



# Isoprene and its Overall Impacts: Review

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## Abstract

A clean environment is a suitable medium for providing requirements that sustain the organisms living therein. Hence, it is a 'natural-store house' to receive and provide the metabolic needs of the biotic and abiotic systems. It also accomplishes the crucial geochemical cycles that maintain their appropriate balance. The metabolites may be quantitatively and qualitatively meagre but cause good and bad impacts. The organisms also contribute to these metabolites. The anthropogenic interference a prime causes of environmental disturbances and renders the environment unsuitable. Isoprene is one of the biogenic and abiogenic volatile organic compounds prominently present in the lower troposphere. Normally, this volatile compound interacts with ozone, hydroxyl and oxides of nitrogen and causes depletion of ozone. Trees that combat unfavorable fluctuations in environmental parameters like high winds, tornadoes, extreme temperature, drought (a complex impact), flood, wild fires, and deficiency of nutrition, experience the influence of isoprene. Mostly the developing countries encounter poor air quality that contains particulate matter, pollutants resulting in respiratory illness, cardiovascular and cancerous ailments. The presence of volatile organic components in human exhaled air indicates their metabolic or the ambient environmental origin. The endogenous organic volatile compounds present in human breath are the biomarkers for the pathophysiological conditions and are of clinical and biomedical significance, specifically during non-invasive estimations. Although, isoprene has attracted researchers but its pathophysiological impacts need more investigations, hence, this presentation to evaluate the effects of isoprene in biosphere.

**Keywords:** Biogenic-Volatile-Organic Compound; Cholesterol; Environment; Global Secondary Organic Aerosol Budget; Isoprene; Lipid Metabolism; Mevalonate-Pathway; Ozone; Pathophysiological Impacts

**Abbreviations:** BVOC: Biogenic Volatile Compounds; DMAPP: Dimethylallyl Pyrophosphate; IPP: Isopentenyl Pyrophosphate; MEP: Methyl-Erythritol 4-Phosphate; PPF: Photosynthetic Photon Flux Density; CRP: C-Reactive Protein.

## Introduction

In atmosphere many non-methane biogenic volatile compounds (BVOC) emanate and isoprene, (2-methyl-1,

3-butadiene) is the dominant one and around 90% is from terrestrial plant. This biogenic volatile compound influences the chemical aspects of atmosphere at least in the lower troposphere (nearer to earth). In a non-polluted atmosphere there are interactions between isoprene and ozone, hydroxyl and nitrogen oxide resulting in atmospheric depletion of ozone and hydroxyl radicals [1,2]. In the polluted atmosphere having high nitrogen contents enhances the formation of ozone in troposphere; this affects

human health and the yield of crops [2,3]. Overall these atmospheric changes elevate the life time of atmospheric methane, efficacy of primary sink, and production of oxidation of hydroxyl radicals [4]. The secondary oxidation of isoprene forms particulate matter inducing haze, smog, and cloud condensation nuclei; this drastically affects the intensity of planetary (earth) albedo i.e., fraction of sun light diffusely reflected by earth. All these changes influence the climatology, astronomy and environmental management. Under normal conditions the earth's albedo ranges within 30-35%. This albedo also depends on the cloud cover, type of the surface, geological and environmental parameters of the planet [3,5]. In nature, isoprene is released mostly by plants like oaks, poplars, eucalyptus and leguminous plants. Even broad-leaf trees and shrubs also emit isoprene; the total isoprene emission is around 600 million tons [6]. This amount is approximately equals to the emission of methane and other hydrocarbons released in atmosphere. The deciduous forests, microscopic and macroscopic algae also add to the amount of isoprene emission [7]. Humans contribute is about 70% of the hydrocarbon exhaled and isoprene is one of the main endogenous of the human breath [8-12]. In one of the experiments conducted, showed 5-400 ppb of isoprene in the exhaled in human breath during exercise; the concentration is on higher side in case of older human. The concentration of isoprene declined in extended duration of exercise [12]. There are reports on isoprene showing no relation to the corresponding pathophysiological impacts or putative metabolic origin from mevalonate pathway. Thus, some of the researchers hesitate to use isoprene for interpretation and correlation with the clinical aspects [13].

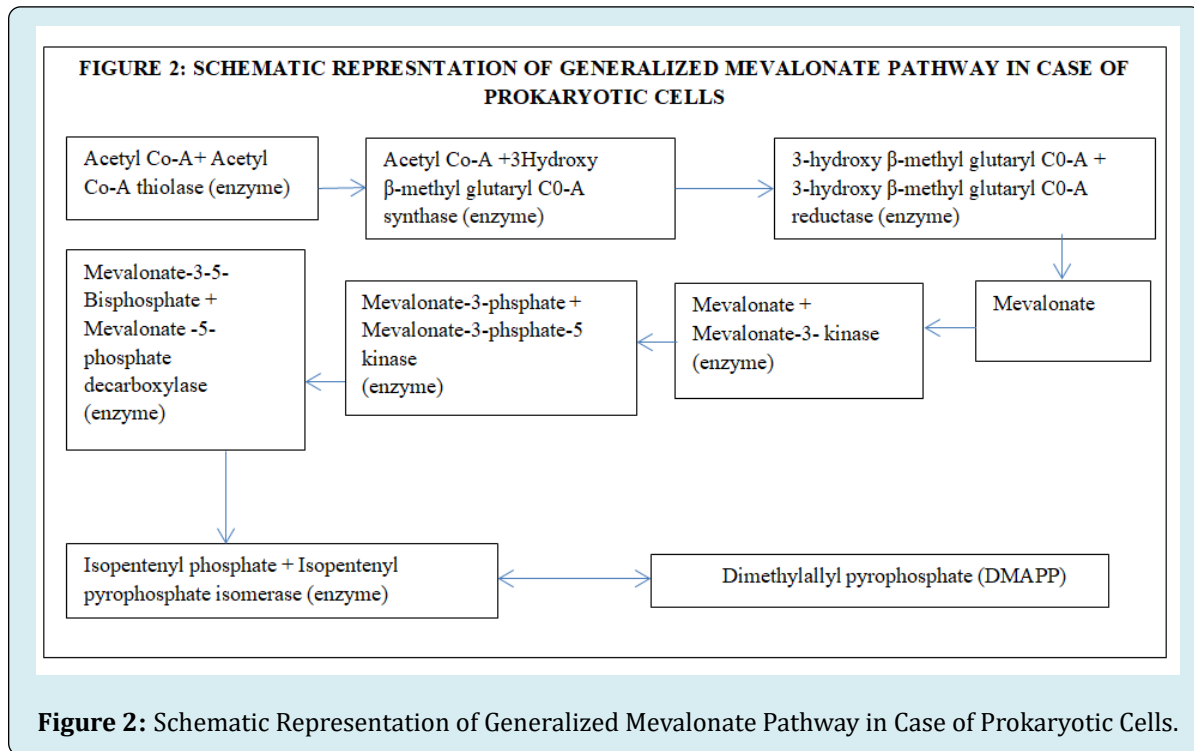
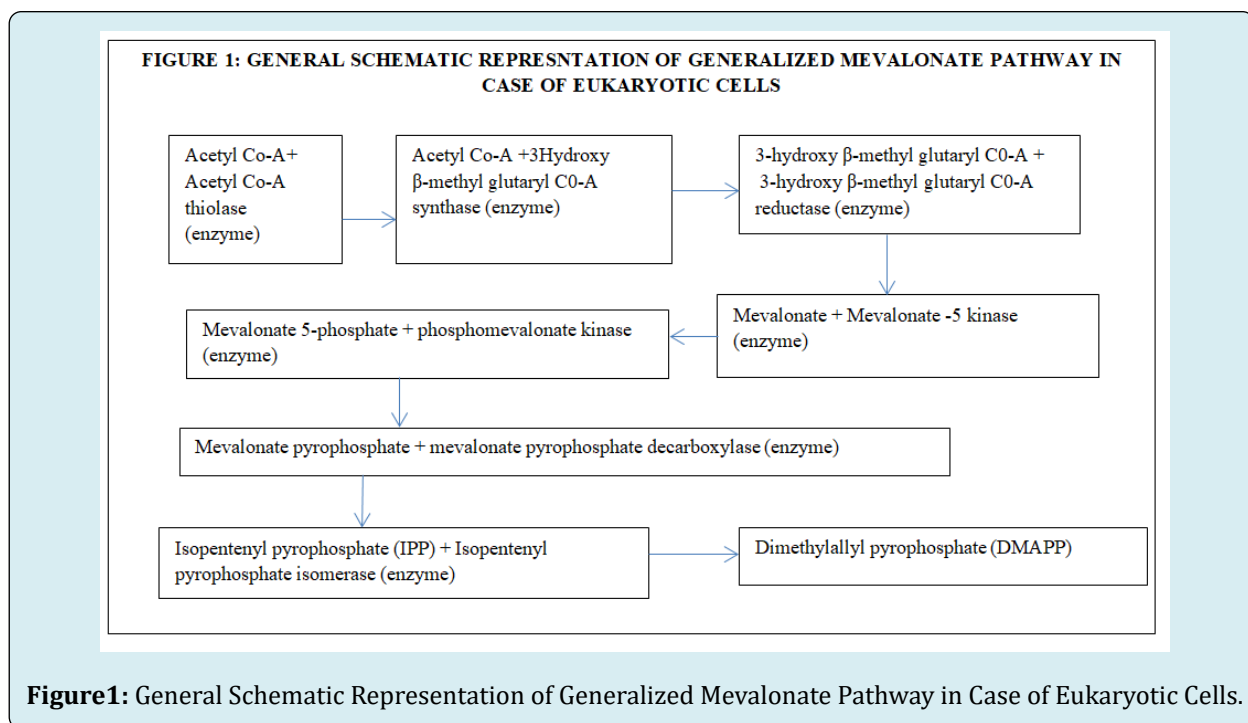
### Basic Mechanism of Synthesis of Isoprene

The enzymatic cleavage of dimethylallyl pyrophosphate (DMAPP) under the influence of enzyme isoprene synthase forms isoprene. The molecule of isopentenyl Pyrophosphate (IPP) structurally contains five carbon atoms and is a common precursor for all natural isoprenoids in classical mevalonate pathway. Isopentenyl pyrophosphate and dimethylallyl pyrophosphate (DMAPP) are the structural components of isoprenoids, also called terpenoids, in a biological system. These compounds also participate in the structural aspects of cholesterol and other steroids carotenoids, saponins and limonoids. There are two metabolic pathways for the formation of isopentenyl diphosphate and dimethylallyl pyrophosphate, namely 'Mevalonate pathway and Non-mevalonate pathway. Mostly mevalonate pathway takes place in plants and non-mevalonate pathway in plant chloroplast, algae, cyanobacteria, eubacteria, and pathogens

like *Mycobacterium tuberculosis* and malarial parasites [14,15].

### Basic Metabolic Mevalonate Pathway and its Significance

The mevalonate pathway is functionally key central metabolic pathway in case of advanced eukaryotic and prokaryotic cells (Figures 1 & 2). Isoprene is the product of cleavage of dimethylallyl pyrophosphate (DMAPP) under the influence of enzyme isoprene synthase. (Dimethylallyl pyrophosphate and isopentenyl diphosphate are metabolic products of Methyl-erythritol-4-phosphate pathway, (MEP Pathway). Basically, the methyl-erythritol 4-phosphate (MEP) pathway initiates by the condensation of pyruvate and D-glyceraldehyde-3-phosphate to 1-deoxy-D-xylulose-5-phosphate. The two key isomers dimethylallyl pyrophosphate and isopentenyl diphosphate are the result of series of enzymatic interactions; it initiates with the change of 1-deoxy-D-xylose-5-phosphate into 2C-methyl-D-erythritol-4-phosphate. The enzymes involved in methyl-erythritol-4-phosphate pathway are of significance during the targeting of drugs to pathogens like malarial parasite and tuberculosis as this path way is of common occurrence in the organisms. The molecule of isopentenyl diphosphate (IPP) structurally contains five carbon atoms and is a common precursor for all natural isoprenoids in classical mevalonate pathway. Isopentenyl pyrophosphate and dimethylallyl pyrophosphate (DMAPP) are the structural components of isoprenoids, also called terpenoids, in a biological system. These also participate in the structural aspects of cholesterol and other steroids carotenoids, saponins and limonoids. There are the two metabolic pathways responsible for the formation of isopentenyl diphosphate and dimethylallyl pyrophosphate, namely 'Mevalonate pathway and Non-mevalonate pathway. When isopentenyl pyrophosphate and dimethylallyl pyrophosphate undergo condensation it synthesizes isoprenoids in a given biosystem. The isoprenoids thus formed, further participate in the formation of cyclic terpenoids, protein prenylation and protein anchoring. Feedback system involving low-density lipoprotein receptors and the enzymes regulate this complete complex process. The mevalonate pathway is helpful in biomedically investigations related to the selected types of cancer and cardiac disorders; it also facilitates the therapeutic drug target regulating process. Mostly mevalonate pathway occurs in plants and non-mevalonate pathway in plant chloroplast, algae, cyanobacteria, eubacteria, and pathogens like *Mycobacterium tuberculosis* and malarial parasites [16-18].



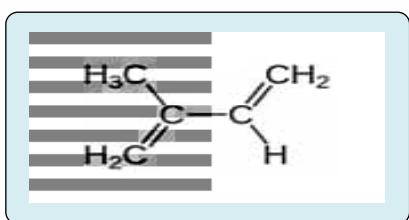
The mevalonate pathway (MAV pathway) and methyl-erythritol-pathway (MEV pathway) exhibit orthogonal nature in a biosystem, thus, each of these do not result in any derogative side effects and act as molecular links between different molecules; the molecules formed are precisely regulated because of the 'well defined interfaces'. As a result there is no side negative interaction in a biosystem [19].

Investigations relating mevalonate pathway and methyl-erythritol-pathway both can help to target organisms that cause malarial, sexually transmitted diseases, tuberculosis, peptic ulcer, and food safety threats. The 'fosmidomycin' compound is effective in the preventive treatment of malaria caused due to *Plasmodium falciparum*. The inhibitors of methyl-erythritol-pathway are the probable guide line for

the development of effective pharmaceuticals [19]. The intermediates of methyl-erythritol-pathway activate gamma delta T-cells; those T-cells that have gamma delta T-cell receptors (one gamma chain and other delta chain) [19,20].

### Physicochemical Properties of Isoprene (Computed Properties)

The molecular formula and structure formula are as follow:



**[Molecular formula:  $C_5H_8$  ( $CH_2=C(CH_3)CH=CH_2$ ) Structure formula**

Mol. Weight: 68.12 g/mol; Hydrogen bond acceptor count: 0; Rotatable bond count: 1; Exact mass: 68.062600255 g/mol; Monoisotopic mass: 68.062600255 g/mol; Topological polar surface area:  $0\text{\AA}^2$ ; Heavy Atom count: 5; Formal charge: 0; Complexity: 51.1; Isotope atom count: 0; Defined Atom Stereocenter count: 0; Undefined atom Stereocenter count: 0; Defined Bind Stereocenter count: 0; Undefined bond Stereocenter count: 0; Covalently-bonded unit count: 1; Compound is canonicalized: yes;

Common physicochemical properties of isoprene; It is colorless liquid with mild aromatic odor; it can be seen as solid or very volatile colorless liquid with characteristic odor; It is hazardous substance with petrol like odor with boiling point  $34.067^\circ\text{C}$  and melting point  $-145.95^\circ\text{C}$ . It is practically insoluble in water (642 mg/L at  $25^\circ\text{C}$ ). It is miscible in organic solvents like ethanol, ethyl ether, acetone and benzene. Its density is 0.679 g/cu cm at  $20^\circ\text{C}$ ; relative density (water=1): 0.7; vapour density 2.35 (air=1); vapour pressure: 550.0 mmHg. It is stable under recommended conditions: common stabilizers are 4-tert-butylpyrocatechol. On heating it decomposes and emits acrid smoke and fumes. Its viscosity is  $0.3\text{mm}^2/\text{s}$  at  $20\text{-}25^\circ\text{C}$ . It has refractive index is 1.42160 at  $20^\circ\text{C}$ .

### Basic Behavior of Isoprene

The isoprene is among the important non-methane organic compounds primarily affecting atmospheric oxygen, ozone, and organic aerosols. Mostly, isoprene is evaluated using satellite based technique and an indirect approach. The indirect approach involves its oxidation compound formaldehyde formation. The source of non-isoprene,

use formaldehyde formed as a result of the oxidation; the relationship of spatial fluctuation in the molecule of isoprene affects this process. To counter act the 'Direct global isoprene' evaluation mode is preferred; this process gives relatively more clear idea about the source, sink and the impacts due to atmospheric parameters. The completely physics retrieval technique the satellite-borne Cross-link Infrared Sounder appears to be very suitable to detect the spectral signature of isoprene in space, and depending on the observations a specific recovering algorithms should be developed using statistical and/or machine learning process such as the Royal Netherlands Meteorological Institute called The Dutch-OMI-NO2algorithm Satellite Aerosol Retrieval algorithm. In biology, system thinking is recent concept and is having contrasting views. This phenomena can be visualized by thinking 'backward' and 'forward' in between two specific biological entities and processes; the system should represent theoretical characteristics of the two [21-23].

### Isoprenene and Isoprenoids

There are two carbon-carbon double bonds in a molecule of isoprene having molecular formula:  $C_5H_8$  ( $CH_2=C(CH_3)CH=CH_2$ ). It is hemiterpene and volatile organic compound. It is a monomer present in natural rubber and acts as structural motif for isoprenoids. Metabolically, it plays significant functional role in plants. Isoprenoids have two to thousands of isoprene units in their molecules. There are one or more functional groups like hydroxyl and carbonyl in the carbon back bone of the isoprenoids. Isoprenoids exist in diversified forms [24]. Isoprenoids are a class of natural products with applications in many fields, including medicine and agriculture. Biosynthesis of isoprenoids has emerged as the most commercially viable option for their mass production. The isoprenoids are the products of an enzymatic pathway uses isoprenol as its substrate instead of a glucose-derived catabolite, making it radically different from naturally occurring pathways or their engineered variants. The pathway is only two steps long and uses a single cofactor, ATP. Isoprenoids decouple from central carbon metabolism and can sustain a very high flux. These advantages make it a noteworthy alternative to known isoprenoid pathways [24].

Isopentenol utilization pathway is an effective mode of natural and biological production of isoprenoid in large scale and its biological synthesis is apparently and inextricably associated with glucose metabolism. The complex regulation, duration of this process, and need of many cofactors are the parameters that limit this metabolic pathway. The 'isopentenol utilization pathway' produces isopentenyl diphosphate or dimethylallyl diphosphate. The isopentenol

isomers isoprenol or prenol after sequential phosphorylation form isopentenyl diphosphate or dimethylallyl diphosphate. Thus isopentenol utilization pathway is useful to form many isoprenoids under controlled flux of this pathway [25].

### Biological Influence of Isoprene

Trees that combat unfavorable fluctuations in environmental parameters experience the influence of isoprene. These environmental parameters like high winds, tornadoes, extreme temperature (cold and hot, around 40°C range), drought (a complex impact), flood, wild fires, [abiotic stress parameters], and deficiency of nutrition induce isoprene pathway in these trees. Even the moderate degree of abiotic stress induces the mechanism of isoprene. Edaphic factors like pH range, high radiation, compaction, contamination, rapid rehydration and germination period also induces isoprene phenomenon [7,9,26]. Isoprene helps to combat such wide fluctuations in trees with large leaves. Isoprene also facilitates the stability of cell membrane during heat stress. The proportion of release of isoprene relates with mass, temperature and area of leaf and particular 'photosynthetic photon flux density' (PPFD). Nocturnal foliage (leaves) release of isoprene is very less while diurnal release during sunny day is up to 25µg/gram dry leaf weight/hour in most of the species of oak. Isoprene resists reactive oxygen species [27]. Isoprene synthesis protects transgenic tobacco plants from oxidative stress [28]. Miller, et al. described the active role of isoprene during homeostatic signalling process when a plant is under rough salinity stresses [29].

### Isoprene in other Individuals

Humans produce about 17mg/day [8,30]. Among humans isoprene is exhaled as a main hydrocarbon in the breath of humans and it ranges between 15 and 70 nmol/litter and 37nmol/litre as its mean value. Its presence is also reported among vertebrates like rat, dog, ewe and cow. Its value in the blood of other animals is mostly lower than 1nmol/L [31,32]. Some species of Actinomycetota or Actinobacteria use isoprene as fuel source for their energy requirements [26].

### Basic Mode of Isoprene Regulation

The mechanism of regulation of isoprene is basically relates to the substrate - DIMETHYL-ALLYL PYROPHOSPHATE (DMAPP) and the enzyme called isoprene synthase. Parameters like CO<sub>2</sub>, O<sub>2</sub>, and light (photoperiod) influence the regulation of isoprene. The effect of parameter temperature depends on substrate and enzyme concentration in the biosystem.

### Pathophysiological Aspects of Isoprene in Relation to Humans and Animals

The exhaled human breath consists of volatile inorganic organic compounds; most gaseous constituents are nitrogen (78.04%), oxygen (16%), carbon-di-oxide (4-5%), inert gases (0.9%) and water vapours; in addition to these gases other gaseous components are nitric oxide (10-50ppb), nitrous oxide (1-2ppb), ammonia (0.5-2 ppm), carbon monoxide (0-6ppm), hydrogen sulfide (0-1.3 ppm). The organic volatile compounds are also present in the exhaled human breath, namely, acetone (0.3-1ppm), ethanol and isoprene (~105ppb), ethane (0-10ppb), methane (2-10ppm), pentene (0.10ppb) [33,34]. The presence of volatile organic components in human exhaled air indicates that these are the products of metabolic activities occurring within human body or might have been entered from the ambient environment. The endogenous organic volatile compounds present in human breath are the biomarkers for the pathophysiological conditions and are of clinical and biomedical significance, specifically during non-invasive estimations. The concentration of isoprene varies with respect to age and gender; its concentration is very low in children in comparison to the adults. The amount of isoprene elevates at puberty and reports suggest higher concentration of isoprene in male as compared to female (adult) [34-36]. Endogenous breath isoprene in human is a metabolic outcome of biochemical pathway but its existence in human breath quite elusive but at the same time it appears to be of clinical significance. Isoprene in breath is one of the abundant endogenous volatile organic compounds and its presence reflects on many clinical health conditions and may act as non-invasive biomarker [13].

The monitoring of breath isoprene is a non-invasive potential biomarker for efficacy of low-lipid therapy, pharmacological procedures, dietary guide-lines and life style in an individual. The cancer screening is another application of investigating human breath isoprene [37]. The amount of isoprene in the breath of lung cancer patients relates with the degree of immune activation and lipid metabolism. The concentration values of isoprene in the breath samples of lung cancer patients on comparison with the values of concentration of immune activation marker neopterin, lipid parameters (routine enzymology) and C-reactive protein (CRP) and isoprene value are of medium range. There exists a correlation between isoprene concentration and total cholesterol and LDL cholesterol but no significant correlation with HDL cholesterol, triglycerides and C-reactive protein (CRP). An inverse correlation between the concentrations of isoprene and neopterin has been observed. The neopterin concentration also relates with total cholesterol, HDL and LDL cholesterol and C-reactive protein (CRP) but not with triglycerides. Thus, isoprene amount is in coordination



with the degree of immune activation and changes in lipid metabolism [13,38].

The isoprene investigations relate with cholesterol levels or rate of synthesis of cholesterol. The rate of production of isoprene dependent on age, diet, exercise, sex, and related investigations provide feasible estimation. There is a correlation between heart rate and exercise; isoprene concentration elevates during initial state of rapid exercise and attains normal steady state as the breath rate and exercise stabilizes. In man, heart rate varies in standing, reclining and sleep positions and so is the rate of breath isoprene. A drug atorvastatin treatment reduces the levels of cholesterol and low density lipoproteins and also the level of isoprene. This aspect reflects on the breath isoprene as a non-invasive biomarker for cholestrogenesis under careful supervision [39].

Whenever there is an increase in the vascular resistance the chances of chronic heart failure also elevate. This elevated vascular resistance also exerted load on left ventricle that lead to progression of myocardial failure, multiple organ failure and death in human. Increased oxidative stress is another parameter playing role in heart failure and affecting peripheral vascular endothelium [40]. The parameters like elevated sympathetic action, release of catecholamines and activation of renin-angiotensin system, vasopressin, endothelium-1 and neuropeptide-Y for the functional aspect of neurogenic and humoral processes influence derogative cardiac issues. These also result in conditions like vasoconstriction, accumulation of fluid and remodelling left ventricle. Physiological conditions in which the antioxidants declines and plasma lipid peroxide levels elevate that lead to heart failure. The free radicals damage the polyunsaturated fatty acids and disturb the free fatty acids. Isoprene is one of the final products of lipid hydroperoxide interaction and is present in the exhaled air (breath) [33,41]. The isoprene level is quite low in the case of patients with heart failure as compared to the control individuals [0.66 nmol l<sup>-1</sup> and 1.12 nmol l<sup>-1</sup> respectively]. The rate for formation of isoprene is also declines significantly [83.3 (23.2) vs. 168 (19.8) pmol min<sup>-1</sup> kg<sup>-1</sup> respectively] [33,40-42]. The isoprene is also identified as n-pentane in case of humans; possibly isoprene and n-pentane separate during investigation using mass spectrometry. One more reason is that the peak obtained for n-pentane responses like isoprene or as a mixture of n-pentane and isoprene during the estimation using gas chromatographic technique [41].

### Isoprene and Cancer

Isoprene, 1, 3-Butadiene and chloroprene come under carcinogenic compounds [43]. Isoprene is a member of group 2B, this group of compound includes probable

carcinogens. The available reports are based on the multiple carcinogenic effects on rats and mice of isoprene. Mostly the reports available are the combined impacts of isoprene 1, 3-butadiene and chloroprene. There is a need to explore deeper into the carcinogenicity of this organic volatile compound. Possibly, the isoprene (endogenous) targets T-cell that have gamma delta T-cell receptors (One gamma chain and other delta chain) and influence the derogative impact [20,21]. Although 1,3-butadiene and isoprene are chemically similar, isoprene is the 2-methyl analog of 1, 3-butadiene and both exhibit different levels of toxicities. Mostly, the level of toxicity of isoprene is very less. In a study in which a comparative relative toxicity and inflammatory gene expression due to 1,3-butadiene and isoprene are evaluated in the presence of nitric oxide involving gas chromatography and mass spectrometry techniques and A549-cell. [A549 cells are the adenocarcinogenic human alveolar basal squamous epithelial cells; these act as a cell line for testing the carcinogenicity of a compound for lung cancer]. 1, 3-butadiene forms acrolein, acetaldehyde, and formaldehyde as photochemical degradation products while isoprene are methacrolein, methyl vinyl ketone, and formaldehyde with range <200ppb of ozone. The levels of cytotoxicity and gene expression for interleukin (IL-8) act as biomarkers for inflammation with the air control. The products formed during photochemical interaction elevate the levels of cytotoxicity and aggravate the expression of gene expression for interleukin (IL-8) resulting in increased inflammation. These observations reflect on the higher ability of these products of photochemical degradation to affect the health in general; these also behave as proinflammatory agents along with 1,3-butadiene and isoprene [44]. There is a dire need of more investigatory studies based on isoprene in the direction of its probable carcinogenic tendency. This is more so in case of the individuals engaged in rubber industry as assumingly they are exposed to isoprene formed as a result of disintegration of butadiene and styrene. The breath analysis appears to most suitable noninvasive mode of investigations related to isoprene. The mode of elevation of isoprene level is ambiguous and its endogenic and metabolic origin appears to be obscure in exhaled breath. It is possible that isoprene may be produced during biosynthesis of cholesterol [45]. It is understandable that glucose has potential to influence the level of isoprene because of the carbohydrate response element-binding proteins [46]. The pulmonary isoprene increases during hypoglycemia, tachycardia and elevated flow of blood and in all probabilities there is either no or least fluctuation in the contents of individual volatile organic compounds or there may be presence of clusters of volatile organic compounds. This may not be so in case of hypoglycemic condition [47]. This observation reflects on the suitability of determination of isoprene or volatile organic compounds as noninvasive mode of investigations related to fluctuation in blood glucose in diabetic individuals

and hypoglycemia [48].

Patients suffering from cystic fibrosis exhibit the mixed symptoms reflecting chronic systemic oxidative stress and free radical formation in their lungs. These systemic symptoms are the result of hyperimmune response, defective ability to scavenge the free radicals, malabsorption and elevated rate of consumption show presence of isoprene in their breath. The high concentration of parameters, like malondialdehyde (MDA), erythrocyte membrane polyunsaturated fatty acids, protein sulphhydryls and protein carbonyl indicate oxidative stress. After antibiotic treatment, the rate of isoprene formation declines significantly as compared to the control samples [13,40]. Based on the single end-expiratory breath samples, the analysis of isoprene in the case of patients with acute myocardial infarction and stable angina and the corresponding control group (age, sex, smoking habits, hypertension, and serum cholesterol level matched) had higher isoprene level in the acute myocardial infarction as compared to those with stable angina. The mechanism of rise in the level isoprene is ambiguous [13,49].

Breath isoprene investigation is helpful to monitor blood cholesterol levels and rate of synthesis of cholesterol. The isoprene level changes with respect to age, state of exercise, position, and diet. On-line determination of breath isoprene detection is done using proton transfer reaction-mass spectrometry technique. The values of breath isoprene elevate as the heart rate increases after exercise and attains stability as the breath rate stabilizes. Atorvastatin treatment lowers the levels of serum cholesterol and low density lipoprotein and the level of isoprene also declines correspondingly. There are indications regarding the endogenous production of isoprene during the day and night, it shows that isoprene can be a possible biomarker for the cholestrogenesis and heart rate [13,50].

Volatile organic compounds like isoprene, acetone, pentane, present in human breath are possible a non-invasive investigative biomarkers that reflect on the metabolic and pathophysiological state of an individual. Such studies are favorable to keep a check on the physiological state during heart surgery with extracorporeal circulation. The study of breath biomarker profiles illustrate the physiological conditions like oxidative and metabolic stress in an individual and helps to avoid poor outcome and probable organ damage during the surgical processes. The concentrations of such volatile organic compounds attain normal state post-surgery about two hours. The exhaled breath isoprene elevated after sternotomy and extracorporeal circulation. (Extracorporeal circulation is used during cardiac surgery in which blood circulation and respiration gets replaced and temperature also gets regulated).

Isoprene level attains normal or previous concentration after half an hour of the process. The isoprene concentration shows correlation with cardiac output [13,51].

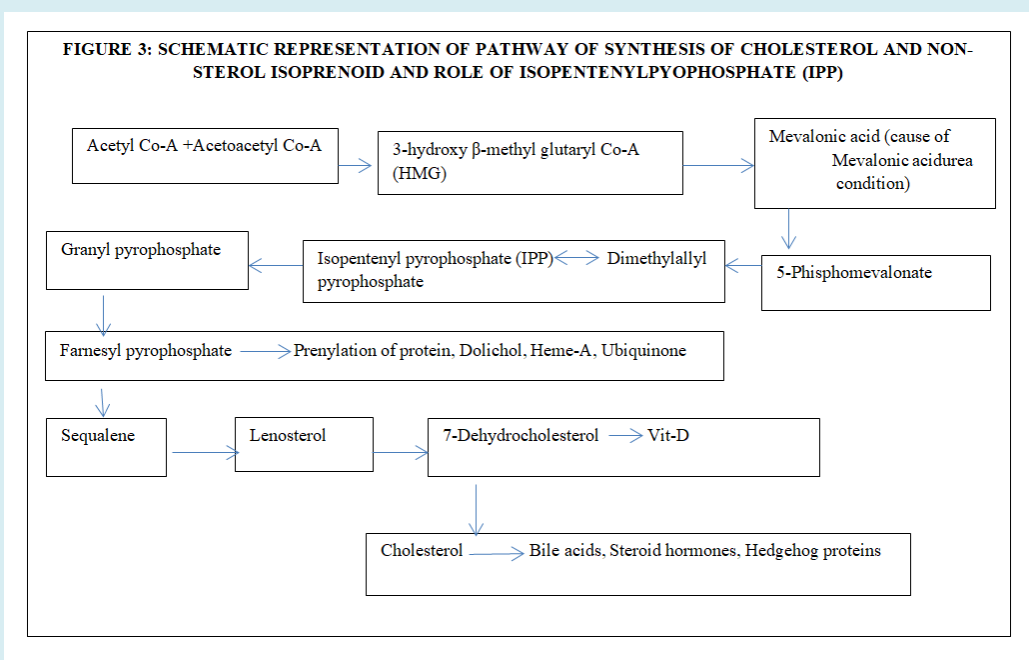
The breath hydrocarbons are the potential non-invasive biomarkers for metabolic status in an individual. There are ample evidences of production of endogenous isoprene during extrahepatic metabolism. This is evident during investigations related to muscular exercise and in patients with Duchenne muscle dystrophy and concentration of isoprene varied from 0.09 to 0.72nmol/l in peripheral blood (venous blood). But direct physiological mechanism appears to be obscure [52].

The mevalonate kinase enzyme along with other enzymes play significant role in the cholesterol metabolism and in biosynthesis of non-sterol isoprene and its deficiency causes mevalonic aciduria, an inheritance deficiency. This metabolic mechanism affects functioning of skeletal and other organs. The ubiquinone, a coenzyme Q-10, causes abnormalities in mitochondrial energy metabolism. There are many manifestations like failure to thrive, microcephaly, dysmorphic features, and neurological deficiencies like cerebellar atrophy, ataxia, and progressive myopathy in the suffering individuals.

Individuals experience febrile episode, a condition in which seizure related with a high temperature without having any serious health issues, exhibit elevated levels of erythrocyte sedimentation rate, count of blood leukocyte, serum C-reactive protein levels, IgD and IgA-1 and urinary leukotriene excretion [13,53]. Dolichols behave as carriers during the formation of carbohydrate chains involved in glycoproteins, ubiquinone (coenzyme Q-10) that helps in the electron transport, isopentenylated transfer RNA (needed for protein synthesis) and prenylated proteins. The prenylated proteins bring about the transduction of intracellular signals. The process of isoprenylation of proteins plays major role during the functioning of proteins of cell that regulate the cellular growth and cell cycle [13,53]. [Isoprenylation, also known prenylation and lipidation, is a process in which hydrophobic molecules are linked to either protein or suitable biomolecule that bring about the attachment with cell member; the prenyl groups (3-methylbut-2-en-1-y) help the process of attachment with cell membrane, [54]. The cholesterol metabolism involves mevalonate and mevalonic acid (Figure 3). Mevalonic acid is a product of interaction between acetyl Co-A and Acetoacetyl Co-A, involving 3-hydroxy  $\beta$ -methyl glutaryl Co-A. Mevalonic acid metabolizes into isopentenyl pyrophosphate (IPP), it isomerates as dimethylallyl pyrophosphate (DMAPP). Isopentenyl pyrophosphate interacts with t-RNA and forms isopentenyl t-RNA. Isopentenyl pyrophosphate

ultimately metabolizes into 7-dehydrocholesterol and finally cholesterol is formed. The 7-dehydrocholesterol also helps in the formation of Vit-D and the final product cholesterol

play significant role in the synthesis of bile acids, steroid hormones and Hedgehog proteins (Figure 3) [13,53].



**Figure 3:** Schematic Representation of Pathway of Synthesis of Cholesterol and Non- Sterol Isoprenoid and Role of Isopentenylpyrophosphate (Ipp).

### Isoprene and Environment

The space around our earth constitutes environment on biosphere and is very essential functional component of biotic and abiotic systems. The physicochemical features of this environment along with its components and the effects of solar radiations are the resultant product of interactions of biotic and abiotic components. The emission of isoprene and 1-3-butadiene varies from place to place, day and night durations, anthropogenic and biogenic conditions, temperature, season, and during heat wave. Generally, Cobb-Douglass production function is used for the isoprene estimation; (this is a widely adopted to show the technical relationship between two or more inputs) [55].

There are urban stressors that induce long term effects on vegetation and biomass [56]. Although, isoprene in very less concentration has a potential to affect the air quality of the specific region and is a topic of research interest and for national and international regulatory environmental agencies.

The parameters like ambient concentration of  $\text{CO}_2$  and duration of light available for photosynthesis, influence the emission of isoprene. Plants which have not been watered for

four days and with 98% declined photosynthesis and 94% reduced leaf conduction exhibit normal level of isoprene emission. Plants having saturated  $\text{CO}_2$  concentration show significant level of isoprene emission. It is evident that isoprene is one of the usual plant metabolites and may not be considered as a response to restricted  $\text{CO}_2$  in the ambient atmosphere. The emission of isoprene is primarily due to plants in the tropospheric region [57]. The parameters like photosynthesis, leaf-gas exchange, and physiological aspects like chloroplast-P, exchange, stomatal conductance, and photorespiration may not influence the isoprene emission drastically but in all probabilities the chloroplast metabolism plays a significant role in the emission of isoprene. The enzyme isoprene synthase (a chloroplastic enzyme) is concerned with the conversion of dimethylallyl diphosphate (DMADP) and results in the formation of isoprene. The balance between inorganic phosphate and adenylate within chloroplast and the temperature affect the effectiveness of isoprene synthase enzyme. The status of photosynthetic electron transport system, stomatal diffusive flux rate, surface of leaf and stomatal conductance are the probable parameters that affect isoprene emission. The intracellular concentration of isoprene due to the closing and opening of stomata and rate of photosynthesis do not affect emission of isoprene [58].



Isoprene exhibits higher reactive capacity in addition to its ability to form ozone; these features of isoprene plays an effective functional role in the formation of ozone. Isoprene emission maximises at noon/midday specifically during summer days with high temperature and solar radiations; the suitable photochemical conditions and higher concentration of OH (hydroxyl radicals) also favour interaction between isoprene and ozone. During maximum rush hours of traffic during morning and evening and low concentration of OH and very weak solar radiation can also induce this interaction [59]. The biogenic volatile organic compounds, specifically isoprene boost the concentration of ozone in urban atmosphere. As the vehicular emission reduces anthropogenic isoprene and other volatile organic compounds also decline, then the biogenic emission appears to be prominently active. There is a difference in the annual concentration of isoprene and average diurnal concentration of isoprene that facilitates the interaction between isoprene and OH in summer and winter seasons. This indicates the role of isoprene emission that participates in atmospheric chemistry [59,60].

### Corelation between Anthropogenic Activitis and Formation of Isoprene and Related Compounds

The poor quality of air, higher particulate pollution resulting in respiratory illness, cardiovascular and cancerous ailments are of common experience in developing countries [61,62]. Forest regions like tropical rainforest and South-eastern forest of US exhibit organic carbon and these are derived from isoprene dependent secondary organic aerosol. In urban regions, organic aerosol is the product of anthropogenic pollution and isoprene derived secondary aerosol depend on the local production of isoprene and higher levels of anthropogenic pollutants. Pollutants like nitrogen oxides and particulate matter induce the formation of isoprene derived secondary aerosol. This takes place when there are high and low conditions favouring oxidation of nitric oxide (NO) these in turn lead to the formation of isoprene derived oxidation products and particulate organosulfates (OSs) and nitooxy-organosulfates [63]. The rate of formation of organosulfates relates to photochemistry as well as sulphate availability in the atmosphere. Further, there is a correlation between these reactants and with products of ozone and particulate sulphate present in a given atmosphere; it varies from place to place as per the industrial area. This reflects on the significant role of anthropogenic emission and products of the organosulfates due to heterogeneous interaction [63].

The organic aerosols are very effective atmospheric components that play significant role in air quality, human health and climate. Mostly secondary organic aerosols are

the products of oxidation of volatile organic compounds; these are released by the organisms (biogenic) and as a result of anthropogenic activities. Generally, biogenic volatile organic compounds like isoprene ( $C_5H_8$ ) and monoterpenes ( $C_{10}H_{16}$ ) act as precursors for the formation of secondary organic aerosol. The large amounts of such biogenic volatile organic compounds in atmosphere and their higher rate of reaction with oxidants present in atmosphere play important role in such interactions. The role of anthropogenic pollutants in the formation of secondary organic aerosols needs thorough investigation as participating components vary for region to region. When  $SO_2$  and oxides of nitrogen emission decline in an atmosphere then biogenic pathways like photo-oxidation and ozonolysis take up the formation of atmospheric isoprene derived secondary organic aerosol. These pathways may show low yield of secondary organic aerosol. Thus, the declined emission of  $SO_2$  and oxides of nitrogen impacts climate and health of the individuals of the region. These formed products have potential to cause elevation of hygroscopicity and decline level of sustainability in the organisms present in the vicinity. These effects need more confirmation and more study is expected [64-66].

The biogenic and anthropogenic volatile organic compounds play prime role in the existence of secondary organic aerosols in a given atmosphere and the process of photooxidation is significant status in the atmosphere of such zones. The overall mechanism of this complex process i.e., formation of secondary organic aerosol from volatile organic compounds is quite ambiguous. This lack of understanding of the mechanism hampers the evaluation the budget of global secondary organic aerosol, its source and impacts on climate. There may be other models of suppression of secondary organic aerosol formation involving photooxidation of aromatic compounds having anthropogenic origin like toluene and p-xylene in the presence of oxides of nitrogen. The related interactions occur in the absence of isoprene and propene resulting in a condition in which secondary organic aerosol are less and there is a mixture of volatile organic compounds; this specific condition exhibits hydroxyl ion (OH) scavenging impact causing reduced consumption of parent aromatic compounds. Further, there are changes in the oxidation of secondary organic aerosol and oxidative pathway like formation of many carbonyl products and addition of isoprene. This complex process renders altered composition of secondary organic aerosol in comparison to single parent hydrocarbon. This reflects on the presence of complex interactions during the degradation process of alkenes and aromatic compounds. These observations are based on the gas phase chemical technique. There is possibility that hydroxyl ion scavenging impact plays a significant role in the atmospheric chemistry in a given region. Other aspect indicates that the global anthropogenic secondary aerosol budget with its diversified influences

induces biogenic isoprene emission, more so in urban regions even if these have plentiful vegetation coverage [67].

The isoprene is non-methane compound emitted into atmosphere; it relates with ozone, formation of aerosol, atmospheric oxidation and influences the nitrogen cycle globally. The emission of isoprene is not fixed and it fluctuates. The interaction between hydroxyl ions (OH) and isoprene help to maintain a sort of balance of isoprene in an atmosphere in a given region. Thus, the hydroxyl ions act as a sink for isoprene. The most common modes of investigating isoprene are 'Cross-track Infrared Sounder technique' and measuring the oxidation product of isoprene and formaldehyde and provide information about the emission of isoprene and atmospheric oxidation. Thus, this mode of investigation depends on the chemical interactions between isoprene and hydroxyl ions. The condition in which the concentration of nitrogen oxides is low the involvement of hydroxyl ion becomes obscure and may provide erroneous observations. This makes the estimation of isoprene relatively better choice to understand the chemical aspects of atmosphere at a given region [68]. The atmospheric isoprene, benzene and toluene exhibit seasonal and intraday variations in a given zone depending on the anthropogenic and biogenic status of the location. Generally, isoprene levels are higher in the zones of vegetation while benzene and toluene are higher levels at traffic sites (anthropogenic sites). These observations are based on the 'Gas-Chromatography Mass Spectroscopy'. The seasonal changes are also possible; isoprene is at peak during summer declines in post-monsoon and winters respectively, at least in subtropical locations. The level of isoprene is highest during afternoon (intraday changes in level of isoprene). Quite often no substantial changes in the level of isoprene at traffic sites. This reflects on the possible combined impacts between isoprene, benzene and toluene. In subtropical locations like Delhi, India, anthropogenic and biogenic percentages are ranging between 60% to 70% at traffic sites and these values decline below 10% in zone of vegetation. In the vegetation zone isoprene participate more in the formation of ozone as compared to benzene and toluene. There is a need for more investigations relating role of isoprene in the formation of ozone as the anthropogenic activities enhance [69].

The atmosphere of Hong-Kong consists of aerosol like secondary aerosol tracers of isoprene, monoterpenes,  $\beta$ -caryophyllene (a natural bicyclic sesquiterpene, a component of many essential oils like clove oil, cannabis, rosemary) and naphthalene; these observations are based on gas chromatography-mass-spectrometric technique. There are some factors that contribute to the atmospheric ambient organic carbon; these factors include secondary organic aerosols, secondary sulfate, burning of biomass, sea salt, marine and vehicular emission. These factors are

evaluated using 'positive matrix factorization technique'. The secondary organic carbon formation includes organic carbon resulting from secondary organic aerosol and secondary sulfate and aging of biomass-burning; these all participate in organic carbon formation. The secondary organic aerosol is also formed from the precursors like monoterpene that participate in photooxidation in atmosphere. The aerosol-phase ring-opening involving isoprene epoxydiols pathway results in this process. The oxides of nitrogen also play significant role in this process. Overall, these interactions continue in the formation of secondary organic aerosol during day and night. The secondary organic carbon, secondary sulfate and related secondary organic carbon along with acidic particles correlate with secondary organic carbon which results from biomass burning [70].

### Volatile Organic Compounds, Isoprene and Nanomaterials

Volatile organic compounds are known for their toxic and carcinogenic nature specifically trichloroethylene and vinyl chloride. The volatile organic compounds are present out-door and indoor air and these play significant role in the formation of atmospheric particulate matter of different sizes; these directly or indirectly derogate the air quality. Nanomaterials play very effective role in mitigating the environmental volatile organic compounds and secondary organic aerosols. The efficacy of these nanomaterials relates with their physicochemical features like porosity, size, electrostatic interaction, surface functionality and chemical composition and the techniques like adsorption, photocatalysis, and catalysis. The biogenic and anthropogenic volatile organic compounds and secondary organic aerosol show coexistence and also complicated interactions specifically, photooxidation. There have been investigations to mitigate volatile organic acids using nanomaterials like carbon nanomaterial, metallic and metal oxide nanomaterials, polymer nanocomposites. One of the most common processes is adsorption of volatile organic compounds from aquatic and areal media. Some of the catalysts in nanoforms using nanometals are in use to mitigate the volatile organic compounds (Table 1). The mixtures of the catalyst used are the products of various methods such as reduction, impregnation, flame spray pyrolysis, deposition or precipitation [71-78].

Suitably functionalized nanomaterials are one of the preferred agents for mitigation or removal of volatile organic compounds. Mesoporous organosilica nanomaterials (size approximately 400nm diameter, surface area 977m<sup>2</sup>/g, pore volume 0.92 cm<sup>3</sup>/g) act as an agents to mitigate hexanal and butyric acid vapours up to 99% of volatile organic compounds present in the given test samples [79].

Sr.NO.	CATALYSTS WITH NANOMETAL	CONCENTRATION	VOLATILE ORGANIC COMPOUND	REFERENCE
		(ppm)		
1	Pt/SiO <sub>2</sub>	1000	TOLUENE	73
2	Pt/TiO <sub>2</sub>	22	FORMALDEHYDE	74
3	Pd/TiO <sub>2</sub>	10	FORMALDEHYDE	75
4	Au/TiO <sub>2</sub>	1000	PROPENE	76
5	Ag/TiO <sub>2</sub>	110	FORMALDEHYDE	77
6	Ag/CeO <sub>2</sub> /SiO <sub>2</sub>	18,000 -22,000	FORMALDEHYDE	78
7	Pt/SiO <sub>2</sub>	1000	Benzene	79

**Table 1:** Catalysts Containing Nanomaterials (Amalgamation) for Mitigation of Volatile Organic Compounds [71].

Volatile Organic compounds like benzene, toluene, ethylbenzene and xylene (BTEX) are among the most common industrial solvents and are released as untreated waste after use, hence, result in pollution. Such harmful pollutants can be remediated using adsorption on multiwalled carbon nanotubes functionalized. This technique involves catalytic vapour deposition and oxidation with the help of sodium hypochloride and as a result these nanomaterials become suitable to adsorb such volatile organic solvents from aquatic medium [80]. These functionalized multiwalled carbon nanotubes have affinity for xylene, ethylbenzene, toluene and benzene respectively in decreasing order [80]. The adsorption process involves interactions based on  $\pi$ - $\pi$  electron donor acceptor mechanism that plays a significant role along with carboxylic oxygen atoms of multiwalled carbon nanotubes and the aromatic rings of these volatile organic compounds [81]. Multiwalled carbon nanotubes are preferred agents to remove chlorobenzenes and other volatile organic compounds using solid-phase extraction as sorbents or C18 silica [82]. Organic-inorganic hydrophobic mesoporous silica when functionalized involving condensation mode with tetraethoxysilane and vinyltriethoxysilane in acidic medium acts as an effective adsorptive agent for p-xylene (85.2%) in comparison to pure silica (56.2%) [83,84]. The high-performance graphene based elastomer composites are other options to scan human breath for isoprene and related compounds. In such composites the interfacial interaction is a significant parameter that empowers their efficacy. The graphene/poly (styrene-b-isoprene-b-styrene) composite is one such example and it is the product of evaporation-induced self-assembly process. These composites should be characterized using techniques such as scanning electron microscopy, UV-vis absorption spectra, tensile testing, Shore-A hardness (one of the scales to establish the level of resistance to deformation or indentation), surface resistance, thermal conductivity and thermogravimetric analysis. These techniques establish their microstructure and other

functional properties. There is involvement of interfacial interactions of  $\pi$ - $\pi$  stacking with phenyl groups of graphene/poly (styrene-b-isoprene-b-styrene) and graphene; these interactions regulate the degree of functionality. The polymer composites that incorporate nanofillers like fullerene, carbon nanotubes, nanodiamonds, and silicates in layer form are some of the most preferred composites for the researchers [85].

Isoprene detector using nanomaterials are very suitable for detecting around 149 test breath samples. In these devices a chemoresistive, formulations using nanomaterials enhance their efficacy to detect ppb concentrations of the gaseous analytes; mass spectrometry technique is suitable to validate these values. These devices are able to investigate breath isoprene dynamics even during physical exercise and at resting conditions [86]. Detection of isoprene in breath sample has become a noninvasive mode of monitoring the breath in normal and pathophysiological conditions. Since the analytes are in very small quantity (60-1250 ppb) there is a need for very sensitive and portable corresponding monitoring device. Nanomaterials have become handy in such cases. The nanomaterials based devices consist of a sorption filter incorporating activated alumina; it eliminates hydrophilic volatiles before the test sample approaches micro-gas-sensor. This micro-gas-sensor has chemoresistive silica-doped tungsten trioxide (WO<sub>3</sub>) nanoparticles that quantify the analyte i.e., isoprene in test sample up to ppb level. Its efficacy during monitoring the breath samples while an individual is exercising or at rest enhances involving breath isoprene dynamics in linear correlation to proton transfer reaction mass spectrometry dimensions; (in these conditions Pearson's coefficient is to be taken as 0.89) (Table 2). Thus, this isoprene monitor is suitable for online investigation of physical activities. In this device the high and variable concentrations of other volatile components like acetone, ethanol and methanol do not interfere with the estimation of isoprene [86].

Sr, No.	Name of the nanomaterials used in sensor	References
1	Ti-doped ZnO	88
2	TiO <sub>2</sub>	89
3	h-WO <sub>3</sub>	90
4	ZnO quantum dots	91
5	Flowers In <sub>2</sub> O <sub>3</sub> (Indium oxide)	92
6	Au loaded pyramid shaped ZnO	93
7	In <sub>2</sub> O <sub>3</sub> nanoparticles	94

**Table 2:** Applications of Nanomaterials in the Semiconducting Metal Oxide Gas Sensor Having Higher Sensitivity Uptom Parts Per Billions [86].

## Conclusion

The anthropogenic interference is one of the prime causes of environmental disturbances and renders the environment unsuitable. The isoprene is non-methane compound emitted into atmosphere; it relates with ozone, formation of aerosol, atmospheric oxidation and influences the nitrogen cycle globally. The emission of isoprene is not fixed and it fluctuates. The interaction between hydroxyl ions (OH) and isoprene help to maintain a sort of balance of isoprene in an atmosphere in a given region. The space around our earth constitutes environment of the biosphere and is very essential functional component of biotic and abiotic systems. The physicochemical features of this environment along with its components and the effects of solar radiations are the resultant product of the interactions of biotic and abiotic components [87-89]. The emission of isoprene and 1-3-butadiene varies from place to place, day and night duration, anthropogenic and biogenic conditions, temperature, season, and during heat wave. Trees that combat unfavorable fluctuations in environmental parameters experience the influence of isoprene. The endogenously and exogenously formed isoprene should be distinguished in the test samples [90-93]. The electrochemical sensors are suitable potential tools for detection of physiopathological conditions like asthma, diabetes, traces of acetone, ethanol, volatile organic compounds and secondary organic compounds and other breath related physiological ailments. An effort must be made to elevate the sensitivity level of the nanomaterial based breath detector. Such devices should be easy to operate, portable, non-specific and provide reproducible and stable observations and nanomaterials like carbon nanotubes are suitable [94]. These devices should be able to nullify the interference of parameters like humidity and temperature with an ability to integrate with internet or software technology. The endogenous organic volatile compounds present in human breath are the biomarkers for the pathophysiological conditions [95,96] and are of clinical and biomedical significance, specifically during non-invasive estimations. The related investigations will provide better

insight and applications in the biomedical field.

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