthy volunteers using selected ion flow tube mass spectrometry (SIFT-MS). Physiol. Meas. 27: 13-22 (2006)
61. Salerno-Kennedy R, Cashman KD. Potential applications of breath isoprene as a biomarker in modern medicine: A concise overview. Wien. Klin. Wochenschr. 117: 180-186 (2005)
62. McGrath LT, Patrick R, Silke B. Breath isoprene in patients with heart failure. Eur. J. Heart Fail. 3: 423-427 (2001)
63. Karl T, Prazeller P, Mayr D, Jordan A, Rieder J, Fall R, Lindinger W. Human breath isoprene and its relation to blood cholesterol levels: New measurements and modeling. J. Appl. Physiol. 91: 762-770 (2001)
64. Nelson N, Lagesson V, Nosratabadi AR, Ludvigsson J, Tagesson C. Exhaled isoprene and acetone in newborn infants and in children with diabetes mellitus. Pediatr. Res. 44: 363-367 (1998)
65. Foster WM, Jiang L, Stetkiewicz PT, Risby TH. Breath isoprene: Temporal changes in respiratory output after exposure to ozone. J. Appl. Physiol. 80: 706-710 (1996)
66. Lechner M, Moser B, Niederseer D, Karlseder A, Holzknecht B, Fuchs M, Colvin S, Tilg H, Rieder J. Gender and age specific differences in exhaled isoprene levels. Respir. Physiol. Neuro. 154: 478-483 (2006)
67. Lirk P, Bodrogi F, Raifer H, Greiner K, Ulmer H, Rieder J. Elective haemodialysis increases exhaled isoprene. Nephrol. Dial. Transpl. 18: 937-941 (2003)
68. Diskin AM, Spanel P, Smith D. Time variation of ammonia, acetone, isoprene, and ethanol in breath: A quantitative SIFT-MS study over 30 days. Physiol. Meas. 24: 107-119 (2003)
69. Capodicasa E, Trovarelli G, Brunori F, Vecchi L, Carobi C, De M, Pelli MA, Buoncristiani U. Lack of isoprene overproduction during peritoneal dialysis. Perit. Dial. Int. 22: 48-52 (2002)
70. Trovarelli G, Brunori F, De Medio GE, Timio M, Lippi G, Pelli MA, Capodicasa E. Onset, time course, and persistence of increased haemodialysis-induced breath isoprene emission. Nephron 88: 44-47 (2001)
71. McGrath LT, Patrick R, Mallon P, Dowey L, Silke B, Norwood W, Elborn S. Breath isoprene during acute respiratory exacerbation in cystic fibrosis. Eur. Respir. J. 16: 1065-1069 (2000)
72. Capodicasa E, Trovarelli G, De Medio GE, Pelli MA, Lippi G, Verdura C, Timio M. Volatile alkanes and increased concentrations of isoprene in exhaled air during hemodialysis. Nephron 82: 331-337 (1999)
73. Chen J, Lu M, Jing Y, Dong J. The synthesis of L-carvone and limonene derivatives with increased antiproliferative effect and activation of ERK pathway in prostate cancer cells. Bioorg. Med. Chem. 14: 6539-6547 (2006)

74. Crowell PL, Siar Ayoubi A, Burke YD. Antitumorigenic effects of limonene and perillyl alcohol against pancreatic and breast cancer. Adv. Exp. Med. Biol. 401: 131-136 (1996)
75. Crowell PL, Chang RR, Ren ZB, Elson CE, Gould MN. Selective inhibition of isoprenylation of 21-26 kDa proteins by the anticarcinogen d-limonene and its metabolites. J. Biol. Chem. 266: 17679-17685 (1991)
76. Ji J, Zhang L, Wu YY, Zhu XY, Lv SQ, Sun XZ. Induction of apoptosis by d-limonene is mediated by a caspase-dependent mitochondrial death pathway in human leukemia cells. Leuk. Lymphoma. 47: 2617-2624 (2006)
77. Lu XG, Zhan LB, Feng BA, Qu MY, Yu LH, Xie JH. Inhibition of growth and metastasis of human gastric cancer implanted in nude mice by d-limonene. World J. Gastroentero. 10: 2140-2144 (2004)
78. Raphael TJ, Kuttan G. Effect of naturally occurring monoterpenes carvone, limonene, and perillic acid in the inhibition of experimental lung metastasis induced by B16F-10 melanoma cells. J. Exp. Clin. Canc. Res. 22: 419-424 (2003)
79. Parija T, Das BR. Involvement of YY1 and its correlation with c-myc in NDEA induced hepatocarcinogenesis, its prevention by d-limonene. Mol. Biol. Rep. 30: 41-46 (2003)
80. Tsuda H, Ohshima Y, Nomoto H, Fujita K, Matsuda E, Iigo M, Takasuka N, Moore MA. Cancer prevention by natural compounds. Drug Metab. Pharmacokinet. 19: 245-263 (2004)
81. Wei A, Shibamoto T. Antioxidant activities and volatile constituents of various essential oils. J. Agr. Food Chem. 55: 1737-1742 (2007)
82. Fraternale D, Giamperi L, Bucchini A, Ricci D. Essential oil composition and antioxidant activity of aerial parts of *Grindelia robusta* from central Italy. Fitoterapia 78: 443-445 (2007)
83. Barra A, Coroneo V, Dessi S, Cabras P, Angioni A. Characterization of the volatile constituents in the essential oil of *Pistacia lentiscus* L. from different origins and its antifungal and antioxidant activity. J. Agr. Food Chem. 55: 7093-7098 (2007)
84. Akutsu H, Kikusui T, Takeuchi Y, Mori Y. Effects of alpha-pinene odor in different concentrations on stress-induced hyperthermia in rats. J. Vet. Med. Sci. 65: 1023-1025 (2003)
85. Zhou JY, Tang FD, Mao GG, Bian RL. Effect of alpha-pinene on nuclear translocation of NF-kappa B in THP-1 cells. Acta Pharmacol. Sin. 25: 480-484 (2004)
86. Loreto F, Velikova V. Isoprene produced by leaves protects the photosynthetic apparatus against ozone damage, quenches ozone products, and reduces lipid peroxidation of cellular membranes. Plant Physiol. 127: 1781-1787 (2001)
87. Singsaas EL, Lerdau M, Winter K, Sharkey TD. Isoprene increases thermotolerance of isoprene-emitting species. Plant Physiol. 115: 1413-1420 (1997)
88. Siwko ME, Marrink SJ, de Vries AH, Kozubek A, Schoot Uiterkamp AJ, Mark AE. Does isoprene protect plant membranes from thermal shock? A molecular dynamics study. Biochim. Biophys. Acta 1768: 198-206 (2007)
89. Logan BA, Monson RK, Potosnak MJ. Biochemistry and physiology of foliar isoprene production. Trends Plant Sci. 5: 477-481 (2000)
90. Velikova V, Pinelli P, Pasqualini S, Reale L, Ferranti F, Loreto F. Isoprene decreases the concentration of nitric oxide in leaves exposed to elevated ozone. New Phytol. 166: 419-425 (2005)
91. Karlberg AT, Boman A, Melin B. Animal experiments on the allergenicity of d-limonene-the citrus solvent. Ann. Occup. Hyg. 35: 419-426 (1991)
92. Larsen ST, Hougaard KS, Hammer M, Alarie Y, Wolkoff P, Clausen PA, Wilkins CK, Nielsen GD. Effects of *R*-(+)- and *S*-(-)-limonene on the respiratory tract in mice. Hum. Exp. Toxicol. 19: 457-466 (2000)
93. Hard GC, Whysner J. Risk assessment of d-limonene: An example of male rat-specific renal tumorigens. Crit. Rev. Toxicol. 24: 231-254 (1994)
94. Wainman T, Zhang J, Weschler CJ, Lioy PJ. Ozone and limonene in indoor air: A source of submicron particle exposure. Environ. Health Persp. 108: 1139-1145 (2000)
95. Karlberg AT, Magnusson K, Nilsson U. Air oxidation of d-limonene (the citrus solvent) creates potent allergens. Contact Dermatitis 26: 332-340 (1992)
96. Li TH, Turpin BJ, Shields HC, Weschler CJ. Indoor hydrogen peroxide derived from ozone/d-limonene reactions. Environ. Sci. Technol. 36: 3295-3302 (2002)
97. Kleno J, Wolkoff P. Changes in eye blink frequency as a measure of trigeminal stimulation by exposure to limonene oxidation products, isoprene oxidation products, and nitrate radicals. Int. Arch. Occ. Env. Hea. 77: 235-243 (2004)
98. Nojgaard JK, Christensen KB, Wolkoff P. The effect on human eye blink frequency of exposure to limonene oxidation products and methacrolein. Toxicol. Lett. 156: 241-251 (2005)
99. Foti C, Zambonin CG, Conserva A, Casulli C, D'Accolti L, Angelini G. Occupational contact dermatitis to a limonene-based solvent in a histopathology technician. Contact Dermatitis 56: 109-112 (2007)
100. Wakelin SH, McFadden JP, Leonard JN, Rycroft RJ. Allergic contact dermatitis from d-limonene in a laboratory technician. Contact Dermatitis 38: 164-165 (1998)
101. Karlberg AT, Dooms-Goossens A. Contact allergy to oxidized d-limonene among dermatitis patients. Contact Dermatitis 36: 201-206 (1997)
102. Topham EJ, Wakelin SH. d-Limonene contact dermatitis from hand cleansers. Contact Dermatitis 49: 108-109 (2003)
103. Lee JA, Budgin JB, Mauldin EA. Acute necrotizing dermatitis and septicemia after application of a d-limonene-based insecticidal shampoo in a cat. J. Am. Vet. Med. Assoc. 221: 258-262, 239-240 (2002)
104. Singh HP, Batish DR, Kaur S, Arora K, Kohli RK. Alpha-pinene inhibits growth and induces oxidative stress in roots. Ann. Bot. - London 98: 1261-1269 (2006)
105. Kasanen JP, Pasanen AL, Pasanen P, Liesivuori J, Kosma VM, Alarie Y. Stereospecificity of the sensory irritation receptor for nonreactive chemicals illustrated by pinene enantiomers. Arch. Toxicol. 72: 514-523 (1998)
106. Rosenberg C, Liukkonen T, Kallas-Tarpila T, Ruonakangas A, Ranta R, Nurminen M, Welling I, Jappinen P. Monoterpene and wood dust exposures: Work-related symptoms among Finnish sawmill workers. Am. J. Ind. Med. 41: 38-53 (2002)
107. Eriksson KA, Levin JO, Sandstrom T, Lindstrom-Espeling K, Linden G, Stjernberg NL. Terpene exposure and respiratory effects among workers in Swedish joinery shops. Scand. J. Work Env. Hea. 23: 114-120 (1997)
108. Falk AA, Hagberg MT, Lof AE, Wigaeus-Hjelm EM, Wang ZP. Uptake, distribution, and elimination of alpha-pinene in man after exposure by inhalation. Scand. J. Work Env. Hea. 16: 372-378 (1990)
109. Pellizzari ED, Hartwell TD, Harris BS 3rd , Waddell RD, Whitaker DA, Erickson MD. Purgeable organic compounds in mother's milk. Bull. Environ. Contam. Tox. 28: 322-328 (1982)
110. Librando V, Tringali G. Atmospheric fate of OH initiated oxidation of terpenes. Reaction mechanism of alpha-pinene degradation and secondary organic aerosol formation. J. Environ. Manage. 75: 275-282 (2005)
111. Stanier CO, Pathak RK, Pandis SN. Measurements of the volatility of aerosols from alpha-pinene ozonolysis. Environ. Sci. Technol. 41: 2756-2763 (2007)
112. National Toxicology Program. Isoprene. Rep. Carcinog. 10: 141-143 (2002)
113. Lynch J. Occupational exposure to butadiene, isoprene, and chloroprene. Chem. Biol. Interact. 135-136: 207-214 (2001)
114. Gervasi PG, Citti L, Del Monte M, Longo V, Benetti D. Mutagenicity and chemical reactivity of epoxidic intermediates of the isoprene metabolism and other structurally related compounds. Mutat. Res. 156: 77-82 (1985)
115. National Toxicology Program. NTP toxicology and carcinogenesis studies of isoprene (CAS No. 78-79-5) in F344/N rats (inhalation studies). Natl. Toxicol. Program. Tech. Rep. Ser. 486: 1-176 (1999)
116. Melnick R. NTP technical report on the toxicity studies of isoprene (CAS No. 78-79-5) administered by inhalation to F344/N rats and B6C3F1 mice. Toxic. Rep. Ser. 31: 1-G5 (1995)
117. Peter H, Wiegand HJ, Bolt HM, Greim H, Walter G, Berg M, Filser JG. Pharmacokinetics of isoprene in mice and rats. Toxicol. Lett. 36: 9-14 (1987)
118. Bond JA, Bechtold WE, Birnbaum LS, Dahl AR, Medinsky MA,

Sun JD, Henderson RF. Disposition of inhaled isoprene in B6C3F1 mice. Toxicol. Appl. Pharmacol. 107: 494-503 (1991)
119. Wilkins CK, Clausen PA, Wolkoff P, Larsen ST, Hammer M, Larsen K, Hansen V, Nielsen GD. Formation of strong airway irritants in mixtures of isoprene/ozone and isoprene/ozone/nitrogen dioxide. Environ. Health Perspect. 109: 937-941 (2001)
120. Rohr AC, Shore SA, Spengler JD. Repeated exposure to isoprene oxidation products causes enhanced respiratory tract effects in multiple murine strains. Inhal. Toxicol. 15: 1191-1207 (2003)
121. Claeys M, Graham B, Vas G, Wang W, Vermeylen R, Pashynska V, Cafmeyer J, Guyon P, Andreae MO, Artaxo P, Maenhaut W. Formation of secondary organic aerosols through photooxidation of isoprene. Science 303: 1173-1176 (2004)
122. Doyle M, Sexton KG, Jeffries H, Bridge K, Jaspers I. Effects of 1,3-butadiene, isoprene, and their photochemical degradation products on human lung cells. Environ. Health Perspect. 112: 1488-1495 (2004)
123. Grassmann J. Terpenoids as plant antioxidants. Vitam. Horm. 72: 505-535 (2005)
124. Aggarwal BB, Shishodia S. Molecular targets of dietary agents for prevention and therapy of cancer. Biochem. Pharmacol. 71: 1397-1421 (2006)
125. Karlberg AT, Basketter D, Goossens A, Lepoittevin JP. Regulatory classification of substances oxidized to skin sensitizers on exposure to air. Contact Dermatitis 40: 183-188 (1999)
126. Windholz M, Budavari S, Stroumtsos LY, Fertig MN. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. 9th ed. Merck & Co., Inc., Rahway, NJ, USA. p. 7248 (1976)
127. Tamas G, Weschler CJ, Toftum J, Fanger PO. Influence of ozone-limonene reactions on perceived air quality. Indoor Air 16: 168-178 (2006)
128. Fabiani R, Rosignoli P, De Bartolomeo A, Fuccelli R, Morozzi G. DNA-damaging ability of isoprene and isoprene mono-epoxide (EPOX I) in human cells evaluated with the comet assay. Mutat. Res. 629: 7-13 (2007)