Is dry eye an environmental disease?

O olho seco é uma doença relacionada a exposição ambiental?

MONICA ALVES1, PRISCILA NOVAES2, MONICA DE ANDRADE MORRAYE3, PETER SOL REINACH4, EDUARDO MELANI ROCHA3

ABSTRACT
Previous studies have revealed that eye contact with either air pollutants or adverse indoor and/or outdoor environmental conditions can affect tear film composition and ocular surface components. These effects are mediated by selective binding of the environmental agents to ocular surface membrane receptors, leading to activation of pro-inflammatory signaling pathways. The aim of the current review was to examine the published evidence associated with environmental factors and ocular surface disease and dry eye. Specifically, the reader will appreciate why it is possible to refer to them as mediators of Environmental Dry Eye Disease (EDED), a singular clinical entity inside DED context, directly caused by pollutants and/or adverse climatic conditions. The indicators and clinical findings are described along with EDED differential diagnosis in its acute and the chronic phases. Based on strong existing evidence of clinical reports and epidemiological observations regarding DED and environmental factors we conclude that there is a straight cause-and-effect relationship between ambient stresses and DED. International standards and web-based tools are described for monitoring worldwide environmental conditions referring localities and populations susceptible to EDED. This information is beneficial to health providers to pinpoint the individuals and predisposed groups afflicted with DED. Such insights may not only improve the understanding and treatment of DED but also help to identify the contributing factors and lower the frequency and progression of EDED.

Keywords: Dry eye syndromes; Lacrimal apparatus diseases; Environmental illness; Environmental pollutants/adverse effects

INTRODUCTION
Epidemiological studies have indicated increasing incidence of dry eye disease (DED) in the worldwide population3-10. This common ocular condition has multiple causes, which are not entirely understood. The emerging awareness that environmental factors can contribute to DED is supported by some recent studies and reflects differences in cultural traditions and exposure to unfavorable working conditions. In these groups, the impact of environmental factors in DED demands further characterization to develop strategies to reduce its incidence4,11. Due to the apparent relationship between the aforementioned environmental influences and DED, this disease can be better defined by delineating Environmental Dry Eye Disease (EDED) as a clinical subtype of DED.

We summarize herein our current understanding of environmental causes for DED. However, this review does not deal with some other relevant exogenous factors, such as usage of drugs and alcohol as their effects were recently well addressed.6,7. In addition, we omitted the effect of nutritional factors on DED, which due to its extension and complexity deserves an entire review.

EDED is not only an association between environmental conditions and well-defined ocular surface inflammatory conditions, but it is considered as a clinical subtype of DED (Table 1). In EDED cases, the inflammatory conditions and ocular discomfort are followed by changes in tear film composition volume and osmolarity, which may persist even after the individuals are no longer exposed to the related environmental factors. In one example of EDED, following an environmental incidence the symptoms persisted for two years.8-10. EDED is strongly influenced by one or more environmental factor. Additionally, improper diagnosis of toxic keratoconjunctivitis, solar keratitis, allergic keratoconjunctivitis or some other types of ocular surface disease can contribute to EDED. These conditions show similar symptoms and environmental factors on the existing condition further leading to EDED. It is likely that some overlap exists among the mediators of these diseases. This review focuses on some unique environmental factors distinctive of EDED (Figure 1).

EDED gained relevance based on the recognition that environmental factors can be deleterious to human health and contribute to DED7,12. The impact of the environment in the pathophysiology

RESUMO
Diversos estudos têm demonstrado que o contato ocular com poluentes ambientais afeta a composição do filme lacrimal e de estruturas da superfície ocular. Tais efeitos são mediados pela ligação de agentes ambientais com receptores na superfície ocular, levando a ativação de mediadores pró-inflamatórios. Estas evidências propõem a avaliação das evidências publicadas, que associam fatores ambientais às doenças de superfície ocular ao olho seco. O leitor compreenderá que é possível inferir olho seco ambiental como uma entidade singular dentro do contexto da doença olho seco, diretamente causada pela exposição a poluentes e/ou condições climáticas adversas. Serão descritos os indicadores e achados clínicos, assim como o diagnóstico diferencial das fases aguda e crônica. A avaliação de relatos clínicos e observações epidemiológicas demonstra uma forte associação entre olho seco e fatores ambientais. O conhecimento sobre parâmetros internacionais e ferramentas de monitorização das condições ambientais no mundo, permite identificar localidades e populações mais susceptíveis ao olho seco ambiental e pode auxiliar na identificação de indivíduos acometidos e grupos predispostos. E desta forma, melhorar o entendimento e tratamento dessa condição, diminuir os fatores associados, sua frequência e progressão.

Descritores: Síndromes do olho seco; Doenças do aparelho lacrimal; Doença ambiental; Poluentes ambientais/efeitos adversos.
of DED has been studied and confirmed in animal models of human DED\textsuperscript{[13-15]}.

As indicated, a healthy and pain-free ocular surface depends on identifying and eliminating factors that cause ambient humidity, airflow and purity, and temperature to intolerable levels. Such an undertaking is needed to preserve tear film qualities commensurate with ocular surface health. This is essential to sustain sufficient corneal refractive power, visual acuity, and ocular comfort\textsuperscript{[5,16,17]}.

A desiccating environment can lead to increase in tear film evaporation and/or decline in its turnover and clearance. These initial events lead to exposure of the ocular surface to hazardous environmental elements that trigger or exacerbate EDED symptoms. Clinical findings have shown that increased numbers of people are affected by EDED because of exposure to environmental factors (Figure 2).

Our purpose herein is to provide a critical appraisal of the clinical and epidemiological evidence indicating that DED is influenced by environmental factors. Secondly, we delineate EDED as a single clinical entity with a unique set of symptoms and clinical findings different from that of either DED or other diseases, such as Sjögren’s syndrome, diabetes mellitus or drug induced, allergic conjunctivitis, toxic or irritative conjunctivitis, and actinic keratitis. Moreover, we will describe standard tools used to monitor environmental conditions and discuss their relevance in EDED epidemiological studies. This review enables the health care providers and researchers to identify the environmental risk factors associated with the development and progression of EDED. This initiative intends to help future studies to improve our understanding and care for this possibly common and complex disease.

Environmental Dry Eye Disease (EDED) can be considered a clinical entity that qualifies the definition of DED\textsuperscript{[16]}. The most relevant causal factor is environmental exposure, such as pollutants and/or adverse climate. On the other hand, causative factors related to systemic diseases (endocrine, metabolic, nutritional, autoimmune, genetic, viral or neurologic), anti-cholinergic, adrenergic or other drug-related side effects are considered as exclusion factors to maintain EDED as a distinct disease entity within the DED envelope.

EDED differential diagnosis comprises the entities shown in table 1. Possible non-environmental factors or undiagnosed causes of DED were also considered as differential (for example a suspected Sjögren’s syndrome was not investigated to fulfill the criteria). From this perspective, diseases that were labeled as “pollution keratoconjunctivitis,” “computer vision syndrome,” and other environmentally related encounters, due to DED clinical presentation would be dif-

### Table 1. Differential diagnosis of Environmental Dry Eye Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Causes</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solar keratitis\textsuperscript{[19]}</td>
<td>UV exposure</td>
<td>Keratosis of exposed skin, burning sensation, redness, punctate keratitis</td>
</tr>
<tr>
<td>Allergic keratoconjunctivitis\textsuperscript{[10,20]}</td>
<td>Allergy</td>
<td>History of allergy, redness, itching, swelling</td>
</tr>
<tr>
<td>Floppy eyelid syndrome\textsuperscript{[21]}</td>
<td>Rubbery, redundant upper tarsus</td>
<td>Lid eversion with minimal pressure. Redness, papillary conjunctivitis</td>
</tr>
<tr>
<td>Corneal hiperalgesia\textsuperscript{[22]}</td>
<td>Up regulated nocireception triggered by corneal damage</td>
<td>Disparity between signs and symptoms, corneal sensory deficit and decreased sensory nerve population</td>
</tr>
<tr>
<td>Ligneous conjunctivitis\textsuperscript{[23]}</td>
<td>Impaired mucosal wound healing and fibrosis due to plasminogen deficiency</td>
<td>Chronic membranous conjunctivitis triggered by local trauma</td>
</tr>
<tr>
<td>Mucous fishing syndrome\textsuperscript{[24]}</td>
<td>Excess of mucous manipulation</td>
<td>Secretion, redness, and foreign body sensation along with signs of epithelial trauma due to discharge of mucus</td>
</tr>
<tr>
<td>Pseudopemphigoid\textsuperscript{[25]}</td>
<td>History of topical drug exposure.</td>
<td>Redness, tearing, itching, and progressive fibrosis of conjunctiva</td>
</tr>
<tr>
<td>Chronic blepharitis\textsuperscript{[26]}</td>
<td>Dysfunction of lipid production and secretion and epithelial metaplasia</td>
<td>Lid erythema, greasy crusting secretion. Redness and irritation of the eye Sborrhea in other sites of the body</td>
</tr>
<tr>
<td>Stevens-Johnsons Syndrome\textsuperscript{[27]}</td>
<td>Autoimmune disease triggered by drug or microorganism</td>
<td>Acute: systemic epithelial bullous swelling. Chronic: ocular surface fibrosis, corneal vascularization, and recurrent epithelial defect</td>
</tr>
<tr>
<td>Toxic keratoconjunctivitis\textsuperscript{[28]}</td>
<td>Toxic agent traumatic, iatrogenic or factitious contact with ocular surface</td>
<td>Variable, depending on agent and time. Commonly, acute epithelial swelling, redness, and tearing</td>
</tr>
</tbody>
</table>

Figure 1. Illustration of conditions whose signs and symptoms may overlap with environmental dry eye disease clinical presentation.

Figure 2. Environmental factors that influence tear film and ocular surface indoors and outdoors (air borne particles, air flow, temperature, ultraviolet rays).
ned as EDED. Patients can be afflicted with EDED due to exposure to a variety of environmental stresses. Conditions that elicit this disease are patient dependent. To establish a minimal normative classification for research and clinical purposes and therapeutic measures, the following environmental factor categories are included:

Indoors: closed ambient like office settings, such as variations in airflow, humidity, time in front of computer and other video displays, and exposure to toxic elements (for example, offices, health care facilities, poorly ventilated confinements such as subway stations and other employment areas).

Outdoors: exposure to open areas with extreme temperatures, gases and/or air suspended particles in the desiccating wind, intense UV exposure, agricultural usage of state of the art technology and gases and/or air suspended particles in the desiccating wind, intense symptoms of hyperemia, swelling, tearing, and dry eye sensation.

pollution had been correlated with ocular surface irritation, resulting in symptoms of hyperemia, swelling, tearing, and dry eye sensations.

Although the clinical signs of EDED can be similar among individuals exposed to either indoor or outdoor environmental factors, the detection preventive, and therapeutic methods are specific for each of these different settings. Additionally, the combined exposure to indoor and outdoor factors is also plausible.

Since the 1960’s, exposures to environmental factors such as air pollution had been correlated with ocular surface irritation, resulting in symptoms of hyperemia, swelling, tearing, and dry eye sensations. EDED patients present a broad range of symptoms, the most common being sour eyes and visual fatigue. The scores obtained from structured questionnaires have been used for the analysis. One of them is the Ocular Symptom Disease Index (OSDI), which evaluates DED severity rather than EDED. In order to correlate ocular surface related DED signs with environmental activities, an interesting activity log for DED was recently developed and tested in patients. However, individual differences in pain perception or exposure to environmental hazards in DED initiation were not evaluated.

EDED is distinguishable from aforementioned, because it is chronic and is associated with environmental factors. Such clinical findings are identifiable by the clinician/researcher investigating the disease. EDED identification stems from controlled observations about pollution-induced alterations, such as blinking rate, tear film break up time (TFBUT), and corneal epithelia damage.

Tear film instability is a consistent finding in studies that showed an association between air pollution and ocular surface damage. Such an effect compromises the corneal epithelial barrier function resulting in corneal and conjunctival epithelial chronic injury and inflammation.

A recent study has described a possible early adaptive response to air pollution in which increased levels of air pollution reduce tear film osmolarity and conjunctival goblet cell density. This negative correlation is indicative of EDED whereby increase in air pollution and/or desiccation are thought to have an early reactive phase followed by a chronic adaptive/metaplastic phase. Clinical findings can help to identify the contributions of exposure time to EDED progression (Table 2).

On the other hand, it is possible that other clinical signs may be associated with the disease, complicating a definitive diagnosis. For example, larger lid opening, lower mucous production, slower blinking rate, and reduced tear film clearance. Such symptoms may be found in different individuals afflicted with different degrees of EDED severity even if they are exposed to the same adverse environmental factors.

Future studies are needed to characterize and weigh the individual contributions of commonly observed environmental factors to EDED progression.

**Epidemiology of Dry Eye Related to Environmental Factors**

Outdoor EDED risk factors include exhaust emissions from automobiles and industrial facilities common in densely populated cities. Furthermore, occupational hazards related to large-scale agriculture and sugar cane processing can lead to exposure to gases, particulate matter, UV exposure, and altered microbiota.

On the other hand, indoor environmental conditions involving low humidity, excessive use of video display units (VDU), and high levels of CO₂ can be equally threatening to ocular surface health.

Case-control studies confirm the cause-effect relationship between the indoor or outdoor environmental conditions and the irritant symptoms in exposed individuals. Also, the individual risk factors are similar to those in other populations afflicted with other types of DED. They include aging, females, allergic or autoimmune conditions, and usage of contact lenses.

Part of the confusion that persists about EDED recognition is because individuals exposed to high air pollution levels are often at greater risk of developing allergies and present more symptoms. Moreover, there is also an association between increase in air pollution and autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus.

There is also speculation about the existence of an “urban allergy syndrome” (Table 3). Such individuals have a higher incidence of ocular surface inflammation and DED.

Although the acceptable levels of pollutants are established by national and world agencies (see below), the cut-off limits of the most harmful pollutants and environmental risk factors to the ocular surface capable to induce EDED are unknown. If more than one factor is involved, depending upon their characteristics they may interact at lower threshold values and induce EDED. Accordingly, the detrimental effects of environmental toxic agents on EDED epidemiology are not entirely understood.

The impact of urban pollution and environmental toxins on the ocular surface has been evaluated in a few case-control studies. These studies reported a high incidence of ocular discomfort, tear film instability, and ocular surface changes among individuals living in highly polluted cities of the world.

Two studies in New Delhi compared the groups of individuals living inside and outside the metropolitan area. A higher frequency of EDED findings with TFBUT <10 seconds, Schirmer Test (ST) <10 mm, and low lysozyme levels in tears were reported among the individuals living within the metropolitan area. The decline in these values correlate with increase in pollutant levels in the metropolitan area compared with the rural area. Another study on 500 volunteers documented

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**Table 2. Clinical findings in early and chronic phases of Environmental Dry Eye Disease, compared with non-exposed individuals**

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>Early reactive phase</th>
<th>Chronic adaptive phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Variable</td>
<td>Low</td>
</tr>
<tr>
<td>Tear film osmolarity</td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td>Hyperemia</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>MGD</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Schirmer test</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>TFBUT</td>
<td>Lower</td>
<td>Lower</td>
</tr>
<tr>
<td>Vital staining</td>
<td>Normal</td>
<td>Altered</td>
</tr>
<tr>
<td>Conjunctival Goblet cells</td>
<td>Higher number</td>
<td>Lower number</td>
</tr>
</tbody>
</table>

**Table 3. Individual and environmental risk factors for Environmental Dry Eye Disease (EDED)**

<table>
<thead>
<tr>
<th>Risk factors for EDED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual</td>
</tr>
<tr>
<td>Environmental</td>
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</tbody>
</table>
Is dry eye an environmental disease?

Dry eye symptoms can be associated with exposure to environmental factors, and studies have shown that air pollution, ultraviolet (UV) radiation, and other environmental factors may contribute to the development of dry eye disease (EDED). A recent study indicated that exposure to NO₂, a traffic-derived air pollutant, can lead to increased goblet cell density in the conjunctiva, a finding that suggests a potential link between air pollution and dry eye symptoms.

In a large-scale study in Indonesia, it was found that agricultural work is not a risk factor for EDED. On the other hand, it has been well established that UV is one of the major risk factors in pterygium, a degenerative condition of the corneal surface resulting in tear film instability. However, a cause and effect relationship still needs to be determined.

A large-scale study in Indonesia had shown that agricultural work is not a risk factor for EDED. Type of agricultural activities, amount, and time of exposures, climatic, chemical, and other environmental conditions need to be controlled in future studies to better understand their contributions as possible risk factors. Such an assessment entails delineating involvement of pesticides, fire, and UV irradiation.

Exposure to NO₂, traffic derived air pollutant, and ocular surface changes were studied in volunteers in Sao Paulo, Brazil, the largest city in Latin America, and compared with individuals from a countryside area. The individuals living in Sao Paulo showed high levels of NO₂ exposure and displayed goblet cell hyperplasia as a result of the chronic insult. The same research group analyzed 55 cases of NO₂ exposure and displayed goblet cell hyperplasia as a result of the chronic insult. Women showed higher frequency of symptoms that include ST<10 mm, and higher impression cytology score.

In Italy, patients who presented to an ophthalmological emergency unit with "eye discomfort," reduced ST values and tear film instability were evaluated during the periods of acute rise in air pollution levels, summer and winter. Road traffic, heating system usage, and photochemical smog levels were reported as the main causes of their symptoms. Subjective symptoms were ocular irritation, such as heavy or tired eyes, foreign body sensation, burning, stinging, and photophobia. Also, impression cytology findings in six areas of bulbar and tarsal conjunctiva were altered in 69% of the subjects. A high level of NO₂ was correlated with an early loss of goblet cells. A total of 15% showed a total loss of goblet cells without keratinization, and 5% had a total loss of goblet cells with mild keratinization. Women showed higher frequency of symptoms that include ST<10 mm, and higher impression cytology score.

In the last few decades, the symptoms were described in workers in poorly ventilated office buildings. SBS includes non-specific ocular, nose and throat irritation, headache, and respiratory symptoms. Emission of the volatile organic compounds (VOCs) from the synthetic materials used in offices and other micro environmental conditions need to be controlled in studies to better understand their contributions as possible risk factors. Such an assessment entails delineating involvement of pesticides, fire, and UV irradiation.

The broad ranges of environmental factors in office ambience associated with the demanding video display unit disrupt ocular surface homeostasis. In epidemiologic and clinical studies it is important to consider the weight of confounding or summing factors such as allergic conjunctivitis, certain oral medications, BAK preservative eye drops, eye make up, blinking frequency, and contact lens wear. The prevalence of indoor EDED can be estimated based on ocular discomfort complaints by office building workers. Based on the studies performed using questionnaires, it ranges from 5% to 40%.

**Table 4. Effects of pollution on ocular surface: summary of epidemiological studies**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Local</th>
<th>n</th>
<th>Endpoints</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Versura</td>
<td>1999</td>
<td>Case-control</td>
<td>Italy</td>
<td>200</td>
<td>Schirmer, Fering, BUT</td>
<td>Abnormal values of BUT 32%, Schirmer 40%, and Fering 45%.</td>
</tr>
<tr>
<td>Gupta</td>
<td>2002</td>
<td>Case-control</td>
<td>New Delhi, India</td>
<td>400</td>
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<td>BUT (odds ratio: 5.63, IC 95% 2.76-11.46)</td>
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<td>500</td>
<td>Symptoms, Lysozyme, Rose bengal, BUT, Schirmer</td>
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In the last few decades, the symptoms were described in workers in poorly ventilated office buildings. SBS includes non-specific ocular, nose and throat irritation, headache, and respiratory symptoms. Emission of the volatile organic compounds (VOCs) from the synthetic materials used in homes and offices together with other micro environmental conditions such as temperature, humidity, lighting and airborne substances can also contribute to EDED. They can cause ocular symptoms, tear film instability, and alterations in ocular surface characteristics of EDED. In 1992, Norn described that "sick building" workers have "pollution keratoconjunctivitis" with decline in BUT values and epithelial alterations detected by lissamine green staining.

The prevalence of indoor EDED can be estimated based on ocular discomfort complaints by office building workers. Based on the studies performed using questionnaires, it ranges from 5% to 40%.

This large range may be due to the design of questionnaire, types of reported symptoms, inclusion of confounding variables that include contact lens wear, medications, and differences in recall periods. For instance, in 56 European buildings across 9 countries, 39% of the individuals showed the mean prevalence of dry eye symptoms.

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The anterior ocular surface forms a mucosal interface with large area continuously exposed to the environment. Comfort, proper visual acuity, and cellular maintenance are guaranteed by complex and harmonic interactions of epithelial cells and accessory glands and tear film compounds. Since the anterior ocular surface is the most densely innervated area of the body, it is very sensitive to irritants and adverse environmental conditions (Figure 3).

Receptor-induced events that mediate signaling pathway of inflammatory responses resulting EDED symptoms such as decline in tear volume and altered composition are not completely understood. The following questions are need to be answered: to what extent the ocular surface discriminates different types of hazards? What makes the transition between an early/reactive phase to a chronic/adaptive phase?

Environmental injury might induce increasing expression of cytokines, growth factors and other molecules that mediate specific signaling pathways, and corneal inflammatory and allergic response. During acute and chronic phases, specific cell types, inflammatory mediators, and neurotransmitters are involved. Such responses vary depending on the nature and intensity of the stimulus and some mediators have been pointed as major contributors in the process of ocular surface damage related to environmental factors. Members of the transient receptor potential (TRP) channel superfamily, which include subfamilies in corneal epithelial and keratocytes, respond to environmental irritants inducing different responses to the central nervous system. Chemical burns in mice induce a specific TRP vanilloid type 1 (TRPV1) channel deregulated inflammatory responses leading to corneal melt and opacification. The injury-induced inflammatory and opacification responses resulting from TRPV1 activation were attributed to the up regulation of pro inflammatory and chemo attractive cytokines. TRPV1 induces downstream events by eliciting time dependent stimulation of the mitogen activated protein kinase (MAPK) cascade in epithelial cells and stromal fibroblasts.

Goblet cell hyperplasia results from exposure to high levels of air pollution by human nasal and respiratory mucosal surfaces that are considerably similar to conjunctiva. However, studies in mice exposed to a desiccating environment showed the opposite response. The differences between the human and mouse may be explained by species-specific responses, complexity of the trigger (humans are frequently exposed to combined factors, such as pollutants and adverse climate), and/or observations collected at different time-points in the disease progression of both the species.

In vitro models are useful to simulate hazardous conditions and assess their effects on the ocular surface at the molecular level. In this regard, the observation that particulate pollutants disrupt meibomian gland lipid structure and consequently the tear film organization was reproduced using benzalkonium chloride (BAK) and quartz particles. This study suggested that BAK affects the surface activity of meibomian lipids and quartz particles adsorbed to meibomian lipids, by removing them from the air/water interface. The authors proposed that a similar mechanism accounts for the effect of particulate pollutants on the tear film lipid layer.

The possibility of measuring specific effects of air pollutants and exposure to other environmental hazards on ocular surface integrity and health will identify the individuals with pathologic correlations to EDED. A recently described method is proven to be useful for this purpose. It comprises a filter paper in a small chamber attached to a belt or other piece of clothing. Air pollutants deposited on filters after different times were eluted and measured. In this direction, a better understanding of EDED inducing factors and underlying mechanisms can be achieved. Such insights will help the development of more efficient preventive and therapeutic strategies.

**Environment monitoring tools**

The environment is being polluted by industrial waste, automobile and truck exhaust fumes, burning of coal and fossil fuels as well as chemical manufacturing. Air pollution can even come from smallscale every day indoor activities, such as dry cleaning, degreasing, and painting. These activities accumulate gases and particles that come in contact with our mucosal tissues, especially the anterior ocular surface.

There is an increasing demand for environmental health indicators capable of measuring the amount of chemical, climatic, and physical hazards. Since 1987, World Health Organization (WHO) published guidelines for air quality are reviewed periodically. Similar guidelines, some with differences in items monitored or cut-off levels are provided by the Environmental Protection Agency (EPA) from the USA and other national or continental agencies (Table 5).

Among outdoor environmental parameters, climatic variables including temperature, atmospheric precipitation, humidity and UV radiation, and air pollutants including particulate matter (PM), CO, NO, O<sub>3</sub>, SO<sub>2</sub> were correlated with ocular and systemic diseases. As mentioned above, the indoor pollutants are same as the more commonly monitored climatic parameters and they include pollen, tobacco...
Is dry eye an environmental disease?

The results guide public health policies and preventive care(94,98-100) . These policies and practices are important not only for groups exposed to the above-indicated environmental risk factors. However, the daily range of pollutants, hazardous agents, confounding factors, and individual variable time-exposure to any of the studied agents can be too large to precisely identify agents responsible for higher EDED incidence in a certain area. These limitations may make it difficult to draw meaningful conclusions. To avoid that, study designs are required to include homogeneous groups with similar habits and comparable exposure times. One report had described that children living close to three petrochemical companies in Nigeria have tetraethyl lead and black carbon tear film (29). Similar studies are necessary to identify the specific pollutants responsible for a cause and effect relationship between an environmental factor and EDED.

Figure 4. A) Double passive NO2 sampler containing a cellulose filter (Energetica, Rio de Janeiro, Brazil) impregnated with an absorbent solution of 2% triethanolamine, 0.03% o-methoxyphenol, and 0.023% sodium metabisulfite inside a small plastic tube with one of its extremities open to ambient air. The nitrite produced during sampling is determined colorimetrically by reacting it with sulfanilamide and 8-anilino-1-naphthalene-sulfonic acid (ANS) and monitoring the absorption at 550 nm wavelength; B) Superior view of the NO2 sampler; C) Portable gravimetric impactor with a flow rate of 1.8 L/min. Air is aspirated into the impactor by a pump, PM is retained by a filter, and the particles in suspension in the air are measured gravimetrically; D) Portable sampler carried in a small bag by a research subject.

Table 5. Websites of agencies that provide guidelines and databases related to the environmental parameters in different regions of the world

<table>
<thead>
<tr>
<th>Agency</th>
<th>Website</th>
<th>Country/area</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Space Agency</td>
<td><a href="http://www.earthobservations.org/geoss_cl_ph.shtml">http://www.earthobservations.org/geoss_cl_ph.shtml</a></td>
<td>Global</td>
</tr>
<tr>
<td>Environmental Protection Agency</td>
<td><a href="http://www.epa.gov/oqaas001/monitoring.html">http://www.epa.gov/oqaas001/monitoring.html</a></td>
<td>USA</td>
</tr>
<tr>
<td>Instituto Nacional de Meteorologia do Brasil</td>
<td><a href="http://www.inmet.gov.br/portal/">http://www.inmet.gov.br/portal/</a></td>
<td>Brazil</td>
</tr>
<tr>
<td>Companhia Ambiental do Estado de Sao Paulo</td>
<td><a href="http://www.cetesb.sp.gov.br/">http://www.cetesb.sp.gov.br/</a></td>
<td>Sao Paulo State, Brazil</td>
</tr>
<tr>
<td>Ministry of Environmental Protection</td>
<td><a href="http://english.mep.gov.cn/">http://english.mep.gov.cn/</a></td>
<td>China</td>
</tr>
<tr>
<td>Department of Sustainability, Environment, Water, Population and Communities</td>
<td><a href="http://www.environment.gov.au/">http://www.environment.gov.au/</a></td>
<td>Australia</td>
</tr>
<tr>
<td>Environment Agency</td>
<td><a href="http://www.environment-agency.gov.uk/">http://www.environment-agency.gov.uk/</a></td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>

Smoke elements, mold, pesticides, carbon monoxide, formaldehyde, and lead among others(35). These indicators are also monitored by national and international health and/or environmental agencies. They are then applied in health analysis studies to correlate diseases with epidemiology, governmental policy directives, and economic studies (12,96,97).

The results guide public health policies and preventive care(94,98-100). They also help comparing environmental hazards in different areas or countries to promote actions that may reduce their effects(101). These agencies lead among others(95).

This approach supports analysis of the health status of individuals or groups exposed to the above-indicated environmental risk factors. The results guide public health policies and preventive care(94,98-100). They also help comparing environmental hazards in different areas or countries to promote actions that may reduce their effects(101). The information collected by the international or governmental agencies are available for public consulting(92). These agencies work together to adopt similar measurement standards, units, and methods, and make the data available to the public through web databases and annual publications(93).

Data on air quality or climate could be used to correlate with clinical observations of incidences of EDED in different cities or regions. However, the daily range of pollutants, hazardous agents, confounding factors, and individual variable time-exposure to any of the studied agents can be too large to precisely identify agents responsible for higher EDED incidence in a certain area. These limitations may make it difficult to draw meaningful conclusions. To avoid that, study designs are required to include homogeneous groups with similar habits and comparable exposure times. One report had described that children living close to three petrochemical companies in Nigeria have tetraethyl lead and black carbon tear film (29). Similar studies are necessary to identify the specific pollutants responsible for a cause and effect relationship between an environmental factor and EDED.

CONCLUSIONS

For several years, environmental factors have been known to be associated with DED. A more extensive and detailed analysis of the association between environmental factors and DED suggest that EDED as a DED subtype will aid efforts to pinpoint different factors responsible for this disease. To this end, we propose that combined clinical and laboratory studies can help identify different environmental factors that induce EDED. At this point, we were able to summarize evidence supporting the association of specific environmental hazards such as pollutants and adverse outdoor and indoor environmental factors with EDED.

DED clinical findings and symptoms resulting from environmental factor mediated anterior ocular surface receptor activation induce pro-inflammatory cytokines, chemo attractant expression, and elaboration of extracellular stromal matrix due to increases in myofibroblast expression. These mechanisms induce tear film instability, stromal immune cell infiltration, and disruption of lacrimal gland mediated tear film volume and composition. Constant exposure to environmental factors may allow the clinician to distinguish between acute and a chronic phase of the disease.

Environmental data monitoring and safety limits obtained from international or governmental agencies may help clinicians to associate DED disease stages with environmental factor exposure. Researchers may be aided in identifying relevant stress to apply to their different model systems to pinpoint the mechanisms mediating responses underlying EDED.

Unfortunately, except for using protective equipment to counter specific hazardous environmental agent stresses, EDED treatment is limited to the same medications and interventions available for other
types of DED.(135)Given this limitation, it remains important to promote novel investigative interventions to treat or minimize EDED damage.

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REFERENCES

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