Evaluation of the Environmental Impact by FTIR Gas Analysis of Organic Solvents Used in the Pharmaceutical Industry

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This paper presents the impact on the atmospheric environment of organic solvents used in pharmaceutical industry, investigated by FTIR gas analysis. The experimental data emphasized that this technique represents a fast and efficient method of analysis for gaseous emissions from studied solvents (ethanol, methanol, acetic acid). The study of the spectra samples indicates a good capability of the method to detect gases in indoor air from different concentrations and volumes of solvents in mixed solutions up to units of ppm and hundreds of micro liters. The results emphasized a good correlation between the concentrations of the solvents in the gaseous phase from the environment and the concentration of the solvent from the analyzed solutions. Moreover, the study shows the persistence in time of the air pollution in the technological areas of pharmaceutical and chemical industries.

Keywords: organic solvents, FTIR gas analysis, indoor air quality

Preventing, limiting and eliminating atmospheric pollution in order to avoid adverse effects on the human health and the environment is a priority and an accelerating trend throughout the world. This is becoming increasingly important, all the more so since, unlike soil and water, there are no efficient means of air treatment.

The atmospheric air plays an essential role both for the life and health of people, as well as for the existence of fauna and flora. The quality of air has great importance for people since every person inhales approximately 10000 liters of air per day [1]. For these reasons many studies of the indoor and outdoor air quality have been done, where the human health effects are also evaluated [2-5]. The chemical and the pharmaceutical industries through their works are potential sources of air pollution. Solvents such as ethanol, methanol, isopropyl alcohol, formic acid, oxalic acid, acetic acid, acetone, acetonitrile and toluene are sources of pollution even though these industries have specific mean to prevent this, such as facilities and devices for retaining and neutralizing pollutants according to the operating rules. Considering the industrial processes in pharmaceutical manufacturing, during the stages of chemical synthesis, in the air of the working environment there may be present different vapor mixtures simultaneously (vapor mixtures generated by solvent mixtures). A part of these vapors are volatile organic compounds that constitute one of the main sources of pollution of indoors air. Because they can be harmful to human health and to the environment it becomes a necessity to design methods for their precise detection in the environment.

One of the most important trends in the development of methods for detecting this kind of solvents responsible with air pollution is the introduction of different types of sensors and techniques, such as IMS techniques, electronic nose technology, gas chromatography and NIR-based chemical/physical sensors [6-8]. They provide on-line monitoring of volatile impurities during the manufacturing process, thereby significantly reducing analysis time and requiring much smaller sample volumes for analysis [9]. On the other side, the solvent incorporation into the active pharmaceutical ingredients may be considered a form of pollution and can be dangerous for human health [10]. Given these considerations, the present work shows a fast and efficient way to monitor the impact of some solvents from the pharmaceutical industry on the quality of indoor air, using FTIR gas investigation. In addition, a comparative study of the concentrations in the indoor air of some solvents and mixtures of solvents used in the pharmaceutical manufactures, have been realized and presented here.

Experimental part
Materials and methods
For the purpose of quantitative spectral characterization and impact assessment on atmospheric air, the Gasmet DX-Series Fourier Transform Infrared (FTIR) Gas Analyzer and the CALCMET SOFTWARE related software, were used. FTIR gas phase spectroscopy has been used in different aims from human breath monitoring [11] to estimating the postmortem interval of human remains [12]. The physical-chemical characteristics of the analyzed solvents (ethanol, methanol, acetic acid), relevant for our study, are presented in table 1.

Ethanol p.a (puriss absolute ≥ 99.8%), Methanol p.a (puriss absolute ≥ 99.9%) and glacial acetic acid (puriss absolute ≥ 99.0 %) were supplied by Sigma-Aldrich, U.S.A.

The Center for Drug Evaluation and Research (CDER) of the USA Food and Drug Administration (FDA) lists four classes of solvents organized by patient safety and environmental considerations. Class I has the highest toxicity and environmental impact, class II compounds may have significant but reversible toxicity, the solvents from class III have low or no proven human toxicity and class IV solvents have insufficient toxicological data [13]. Considering these categories, the solvents used in this paper belong to class II (methanol) and class III (acetic acid, ethanol). Class II solvents are most commonly organic solvents responsible for VOC emissions that increase the

global greenhouse effect and photochemical Ozone formation at ground level. The solvents coming from class III are generally accepted as green selection and they can be used as environmentally friendly solvents for manufacturing [10,14].

In order to analyze the indoor air quality, we designed an experimental setup (fig.1) that would provide meaningful correlations with the real conditions in the industry. The samples were situated on a plate (mimicking a typical synthesis oven used in the drug industry) inside a glass cylinder (representing the main synthesis chamber of the facility) that covered the sample and the FTIR sensor. The measurements were done consecutively, first the solvents and after that the mixtures, in order specified in tables 2 and 3. Only natural ventilation was used during the experiment. An air sample was recorded, under the glass cylinder, at the beginning and one hour after the samples' measurements. To emphasize the accuracy of this method we used a series of concentrations for the solvents (methanol and ethanol 10, 20, 30, 50% 60 in 100 µL solution, and acetic acid 1%, 2%, 2.5% in 100 µL and 200 µL solution).

Fig.1 Experimental setup

S1-S12 aqueous solutions of ethanol, methanol and acetic acid were prepared by dilution and homogenization in a dry glove box under a nitrogen atmosphere in order to avoid air oxidation or contamination with moisture. To obtain the solutions from table 2, solvents of analytical grade were used, and the dilution in Millipore ultrapure water was performed.

M1-M16 binary and tertiary mixtures were prepared in a dry glove box under a nitrogen atmosphere to avoid air oxidation or contamination with moisture. Binary and tertiary mixtures of the components were prepared by homogenization of equal volumes of the aqueous solutions (S1-S12) according to table 3.

All the experiments were performed at an atmospheric pressure of 1017.1 ± 0.3 hPa.
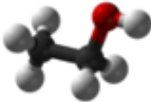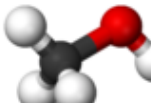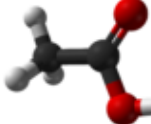
Results and discussions

After the direct measurements with FTIR Gazmet, the samples' spectra were analyzed in the range (4500-500 cm^{-1}) using the KnowItAll® Informatics System 2017 [15]. The first step in the spectral processing was to remove the CO_2 region. After that, a linear baseline correction was made, followed by a smoothing based on the Quad Cubic Savitzky Golay filter (15 points). The last step was represented by the normalization of the graph to one. All the graphs are presented in % transmittance.

The results of FTIR spectra (figs. 2-5 and table 4) were consistent with previous published data [16-19].

We compared spectra of the same combination of solvents in solution but with different concentrations (fig.2). It can be observed that transmittance reduced to half close to 3000 and 1000 cm^{-1} for the mixture of methanol and acid acetic in 100 µL solution (M9, M10) while the concentrations of solvents increased twice (fig. 2a). This behavior comes from the overlap of the methanol spectrum

Table 1
PHYSICOCHEMICAL CHARACTERISTICS OF THE SOLVENTS ANALYZED

Sample	Molecular formula	Molecular Weight g/mol	Structural formula	Vapor pressure hPa (at 20 °C)	Appearance and color	Relative Density at 20°C g·cm^{-3}	Relative polarity
Ethanol	C_2H_6O	46.07		59.5	Colorless liquid	0.789	0.654
Methanol	CH_3OH	32.04		130.2	Colorless liquid	0.791	0.762
Acetic acid	$C_2H_4O_2$	60.05		15.4	Colorless liquid	1.049	0.648

Volume	Solvents					
	Ethanol Concentration /Sample code		Methanol Concentration /Sample code		Acetic Acid Concentration /Sample code	
100µL	10%	*S1*	10%	*S5*	1%	*S9*
	20%	*S2*	20%	*S6*	2%	*S10*
200 µL	10%	*S3*	10%	*S7*	1%	*S11*
	20%	*S4*	20%	*S8*	2%	*S12*

Table 2
CODIFICATION OF THE SOLVENTS SAMPLES SAMPLES OBTAINED FROM DIFFERENT SOLVENT CONCENTRATIONS IN DIFFERENT SOLUTION VOLUMES

Table 3

Table 3

CODIFICATION OF THE MIXTURES SAMPLES OBTAINED FROM DIFFERENT COMBINATIONS BETWEEN SOLVENTS WITH DIFFERENT
CONCENTRATIONS IN DIFFERENT SOLUTION VOLUMESOBTAINED

Volume	Solvent Mixtures							
	Ethanol + Methanol		Ethanol + Acetic acid		Methanol + Acetic acid		Ethanol + Methanol + Acetic acid	
100 µL	10% Ethanol + 10% Methanol	M1	10% Ethanol + 1% Acetic acid	M5	10% Methanol + 1% Acetic acid	M9	10% Ethanol + 10% Methanol + 1% Acetic acid	M13
	20% Ethanol + 20% Methanol	M2	20% Ethanol + 2% Acetic acid	M6	20% Methanol + 2% Acetic acid	M10	20% Ethanol + 20% Methanol + 2% Acetic acid	M14
200 µL	10% Ethanol + 10% Methanol	M3	10% Ethanol + 1% Acetic acid	M7	10% Methanol + 1% Acetic acid	M11	10% Ethanol + 10% Methanol + 1% Acetic acid	M15
	20% Ethanol + 20% Methanol	M4	20% Ethanol + 2% Acetic acid	M8	20% Methanol + 2% Acetic acid	M12	20% Ethanol + 20% Methanol + 2% Acetic acid	M16

Table 4
FTIR CHARACTERISTIC OF SOLVENTS

Indexed band-acetic acid (cm^{-1})	Indexed band-ethanol (cm^{-1})	Indexed band-methanol (cm^{-1})	Functional group	Comments
3660	3631	3670	-OH	O–H stretching mode of (-OH) groups. Overlay in ethanol/methanol/acetic acid is very large
2343	2975	2971	-CH	Symmetric & asymmetric range for C-H stretching vibration of CH3/CH2 groups
1701	-	-	C=O	Stretching vibrations of the carbonyl C=O groups
1518	1503	1508	-CH	C-H bending vibration of CH3/CH2 groups
1066	1050	1055	C-O	C–O stretching vibration
-	886	-	C-C	C–C stretching vibration

where the energy is absorbed due to C-H bonds stretching at wavenumber 2971 cm^{-1}, respectively due to C-O bonds stretching at 1055 cm^{-1} and acetic acid spectrum where the energy is absorbed due to C-O bonds at 1066 cm^{-1}.

Figure 2b shows the spectra for the mixture of methanol (10%), ethanol (10%) and acetic acid (1%) in 200 µL solution comparative with the same mixture of solvents that have double concentrations. In this case, the
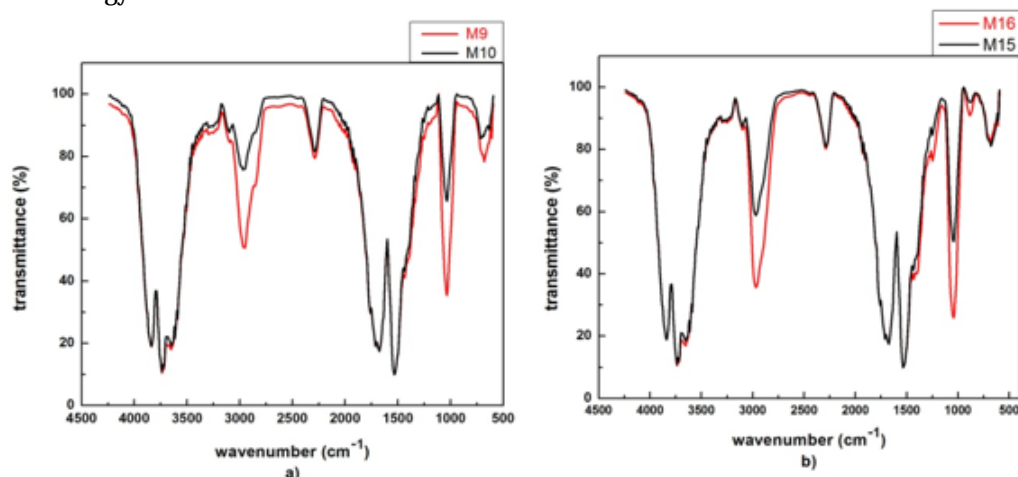

Fig.2 Comparative FTIR spectra for different solvents concentrations in the same volume of solution: a) M9 (mixture of methanol 10% and acetic acid 1% in100 µL) respectively M10 (mixture of methanol 20% and acetic acid 2% in100 µL); b) M15 (mixture of methanol 10%, ethanol 10% and acetic acid 1% in 200 µL) respectively M16 (mixture of methanol 20%, ethanol 20% and acetic acid 2% in 200 µL)

transmittance decreases close to 3000, 1000 and 900 cm^{-1} and it is proportional with the solvents concentrations due to the absorption of energy by the different bonds stretching relative to these frequencies. The overlap of ethanol, methanol and acetic acid spectra is responsible for this pattern. The contribution of ethanol to the decrease of transmittance at the specified wavenumbers is due to C-H bonds stretching at wavenumber 2975 cm^{-1}, respectively C-O bonds stretching at 1050 cm^{-1} and C-C at 886 cm^{-1} [16-19].

In figure 3, it can be observed that there is a proportionality between spectra for different volumes of solutions of methanol 10% and acetic acid 1%. The solution of 100 μL has double values for transmittance at 3000 and 1000 cm^{-1} in comparison with the solution with volume of 200 μL. That means the FTIR Gazmet is very sensitive to approach different concentrations and quantities of solvents even when there are very small amounts present in the sample.

Figures 4 and 5 show the spectra of solvents in comparison with the spectra of mixture solutions. The sp...........................e of the
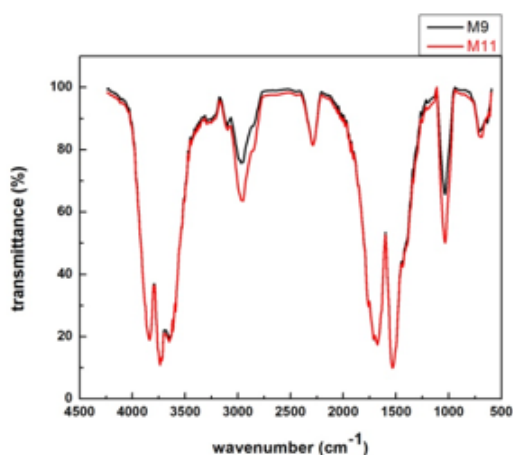

Fig.3 Comparative FTIR spectrum for different mixtures volumes and the same solvents concentrations: M9 (Methanol 10% acetic acid 1% in 100 μL), respectively M11 (methanol 10% acetic acid 1% in 200 μL)

absorption bands characteristic of each solvent component. For all the samples, the values of transmittances in the cases of mixtures comparative with solvents attest that the proportionality with the concentration of the solvents is respected.

To identify the persistence in time of the emissions of gases in the industrial activities (pharmaceutical or chemical) that use these types of solvents, we took
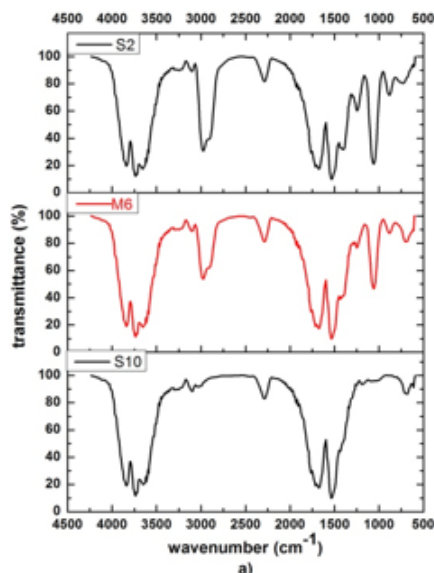

Fig.4 a) FTIR spectra of ethanol 20% and acetic acid 2% mixture (M6) in comparison with single acetic acid 2% (S10) and ethanol 20% (S2)
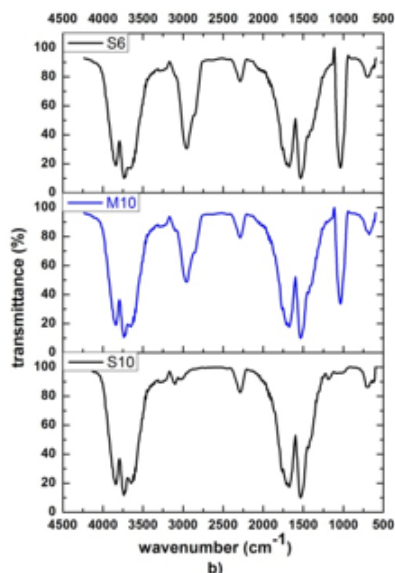

Fig.4 b) FTIR spectra of methanol 20% and acetic acid 2% mixture (M10) in comparison with single acetic acid 2% (S10) and methanol 20% (S6)
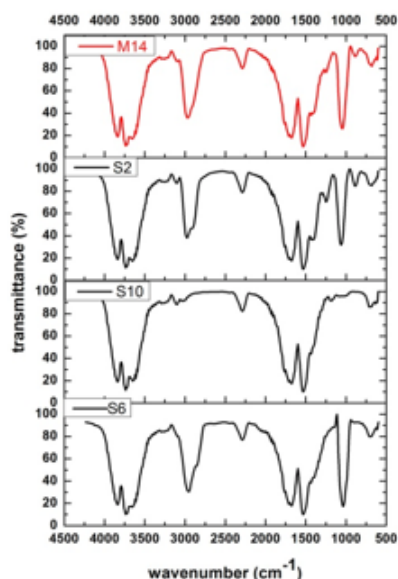

Fig.5 FTIR spectra of ethanol 20%, methanol 20% and acetic acid 2% mixture (M14) in comparison with single acetic acid 2% (S10), ethanol 20% (S2) and methanol 20% (S6)

samples of air under the glass cylinder before the experiment and one hour after the measurements. From figure 6, one can observe the persistence of the solvents (ethanol, methanol, acetic acid), in the ambient air, one hour after the samples' measurements.

From figure7, it can be observed that there is a proportionality between the concentrations of solvents in solutions and the measured concentrations of the gas phase solvents in the air under the glass cylinder. Taking into account the lower detection limit, which is very small (acetic acid from solution of 1% acetic acid), we can affirm that the ability of the device to detect indoor gases is very good. The difference between the detected concentrations in ppm of ethanol and methanol derived from the same concentrations of solutions is due to different vapor pressures of ethanol and methanol. For the mixtures of ethanol-methanol solutions (fig.8) the detected concentrations of the emitted gases are in good agreement with the solvents concentrations and volumes. The concentrations of methanol and ethanol in mixtures are about half of the concentrations of the individual solvents according to the method to obtain mixtures, described in chapter 2.
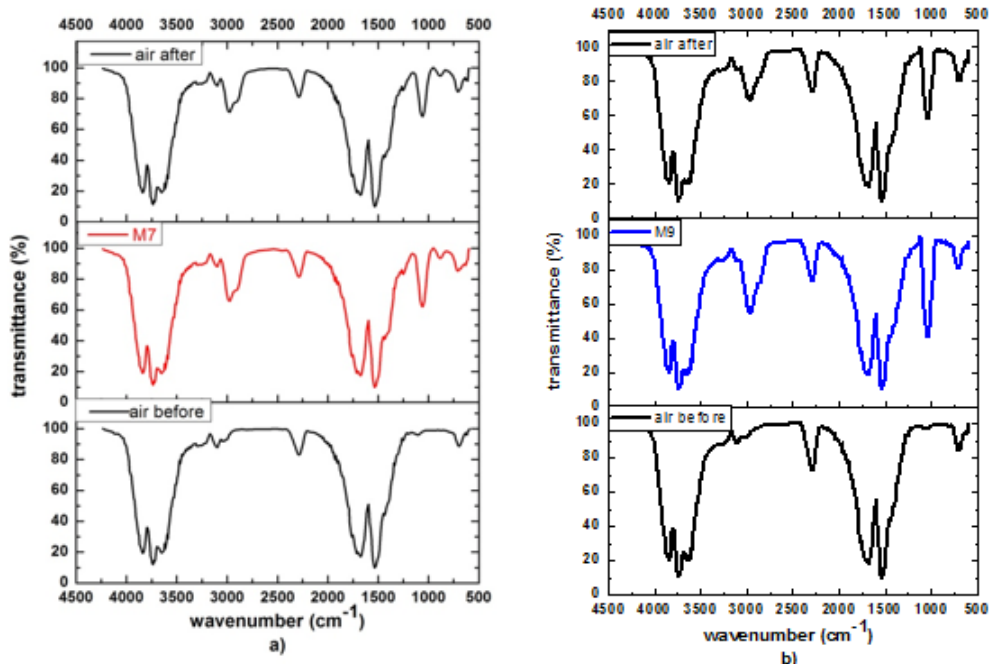
Fig.6 Comparative FTIR spectrum for: a) air under the glass cylinder before the measurement of sample M7 (bottom); M7 (ethanol 10% acetic acid 1% in 100 µL); air under the glass cylinder after the measurement of sample M7 (up); b) air under the glass cylinder before the measurement of sample M9 (bottom); M9 (methanol 10% acetic acid 1% in 100 µL); air under the glass cylinder after the measurement of sample M9
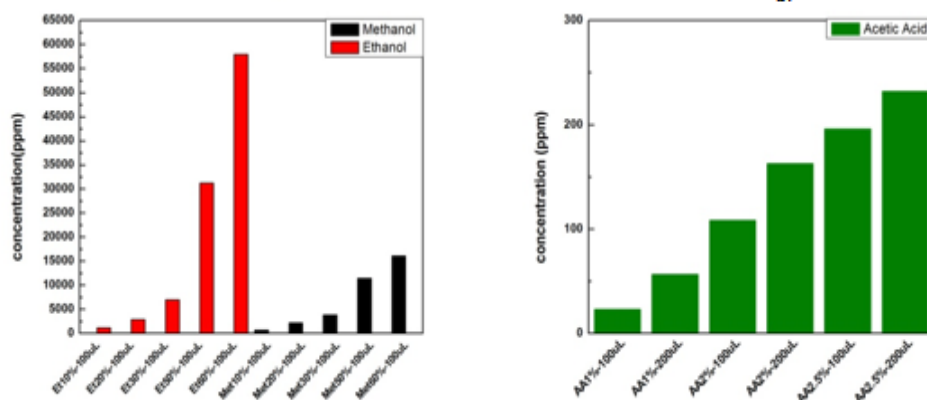

Fig.7 Measured concentrations of methanol, ethanol (left) and acetic acid (right), with Gazmet FTIR derived from single solution samples, in the air under the glass cylinder
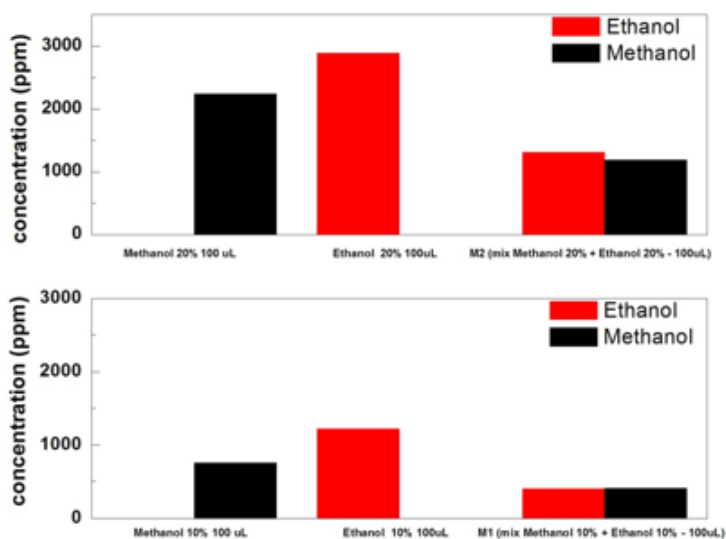

Fig.8 Comparison of measured concentration of methanol and ethanol derived from solutions of 100 µl, single and mixture, with Gazmet FTIR, in the air under the glass cylinder

Conclusions

The paper presents a procedure for fast and efficient analysis of gases emissions from solvents used in the chemical industry and especially in the pharmaceutical manufacturing, using FTIR spectroscopy. The measurements have highlighted the correlation between the concentration of gaseous solvents in the air and the concentrations of solvents in solutions. Moreover, this was proven to be an accurate method to measure concentrations of gases derived from mixtures of solvents, up to low values (units of ppm).

Looking at the FTIR spectra of analyzed samples, the transmittances of the binary and tertiary mixtures of the components comparative with individual solvents are in compliance with the concentration of the solvents in their respective solutions. The measurements indicate the persistence in time of the indoor air pollution in the pharmaceutical industries. Consequently, the stakeholders must take measures for ventilation and filtration of the air inside the manufactures.

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