

# Health in danger: "Sick buildings syndrome"

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#### Elisabeth Maria Ferreira Severo<sup>1</sup>

#### ABSTRACT

Sick Building Syndrome (EDS) was recognized by the World Health Organization (WHO) in 1982. It is a set of diseases triggered by the proliferation of infectious microorganisms and chemical particles in closed buildings.

The users of these buildings, in general, are affected by various pathologies, which leads to greater absenteeism at work, resulting in a decrease in the productivity of workers.

This syndrome increases with each passing day, especially in large urban centers, bringing problems to the occupational health of the population, and this work is fundamental to understand the mechanisms that cause this pathology, as well as its prevention, providing important information to have healthier built environments.

Keywords: Sick Building Syndrome, Occupational Diseases in Buildings, Health Hazards.

<sup>&</sup>lt;sup>1</sup> Dr. - Construct/Gequaltec - Faculty of Engineering, Porto University, 4200-465, Porto, Portugal. E-mail: esevero00@gmail.com



## **INTRODUCTION**

Whereas most of the population spends much of their time inside buildings, such as workplaces (Shopping Malls, Commercial Buildings), Schools, Housing, Public Buildings, among others.

These buildings can offer unfavorable conditions that can trigger discomfort, dissatisfaction, increase the risk of accidents, decrease productivity, increase costs and cause damage to the health of their occupants (IIDA, 1992).

Well-being in buildings is directly related to indoor air quality, ambient temperature, light, and peer relationships.

The biggest problem occurs in commercial buildings, where the circulation of people is greater. According to the World Health Organization, people spend at least 80% of their time indoors, breathing around 10,000 liters of air a day.

With the evolution of architecture, a great diversity of products for upholstery, finishing and furniture have emerged, which contain chemical substances that are dispersed in the indoor air of buildings. These materials were developed without a major concern for their emissions. The deterioration of indoor air is due to these emissions of chemical substances, volatile organic compounds, which are part of the composition of construction, cleaning and furniture materials (BRICKUS, AQUINO NETO, 1999).

The first reports of damage to health due to diseased buildings were around the 1970s.

In 1976, at the Bellevue Stratford Hotel in Philadelphia, an extreme case of Sick Building Syndrome occurred during the convention of the American Legion of Veterans, which brought together approximately 4,000 former soldiers. The participants began to fall ill, with cough, fever and difficulty breathing (called Legionnaires' lung disease) and unfortunately more than 30 of them died. After a series of investigations, it was discovered that the cause of the disorder had been the presence of the bacterium Legionella Pseumophila in the hotel's ventilation system (STERLING; COLLETT; RUMEL, 1991).

It wasn't until 1980 that the World Health Organization (WHO) recognized Sick Building Syndrome (EDS) as a disease.

In Brazil in 1998, former Minister of Communications Sérgio Motta died of respiratory failure due to legionellosis, prompting the Ministry of Health to regulate air-conditioned environments.



## SICK BUILDING

## DEFINITIONS

The **sick building syndrome** refers to the cause-and-effect relationship between the conditions of an internal environment and the aggression to the health of the occupants, with polluting sources of physical, chemical or biological origin. A **building** is considered **sick** when about 20% of its occupants have health problems associated with staying inside. Construction-related symptoms can have a substantial impact on health (eCYCLE, 2022).

For the Institute of Public Health of Portugal, sick building syndrome (EDS) is defined as "a situation in which the occupants/workers of a building experience occupational discomfort and/or acute health problems. It can also be called "Building-Related Diseases" (DRE) when the symptoms of a specific disease are related to a particular building and are attributed to airborne contaminants (SILVA, 2017).

The WHO has identified two types of diseased buildings:

## **Temporarily Diseased Buildings**

Are those in which newly constructed buildings, or with recent refurbishment, have irregularities that disappear over time (approximately six months). It causes temporal EDS, in which symptoms diminish or disappear over time.

## **Permanently Ill Buildings**

When symptoms persist despite measures being taken to address the problems. They may have design errors, lack of maintenance, or other factors that caused permanent damage.

## BRAZILIAN LEGISLATION ON BUILDINGS

Soon after this tragedy with the former Minister, the National Health Surveillance Agency (ANVISA) published Ordinance No. 3,523 of August 1998, establishing a technical regulation containing basic measures regarding the procedures for visual verification of the state of cleanliness, removal of dirt by physical methods and maintenance of the state of integrity and efficiency of all components of air conditioning systems. to ensure indoor air quality and the prevention of health risks to the occupants of air-conditioned environments. The Ordinance also requires all artificially air-conditioned environments for public and collective use to prepare and maintain a plan for the maintenance, operation and control of air conditioning systems (BRASIL, 2003).

In October 2000, ANVISA published Resolution 176 with the objective of creating criteria that would evaluate the adequacy of the procedures adopted by the maintenance companies of the establishments containing biological, chemical and physical parameters through which it is possible



to evaluate the quality of indoor air (BRASIL, 2003a). In 2003, ANVISA published Resolution No. 9, which contained revised technical guidelines from the previous Resolution. (BRAZIL, 2003b). In 2003, Resolution/RE No. 9 contained revised techniques from the previous one (BRASIL, 2003c).

## FACTORS OF THE SICK BUILDING

According to Environmental Health Magazine, about 60% of people living in diseased buildings may experience complications from Sick Building Syndrome.

To stop this problem, new buildings must be designed with safer materials. It is necessary to design ventilated environments with renewed air, in addition to always having adequate maintenance.

The most common symptoms are: eye irritation, respiratory manifestations (nose and throat), mental fatigue, headache, airway infection, cough, hoarseness, difficulty breathing, itching, joint pain and tearing, and skin rashes and irritation. These symptoms can appear alone or in combination.

The causes that contaminate the internal environment can originate from chemical, biological, physical, psychosocial and other factors.

**Chemical Factors** - are the most contaminating. Chemical contaminants include Volatile Organic Compounds (VOCs), Particulate Matter, Carbon Monoxide, Asbestos, Nitrogen Dioxide, Ozone, Formaldehyde, Sulfur Dioxide, Ammonia and Radon 222. Radon gas seeps from the ground, usually has its highest concentration at the lowest level of the building and infiltrates the foundations and accumulates inside the buildings with cracks in the concrete, floor drains, sewage pumps, exposed soil and building drains, at points of connection of the building (floor and wall mortars, loose and loose pipes), in groundwater installations of artesian wells, cisterns, and can also originate from outdoor air, water, and natural gas (SEVERO; SOUSA (2018). According to the National Institute of Metrology, Quality and Technology (Inmetro), about 42.3% of 78 establishments for private and collective use are contaminated by chemical pollutants.

Table 1 shows a list of the main chemical pollutants, their source of emanation, as well as their effects on humans, according to Resolution RE/ANVISA 176/2000.



Table 1 - Main chemical pollutants
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Agentes químicos	Principais fontes em ambientes interiores	Principais medidas de correção em ambientes interiores
со		Manter a captação de ar exterior com baixa concentração poluentes; restringir as fontes de combustão; manter a exaustão em ári que ocorre combustão; eliminar a infiltração de CO provenie fontes externas; restringir o tabagismo em áreas fechadas.
CO2	Produtos de metabolismo humano e combustão.	Aumentar a renovação de ar externo; restringir as fon combustão e o tabagismo em áreas fechadas; eliminar a infiltra fontes externas.
NO2	Combustão.	Restringir as fontes de combustão; manter a exaustão em án que ocorre combustão; impedir a infiltração de NO2 provenie fontes externas; restringir o tabagismo em áreas fechadas.
03	Máquinas copiadoras e impressoras a laser.	Adotar medidas específicas para reduzir a contaminação ambientes interiores, com exaustão do ambiente enclausuramento em locais exclusivos para os equipamento apresentem grande capacidade de produção de O3.
Formaldeído	mobiliário, cola, produtos	Selecionar os materiais de construção, acabamento e mobiliá possuam ou emitam menos formaldeído; usar pr domissanitários que não contenham formaldeído.
Material particulado	Poeira e fibras.	Manter filtragem de acordo com NBR-6402 da ABNT; isolamento termo acústico que possa emitir fibras minerais, org ou sintéticas para o ambiente climatizado; reduzir as fontes ir e externas; higienizar as superfícies fixas e mobiliários sem o vassouras, escovas ou espanadores; selecionar os materi construção e acabamento com menor porosidade; adotar m específicas para reduzir a contaminação dos ambientes int (vide biológicos); restringir o tabagismo em áreas fechadas.
Fumo de tabaco	Queima de cigarro, charuto, cachimbo, etc.	Aumentar a quantidade de ar externo admitido para renovação exaustão dos poluentes; restringir o tabagismo em áreas fechadas
cov	Cera, mobiliário, produtos usados em limpeza e domissanitários, solventes, materiais de revestimento, tintas, colas, etc.	Selecionar os materiais de construção, acabamento, mobiliário produtos de limpeza e domissanitários que não contenham C( que não apresentem alta taxa de volatilização e toxicidade.
COS-V	Queima de combustíveis e utilização de pesticidas.	Eliminar a contaminação por fontes pesticidas, inseticidas e a de combustíveis; manter a captação de ar exterior afasta poluentes.

Source: BRASIL (2000). Resolution RE/ANVISA 176/2000

#### **Biological Factors**

These are bacteria, fungi, protozoa, arthropods, viruses, etc.

Bioaerosols are particles of biological origin suspended in the ambient air and encompass viruses, bacteria, fungi, spores and pollens. In fungi, the most common are Penicillium and Aspergillus, and the main bacteria are Bacillus, Staphylococus and Legionella Pneumophila (SRIKANT *et all*, 2008 and STETZENBACH *et all*, 2004).

The inhalation of these particles can cause varied respiratory symptoms and depends on the biological properties, chemical composition of the particles, number of particles inhaled, the place where they are deposited in the respiratory system and the sensitivity of the individual (GHOSH & SRIVASTAVA, 2015).

The most common problems are irritating effects, especially of the eyes, nose and skin, allergic reactions such as asthma and rhinitis, infections (pneumonia, tuberculosis, Legionnaires'



disease) and toxic reactions. Individuals with weakened immune systems, such as AIDS patients or those undergoing chemotherapy, are of particular importance, as they are more susceptible to contracting infections when exposed to microorganisms (APA, 2009). Chart 2 shows the main biological factors according to Resolution RE/ANVISA 176/2000.

<b>Biological agents</b>	Main Sources in Indoor Environments	Main Correction Measures in Indoor	
		Environments	
Bacteria	Stagnant water reservoirs, cooling towers, condensate trays, dehumidifiers, humidifiers, air conditioner coils, and humid and hot surfaces.	Carry out the cleaning and maintenance of cooling towers; sanitize condensate reservoirs and trays or maintain continuous treatment to eliminate sources; eliminate infiltrations; sanitize surfaces.	
Fungi	Humid environments and other sources of fungal multiplication, such as moist organic porous materials, ceilings, walls and damp insulation; outdoor air, inside conditioners and ducts without maintenance, potted soil with plants.	sources; eliminate contaminated porous	
Protozoa	Contaminated water reservoirs, trays, and maintenance-free conditioner humidifiers.	Sanitize the reservoir or maintain continuous treatment to eliminate the sources.	

Table 2 -	Main	biological	pollutants
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Table 2 - Main biological pollutants - continue	ed
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<b>Biological agents</b>	Main Sources in Indoor Environments	Main Correction Measures in Indoor	
		Environments	
Virus	Human host.	Adjust the number of occupants per m2 of area with increased air renewal; avoid the presence of infected people in air- conditioned environments	
Algae	Cooling towers and condensate trays.	Sanitize condensate reservoirs and trays or maintain ongoing treatment to eliminate sources.	
Pollen	It's external.	Maintain filtration according to NBR- 6401 of ABNT	
Arthropod	Household dust.	Sanitize fixed surfaces and furniture, especially those covered with fabrics and carpets; restrict or eliminate the use of these coatings.	
Animals	Rodents, bats and birds.	Restrict access, control rodents, bats, birds' nests and their excrement.	

Source: BRASIL (2000). Resolution RE/ANVISA 176/2000



#### **Physical Factors**

Noise level, lighting, electromagnetic fields, temperature and humidity are all factors that influence having a sick building.

a) Ventilation – when ventilation is ineffective there is a gradual increase of pollutants in the air, which leads to problems with indoor air quality. Several studies indicate inadequate ventilation as the most important cause of EDS and the main cause of IAQ. The ventilation efficiency of a sealed building can be judged by indoor CO2 levels.
b) Temperature - Thermal comfort is determined by several parameters, including air temperature, relative humidity, heat production by the human body, clothing, wind, activity level and others. Comfort occurs when the body temperature is kept within the small ranges, skin humidity is low and the air movement are similar.
The optimum temperature of workplaces varies between 18 °C and 22 °C, except in certain climatic conditions, where it can reach 25 °C. When indoor temperatures in closed environments exceed 22 °C, certain symptoms may occur, such as: irritation of the mucous membranes, headache, lethargy and tiredness (ION & SEBARCHIEVICI,

2011).

c) **Humidity** – According to the Portuguese Environment Association, relative humidity below 25% is associated with increased discomfort and the sensation of dry mucous membranes and skin, which can lead to irritation. On the other hand, relatively low humidity values also increase static electricity, causing discomfort and can hinder the use of electronics such as computers, photocopiers, etc. (APA, 2009).

d) Lighting – Both the lack or excess of lighting, as well as the intensity of brightness (especially with computer work without breaks), chromatic spectrum and color temperature can cause changes in behavior, affect the quality of vision, causing the occurrence of accidents, in addition to visual discomfort (visual fatigue, eye irritability, headaches, muscle pain, difficulty concentrating), tiredness, depression, loss of productivity, and general discomfort (JAFARI & ASGHAR, 2015).

e) Noise – It can be very harmful to the health of workers, and can even lead to hearing loss. Prolonged exposure to noise decreases workers' coordination and concentration, affecting the performance of tasks, increasing the likelihood of errors and accidents. The table shows the impact of noise on the health of individuals according to the degree of noise, according to Annex I of NR 15, updated in 2022:



	ontinuous or Intermittent Noise - NR 15
NOISE LEVEL dB(A)	MAXIMUM PERMISSIBLE DAILY
	EXPOSURE
85	8 hours
86	7 hours
87	6 hours
88	5 hours
89	4 hours and 30 minutes
90	4 hours
91	3 hours and 30 minutes
92	3 hours
93	2 hours and 40 minutes
94	2 hours and 15 minutes
95	2 hours
96	1 hour and 45 minutes
98	1 hour and 15 minutes
100	1 hour
102	45 minutes
104	35 minutes
105	30 minutes
106	25 minutes
108	20 minutes
110	15 minutes
112	10 minutes
114	8 minutes
115	7 minutes

 Table 1 - Tolerance Limits for Continuous or Intermittent Noise - NR 15

Font: BRASIL (2021) NR-15 – Anexo 1

#### **Psychosocial Factors**

Workplace problems such as stress, violence, harassment and others have been identified as psychosocial factors, leading to reduced performance, increased absenteeism and increased accident rates.

#### **Other Factors (Gender)**

There are strong indications that females suffer more from Sick Building Syndrome than males.

#### **HEALTHY BUILDING**

Florence Nightingale (1863), nurse who became known with the following Quote: "It may seem a strange principle to declare as the first requisite in a Hospital that it should do the sick no harm." Its objective was to strengthen an environment that would stimulate health in the hospital environment. Its concepts involved the issue of the environment and its environmental components such as: physical, social and psychological in which all are interrelated with each other (GEORGE, 2000 and SILVA, 2017).

Today it turns out that this theory applies not only to the hospital environment, but also to any type of building. A healthy building should be a pleasant, inviting environment, inducing relaxation, tranquility and joy, it should be a healthy space.



In 2020, nine fundamentals of healthy building were listed in the Book: "*Healthy Buildings – How Indoor Spaces Drive Performance and Productivity*" by Professors Allen and Macomber from the T.H. Chan School of Public Health as shown in Figure 1 and described below:

## VENTILATION

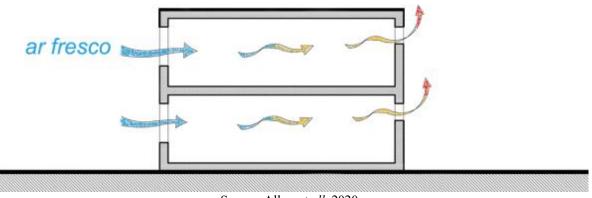
External pollutants can penetrate the interior of the building and compromise people's health. It is necessary to create means to ensure a minimum quality of ventilation in all environments of the project.

Buildings typically recirculate some of the air, which has been shown to lead to a higher risk of infection during outbreaks, as contaminated air in one area circulates to other parts of the building.

For those buildings with mechanical ventilation systems, it is recommended to check that the system is on whenever the building is occupied, and then increase the fresh air intake rates.

For homes and buildings without central systems, opening windows plays an important role in releasing stale indoor air.

Figure 1 – Project with natural ventilation



Source: Allen at all, 2020.

Good filters and frequent cleaning of the surface are important, indoor humidity levels should be adjusted and overcrowding should be avoided.

## AIR QUALITY

One of the main fundamentals of healthy building, since the presence of volatile organic compounds (VOCs) among others can bring respiratory problems.

If it is absolutely necessary to recirculate the air, you can minimize cross-contamination by increasing the level of filtration.



Most buildings use low-quality filters that can capture less than 20% of viral particles. Most hospitals, however, use a filter with a MERV rating of 13 or higher. And for good reason – they can capture more than 80% of airborne viral particles.

For buildings without mechanical ventilation systems or if you want to supplement your building's system in high-risk areas, portable air purifiers can also be effective in controlling particulate concentrations in the air.

Most quality portable air purifiers use HEPA filters, which capture 99.97% of particles.

The government should also give local authorities the power to compel building owners and managers to carry out indoor air quality checks immediately and implement measures for all facilities used by the public, including schools, hospitals and commercial offices, etc.

#### THERMAL HEALTH

It is important to keep the temperature and relative humidity within the ranges considered ideal for each environment, as well as to monitor thermal conditions and reduce solar heat gain to save energy and reduce environmental impacts.

#### WATER QUALITY

Water tests should be done regularly to monitor the amount of residual disinfectants, such as chlorine, the pH level, and temperature, as well as to identify the possible presence of bacteria that may pose a risk to people.

#### HUMIDITY

It is necessary to protect the building envelope, from the roof to the waterproofing, to prevent the entry of water and the proliferation of mold and moisture. It is important to regularly check the plumbing pipes for signs of leakage or standing water. Some viruses survive better when the relative humidity (RH) is low. Allen and Macomber's research team found that increasing the RH between 30 and 50 percent led to a 32 percent drop in influenza virus survival. Early results show that the coronavirus survives better on surfaces with a RH of 20%. In general, humid conditions are thought to increase the growth of bacteria, fungi, and other biological contaminants. But some viruses, such as the flu, survive better when humidity is low.

A portable humidifier can be a good strategy to increase the humidity of environments, as shown in Figure 2.





Source: Allen at all, 2020.

#### **DUST AND PESTS**

The **foundations of the healthy building** are also concerned with the ingress of dust and pests. The recommendation is to clean all surfaces and, in the case of the floor, vacuum it regularly with a HEPA (*High Efficiency Particulate Arrestance*) vacuum cleaner to pick up even microparticles.

#### NOISE

Noise pollution depends on a number of factors, but it can be controlled by defining "noise zones" in different building areas, using materials that absorb sound and minimise reverberation, and creating quieter areas in commercial buildings.

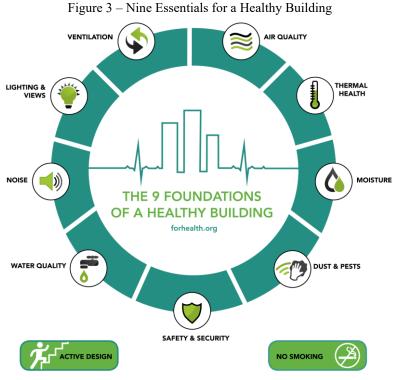
## LIGHTING AND VIEWS

Projects must follow good lighting practices in the environments, controlling the amount of light and glare. It is ideal to maximize access to natural light through windows and to control light intensity, spectrum, and time.

## SAFETY AND SECURITY

The building needs to meet all safety norms and standards, such as fire suppression systems and smoke detectors, as well as invest in equipment such as surveillance systems and safe visitor flow control.





Source: Allen at all, 2017.

## **CONCLUSIONS**

The internal environment of buildings, especially in Brazil, is still little studied. In which there is no simple and single solution for sick buildings since the reactions in the occupants are multifactorial.

Proper fresh air renewal and ventilation eliminates or minimizes many symptoms such as: irritations to the eyes, nose, throat and skin due to chemicals present in the air.

As already mentioned, suitable filter systems will remove dust. These filters should be changed periodically, usually at the time of maintenance.

Sick Building Syndrome has a multidisciplinary approach and involves professionals from architecture, engineering (especially occupational safety engineers), medicine (epidemiologists) and public health authorities.

On the other hand, Allen and Macomber (2020) bring us nine fundamentals of Healthy Building, which are: Ventilation, Air Quality, Thermal Health, Water Quality, Humidity, Dust and Pests, Noise, Lighting and Views, and Safety and Protection.

No less important is to emphasize the importance that projects must have regarding the specification of indoor air circulation and the control of air flow in order to have healthy environments.

It is also important that local authorities create specific legislation to require indoor environmental quality in buildings, including schools, hospitals, commercial offices, among others.



Much still needs to be done to prevent Sick Building Syndrome, and entrepreneurs have a very important role in understanding productive work spaces, they must be aware of the various sources of the problem, whether chemical, biological or physical. For better decision-making, it is necessary that preventive measures are adopted, so that we will have a healthy, comfortable and productive environment.

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#### **REFERENCES**

- 1. Allen, J. G., Bernstein, A., & Xiadong, C. (2017). The 9 Foundations of a healthy building.
- 2. Allen, J. G., & Macomber, J. D. (2020). Healthy Buildings How Indoor Spaces Drive Performance and Productivity.
- 3. APA. (2009). Qualidade do Ar em Espaços Interiores-Guia Técnico, 1-53.
- 4. Brasil. (2003). Ministério da Saúde. Portaria nº 3523, de 28 de agosto 1998. Disponível em: [URL]. Acessado em 06 de agosto de 2022.
- 5. Brasil. (2003a). Ministério da Saúde. Resolução nº 176, de 24 de outubro de 2000. Disponível em: [URL]. Acessado em 06 de agosto de 2022.
- 6. Brasil. (2003b). Ministério da Saúde. Resolução no. 9, de 16 de janeiro de 2003. Disponível em: [URL]. Acessado em 06 de agosto de 2022.
- 7. Brasil. (2003c). Ministério da Saúde. RE/Resolução no. 9, de 16 de janeiro de 2003. Disponível em: [URL]. Acessado em 06 de agosto de 2022.
- 8. Brasil. (2021). NR-15 Anexo 1 Atividades e Operações Insalubres. Disponível em: [URL]. Acessado em 09 de agosto de 2022.
- 9. Brasil. (2000). Resolução RE/ANVISA 176/2000. Disponível em: [URL]. Acessado em: 09 de agosto de 2022.
- 10. Brickus, L. S. R., & Aquino Neto, F. R. de. (1999). Indoor air quality and chemistry. Química Nova, Jan./Feb. 1999, vol.22, no.1, p.65-74.
- 11. eCycle. (2022). Edifício fechado abriga diversos perigos para a saúde. Alergias, dores de cabeça e piora de condições pré-existentes como asma. Disponível em: [URL]. Acessado em 06 de agosto de 2022.
- 12. George, J. B. (2000). Teorias de enfermagem: dos fundamentos para à prática profissional (4th ed.). Porto Alegre: Artes Médicas Sul.
- 13. Ghosh, B., Lal, H., & Srivastava, A. (2015). Review of bioaerosols in indoor environment with special reference to sampling, analysis and control mechanisms. Environmental International, 85, 254–272.
- 14. Iida, I. (1992). Ergonomia Projeto e Produção. São Paulo: Edgard Blucher.
- 15. Ioan, S., & Sebarchievici, C. (2011). Olfactory Comfort Assurance in Buildings. Chem. Emiss. Control. Radioact. Pollut. Indoor Air Qual. Ed. 407–428.
- 16. Jafari, M. J., & Asghar, A. (2015). Association of Sick Building Syndrome with Indoor Air Parameters, 14, 55–62.
- 17. Severo, E., & Sousa, H. (2018). O Risco do Radônio em Ambientes Internos. Invesigação Qualitativa em Ciências Sociais. Volume 3. Atas CIAIQ 2018.



- 18. Silva, A. E. S. (2017). Síndrome do Edifício Doente. Trabalho Final Mestrado integrado em Medicina. Faculdade de Medicina Lisboa, Lisboa, PT.
- 19. Srikanth, P., Sudharsana, S., & Steinberg, R. (2008). Bio-aerosols in indoor environment: Composition, health effects and analysis. Indian Journal of Medical Microbiology, 26, 302.
- 20. Sterling, T. D., Collett, C., & Rumel, D. (1991). A Epidemiologia dos "Edifícios Doentes". Revista de Saúde Pública, São Paulo, 25, 56-63.
- 21. Stetzenbach, L. D., Buttner, M. P., & Cruz, P. (2004). Detection and enumeration of airborne biocontaminants. Current Opinion in Biotechnology, 15, 170–174.