APPENDIX A6.1.3.21 ISOPRENE - FACTSHEET

	HPHC	BoExp assessed by PMI
IUPAC name	2-methylbuta-1,3-diene	NA
Usual abbreviation	IP	
Other names	2-methyl-1,3-butadiene, isopentadiene, 2-Methylbutadiene, isoterpene, 3-methyl-1,3-butadiene, β-methylbivinyl,	
CAS number	78-79-5	
Formula and molecular weight	C_5H_8 MW: 68.12	

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Main characteristics

Chemical class	Aliphatic diene
HPHC lists	FDA-93 [1]; FDA-18 [2]; HC [3, 4]; PMI-58; WHO-39 [3]
Source in cigarettes	Primary source in indoor air is environmental tobacco smoke Amount in MSS (3R4F): 395 µg (ISO); 863 µg (HCI) [4] Smoke phase: gas/vapor phase [5] Presence in tobacco / pyrosynthesis (T°): present in un-combusted tobacco / 500-800°C [6]; possible precursors for isoprene in tobacco are solanesol, and resinous, ether-extractable compounds [7].
Other sources [8-10]	Isoprene's production and use as a monomer in the manufacture of polyisoprene, synthetic rubber, butyl rubber and as a copolymer in the production of synthetic elastomers may result in its release to the environment through various waste streams. Isoprene has been shown to be a biogenic emitted from many tree and plant species. Isoprene occurs in the environment as emissions from vegetation, particularly from deciduous forests, and as a by-product in the production of ethylene by naphtha cracking. Human exposure to isoprene is largely due to its generation during endogenous processes, particularly isoprenoid biosynthesis, as it is the major hydrocarbon exhaled by humans. Isoprene emissions from natural sources exceed those from industrial output by approximately 300-fold. Nevertheless, smoking increases isoprene exposure significantly and environmental tobacco smoke is the primary source of isoprene in indoor air.
Toxicity class (FDA) [1]	CA
Toxicity – CA	IARC: group 2B: possible carcinogenic to humans. No human carcinogenicity data were available to the IARC Working Group [9]. Isoprene was tested for carcinogenicity in male mice and in male rats by inhalation exposure in one-year studies [9, 11]. In mice, exposure to isoprene resulted in increased incidence of benign and malignant tumors of the lung, liver and forestomach and of Harderian gland adenomas. The study by inhalation in rats was inadequate for an assessment of carcinogenicity [12, 13]. Based on animal cancer data, isoprene and chloroprene are listed in the NTP's Report on Carcinogens (RoC) as reasonably anticipated to be a human carcinogen [13]. Epidemiology data for isoprene are not considered adequate to evaluate the potential carcinogenicity of these agents in humans [14].

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Toxicity – RT	Increasing duration of employment of isoprene rubber production workers showed a correlation with the prevalence and degree of various effects [12]. Effects noted in these workers were subtrophic and atrophic processes in the upper respiratory tract, catarrhal inflammation, and degeneration of the olfactory tract.
Toxicity – CT	-
Toxicity – RDT	-
Toxicity – AD	-
Toxicity - others	All available toxicity data can be found on the Website Aggregated Computational Toxicology Resource [15].

ADME properties

Absorption and distribution [8, 16] – Studies on inhalation pharmacokinetics of isoprene were conducted in rats and mice to investigate possible species differences in metabolism of this compound. Pharmacokinetic analysis of isoprene inhaled by rats and mice revealed saturation kinetics of isoprene metabolism in both species, with a rate of isoprene metabolism in mice that was about two or three times that in rats. Blood, liver and especially fat are the major tissues containing isoprene after inhalation in rats. Body fat appears to be a reservoir for both isoprene metabolites and isoprene itself.

Metabolism [8, 9, 11] - Isoprene is formed endogenously in humans and is generally the major hydrocarbon in human breath up to 70%). The quantity exhaled per day per individual was estimated to be of 2-4 mg [13]. Concentrations in blood range from 15 to 70 nmol/L (1.0 to 4.8 µg/L) The endogenous production rate of isoprene was calculated to be 0.15 µmol/kg per hour [17]. The biotransformation of isoprene is similar to that of 1,3-butadiene, which involves initial oxidation to 1,2-epoxy-3-butene followed by hydrolysis to 3-butene-1,2-diol, conjugation with glutathione, or further oxidation to diepoxybutane. Cytochrome P450 2E1 (CYP2E1) is the major enzyme involved in the hepatic metabolism of both isoprene and 1,3-butadiene. Isoprene is metabolized to 3,4-epoxy-3-methyl-1-butene (EPOX-I) and 3,4-epoxy-2-methyl-1-butene (EPOX-II) by liver microsomal cytochrome P450 -dependent monooxygenases [18]. In rodents, 3,4-Epoxy-3-methyl-1-butene (half-life 85 min) was found to be the main metabolite, although the stable 3,4-epoxy-2-methyl-1-butene was also formed at amounts of 14-25% with respect to the main epoxide [18].

The epoxide intermediates of isoprene biotransformation may undergo hydrolysis to form vicinal diols, may be conjugated with glutathione, or may be further oxidized to isoprene diepoxide (2-methyl-1,2:3,4-diepoxybutane) [11]. Both isoprene monoepoxides are further oxidized to mutagenic isoprene diepoxide by rat, mouse, and human liver microsomes. Differences in epoxide hydrolase activity between different species may be of importance for toxicological outcomes: rates of metabolism are about 14 times faster in mice and about eight times faster in rats than in humans [19]. In rats, the percentage of the inhaled isoprene that is metabolized decreases with increasing exposure concentration [16].

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Isoprene-derived hemoglobin adducts were detected in the blood of rats and mice exposed to [^{14}C]-isoprene by intra- peritoneal injection or by inhalation [11]. DNA adducts formation in vitro has also been investigated [10]. Data on human adducts could not be located.

Excretion [11] - About 90% of isoprene produced endogenously in humans is metabolized and 10% is exhaled unchanged. About 75% of the total metabolites is excreted in urine (Figure 1), which is independent of inhaled isoprene concentration. At very high levels of exposure, however, a significant proportion of the metabolites are excreted in faeces in rats [11, 17].

Vinyl lactic acid (2-hydroxy-2-methyl-3-butenoic acid) was identified as the major urinary metabolite of isoprene metabolism in F344 rats [20], and has been used as biomarker of exposure to isoprene in rat studies [11]. The maximal metabolic elimination rate of inhaled isoprene in mice is about three times greater than that in rats. The whole body half-life of isoprene was 6.8 minutes in rats and 4.4 minutes in mice [21]. No study describing half-life in humans could be located.

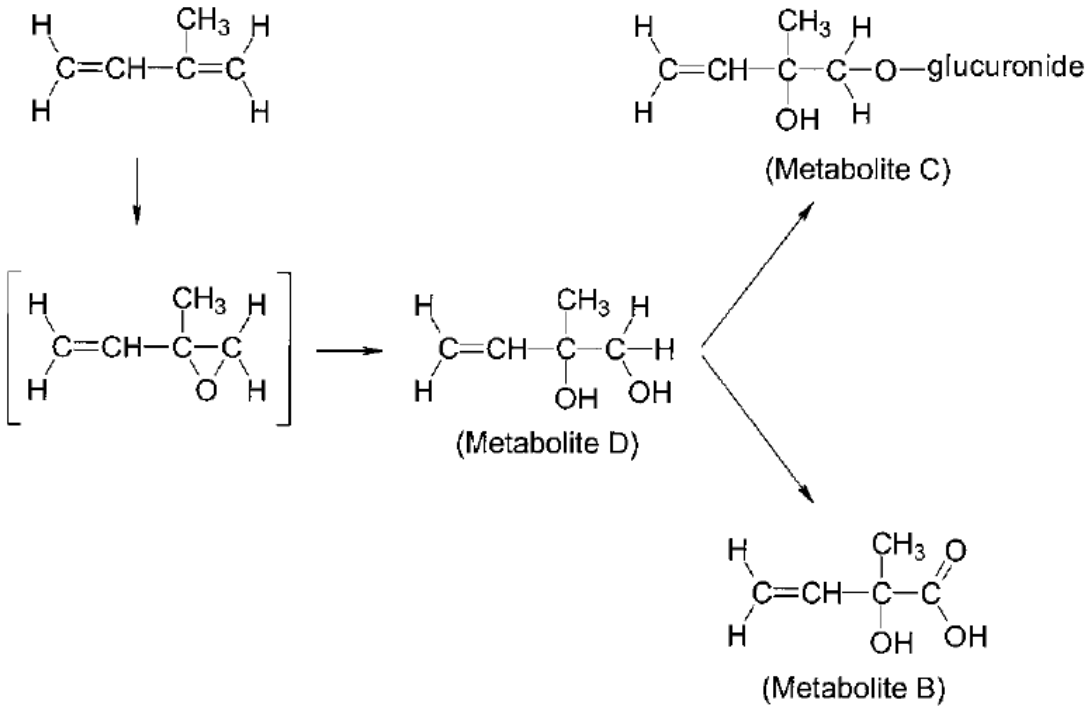


Figure 1 Proposed metabolic pathway for excretion of isoprene in urine of rats and mice [20]

Metabolite B = 2-hydroxy-2-methyl-3-butenoic acid (53%); metabolite C = glucuronide conjugate of metabolite D (13%); metabolite D = 2-methyl-3-buten-1,2-diol (23%)

Figure by Buckley LA, Coleman DP, Burgess JP, Thomas BF, Burka LT, Jeffcoat AR. Identification of urinary metabolites of isoprene in rats and comparison with mouse urinary metabolites. Drug Metab Dispos. 1999; 27(7):848-54. Reprinted with permission of the publisher. Copyright © 2016 by the American Society for Pharmacology and Experimental Therapeutics.

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Exposure levels in smokers and non-smokers

Because of the high amount of endogenous production of its very short half-life, isoprene levels in humans have not been reported as being reliable to distinguish smokers and non-smokers. Isoprene in exhaled breath has been shown to be slightly increased in smokers, when compared to non-smokers, however increase was small (< 2-fold) [22].

List of abbreviations

3R4F	Kentucky 3R4F reference research cigarette [23]
AD	Addictive
ADME	Absorption and Distribution, Metabolism, and Excretion
CA	Carcinogen
CAS number	Chemical Abstracts Service number
CT	Cardiovascular toxicant
FDA	Food and Drug Administration
HC	Health Canada
HCI	Health Canada Intense regime [24]
HPHC	Harmful and Potentially Harmful Constituents
IARC	International Agency for Research on Cancer
ISO	International Organization for Standardization smoking regime [25]
IUPAC	International Union of Pure and Applied Chemistry
MSS	Main stream smoke
MW	Molecular weight
NTP	National Toxicology Program
PMI	Philip Morris International
RDT	Reproductive or developmental toxicant
RT	Respiratory toxicant
WHO	World Health Organization

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