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Review

Indoor air humidity, air quality, and health – An overview

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ABSTRACT

There is a long-standing dispute about indoor air humidity and perceived indoor air quality (IAQ) and associated health effects. Complaints about sensory irritation in eyes and upper airways are generally among top-two symptoms together with the perception "dry air" in office environments. This calls for an integrated analysis of indoor air humidity and eye and airway health effects. This overview has reviewed the literature about the effects of extended exposure to low humidity on perceived IAQ, sensory irritation symptoms in eyes and airways, work performance, sleep quality, virus survival, and voice disruption. Elevation of the indoor air humidity may positively impact perceived IAQ, eye symptomatology, and possibly work performance in the office environment; however, mice inhalation studies do not show exacerbation of sensory irritation in the airways by low humidity. Elevated humidified indoor air appears to reduce nasal symptoms in patients suffering from obstructive apnea syndrome, while no clear improvement on voice production has been identified, except for those with vocal fatigue. Both low and high RH, and perhaps even better absolute humidity (water vapor), favors transmission and survival of influenza virus in many studies, but the relationship between temperature, humidity, and the virus and aerosol dynamics is complex, which in the end depends on the individual virus type and its physical/chemical properties. Dry and humid air perception continues to be reported in offices and in residential areas, despite the IAQ parameter "dry air" (or "wet/humid air") is semantically misleading, because a sensory organ for humidity is non-existing in humans. This IAQ parameter appears to reflect different perceptions among other odor, dustiness, and possibly exacerbated by desiccation effect of low air humidity.

It is salient to distinguish between indoor air humidity (relative or absolute) near the breathing and ocular zone and phenomena caused by moisture-damage of the building construction and emissions therefrom. Further, residential versus public environments should be considered as separate entities with different characteristics and demands of humidity. Research is needed about particle, bacteria and virus dynamics indoors for improvement of quality of life and with more focus on the impact of absolute humidity. "Dry (or wet) air" should be redefined to become a meaningful IAQ descriptor.

1. Introduction

Yaglou (1937) concluded that "Artificial humidification, about which so much is heard on connection with winter air conditioning, was shown in the first part of this paper to be relatively unimportant from the standpoint of comfort and, so far is known, not essential from the standpoint of health. While a relative humidity of between 40 and 60 percent would probably be more normal and perhaps more healthful than between 20 and 30 percent, it is practically impossible to maintain this high range in cold weather because excessive condensation and freezing on the windows and sometimes inside the exposed walls".

Indoor air humidity, in terms of perceived dry air (dryness) and potentially associated health effects is an important parameter (relative (**RH**) or absolute (**AH**)) both in the aircraft and office environment. A long-standing dispute continues about the health relevance of RH and the cause(s) of perceived "dry air", a very common and abundant complaint about perceived indoor air quality (**IAQ**) in office-like environments. Further to this, causation of perceived sensory reactions in eyes and upper airways, among top-two reported symptoms in offices, continue to be a puzzle, despite several identified risk factors that influence the development of eye symptoms have been identified (Wolkoff, 2017); the risks of symptoms in the upper airways remain largely unexplained. Furthermore, there is an increasing recognition of the impact of humidity, e.g. on virus survival and transmission and sleep quality, regarding derivation of a safe limit for indoor air humidity (Derby et al., 2016).

Nagda and Hodgson (2001) reviewed the indoor air literature and concluded that slightly elevated RH would have a beneficial effect on perceived IAQ; in part based on the conclusion that experimental outcomes appeared to be strongly dependent upon the experimental

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design. A conclusion that was further supported by Wolkoff and Kjærgaard (2007). It was unclear, however, whether the conclusion reached by Nagda and Hodgson (2001) would include typical sensory and CNS-related symptoms as commonly encountered in office environments. Contrary to this, the pollutant hypothesis was reintroduced partially based on short-term assessments of the emissions from building materials (Fang et al., 1999) and by Sundell and Lindvall (1993) and Fang et al. (2004). These authors concluded that indoor air pollutants, like volatile organic compounds (**VOCs**), were the most likely cause of reported dry air by exposure to sensory irritants. Furthermore, it was concluded that high RH as well as high temperature were detrimental to the immediately perceived IAQ (a snapshot of perception) by "sniffing" the emission from building materials (Fang et al., 1998). In that context, Fanger (2000) concluded that IAQ should be perceived as "dry and cool" in office environments, i.e. low RH and not too warm. Sun et al. (2009) and Qian et al. (2016) further advocated this stating that the perception of dry air is more likely related to "sensory irritants", despite lack of a clear scientific rationale.

Thus, there is a need for a balanced and integrated analysis of the impact of indoor air humidity on associated health effects as opposed to the well-known problems associated with moisture-damaged buildings (World Health Organization, 2009). As pointed out the relationship between health, indoor air humidity and pollution is complex and remains a challenge (Davis et al., 2016a; Derby et al., 2016). Thus, the focus of this overview is effects in the public domain of perceived IAQ, sensory irritation in eyes and airways, work performance, infection by virus, sleep quality, and the voice.

2. Method

This overview integrates and analyzes studies about how "extended" exposure to low relative (absolute) humidity impacts health, IAQ, work performance, sensory effects in the eyes and airways (sensory symptoms), transmission and survival of influenza virus, sleep quality, and the vocal cord. Searches in PubMed and Google Scholar were carried out for "humidity" in combination with: "airways", "asthma", "eyes", "indoor air quality", "particles", "pungency", "mucociliary clearance", "sensory irritation", "throat irritation", "ocular surface", "sleep quality", and "voice or vocal cords", and combined with own selection of literature compiled during the last decade up to September 2017, cf. Arundel et al. (1986), Derby et al. (2016), Nagda and Hodgson (2001), Wolkoff and Kjærgaard (2007). Health effects of moisture damage (dampness) of construction products and mold-related issues (e.g. microbiological contaminants) and dust mites are excluded from this overview, cf. Hurraß et al. (2017) and World Health Organization (2009).

2.1. Absolute and relative humidity definition

Humidity is usually measured by a hygrometer and reported as relative − % water vapor in the room air relative to the total amount of vapor in the same room air may contain at given temperature; absolute humidity amounts the water in grams per kg of air (g/kg) at a defined pressure. Thus, indoor AH appears to correlate better with outdoor AH than outdoor and indoor RH in some regions, but not in others, in part depending on season, building style, and ventilation (Nguyen et al., 2014; Zhang and Yoshino, 2010).

3. Results of overview

3.1. Offices – symptoms, perception of IAQ (VOCs, particles), and work performance

3.1.1. Symptoms in offices

Irritation in eyes and upper airways are among top-two reported symptoms in office questionnaire studies (Brightman et al., 2008; Bluyssen et al., 2016; Wolkoff, 2013). There are minor differences between the studies which in part reflect the recall period, usually one symptom per week during the last four weeks. The reported prevalence is generally from 20 to 40%.

Several questionnaire studies in offices have shown associations between low RH (5–30%) and increased prevalence of complaints about perceived dry and stuffy air and sensory irritation of the eyes and upper airways, see Table 1. However, many intervention studies have shown

Table 1
Studies in office environments, homes, schools, and hospitals.

Authors Environment	Study	Observation
Angelon-Gaetz et al. (2016) Schools	Teachers (n = 122) reported daily symptoms in 4–12 weeks diaries.	Modest, but not significant, increase in respiratory (asthma-like) symptoms over 5 days, both at low (< 30%) and high RH (> 50%) in comparison to referent teachers (30–50% RH). No effects of RH on cold/allergy symptoms.
Azuma et al. (2015, 2017) Offices	- Workers (n = 3335) in 320 offices responded to questionnaire.	Both studies showed strong correlation between perceived air dryness and report of eye irritation.
	- Workers (n = 3024) in 489 offices responded to questionnaire.	General symptoms were also associated with perceived humidity in the summer season.
Bakke et al. (2007,2008) Offices	Four university buildings, 2 complaint and 2 control buildings. Questionnaire and examination of the precorneal tear film (PTF) stability, nasal patency and inflammatory markers in nasal lavage fluid in university staff members.	Stuffy or dry air was significantly associated with low RH (15–35% RH). Otherwise no significant exposure differences between complaint and control buildings and no significant difference in objective signs.PTF stability (NBUT/SBUT) was improved at higher RH and perception of air dryness was reduced.
Brasche et al. (2005) Offices	Data from office workers (n = 814)	No clear conclusion about RH and reported eye symptoms or PTF stability. Indication that high RH might be protective, and particles associated with epithelial damage of the PTF.
Hashiguchi et al. (2008) Hospital	Temperature and RH measured for 3 months in hospital in sickrooms and wardens during winter. Symptoms and comfort was reported once a week by staff (n = 45) and patients (n = 36). Humidifiers were installed after 2 months in half of the rooms.	Humidification from 33 to 44% RH, on average, resulted in decrease of thermal discomfort and perceived air dryness among the staff, but not among the patients.
Lindgren et al. (2007) Aircraft	Cabin attendants (n = 58) and pilots (n = 22). Double blinded 3–10% increase of RH by ceramic humidifier during long-haul flights.	Significantly lower concentration of respirable particles at elevated RH from 6 to 1 μg/m^3; similar observation for mold and bacteria. Cabin air quality significantly improved at elevated RH by being perceived less dry and fresher.

(*continued on next page*)

Table 1 (*continued*)

Authors Environment	Study	Observation
Lukcso et al. (2016) Offices	Office workers (n = 7637; response rate 49%) in 12 buildings. Subset wore personal sampling equipment and underwent medical examination. Symptoms experienced over the last 4 weeks.	Low RH was significantly associated with lower respiratory and sick-building syndrome-type symptoms, thus suggesting that low RH may exacerbate upper and lower airway symptoms.
Nordström et al. (1994) Hospital	Blinded steam air humidification to 40–45% RH in two units and compared with two control units of 25–35% RH in a 4 months period. Air quality and symptoms were reported before and after intervention in hospital staff (n = 104).	Significant decrease of perceived air dryness and airway symptoms. Weekly sensation of air dryness was 24% in humidified units contrary to 73% in the non-humidified units. Perceived IAQ was unchanged in control unit.
Norbäck et al. (2000) See also Nordström et al. (1994) Hospital	Longitudinal 6 weeks study with blinded steam humidification in hospital with two units with independent ventilation systems, outside of pollen season. Staff (n = 26, 100% female; 14 in humidity group and 12 in non-humidity control group) were investigated before and after humidification applied in one of the units for a period of 6 weeks. Questionnaire and medical examination before and after.	The perception of air dryness was reduced significantly (p = 0.04) from 73 to 36% in the humidification unit by increase of RH from 35 to 43%, while only slightly reduced in the control group (90–81%). Perception of dustiness and stuffy air remained unchanged. No changes in the PTF stability (SBUT), nasal patency (rhinometry), and inflammatory markers in nasal lavage fluid. Cannot be excluded that outdoor RH may have influenced, also, although exposed subjects and controls were investigated on the same days.
Reinikainen et al. (1992) Offices	Office workers (n = 290) and cross-over trial, in two wings. Slight increase of temperature during humidification.	Dryness symptom score (dryness, irritation or itching of the skin and eyes; dry throat and nose) was significantly smaller ($p < 0.01$) during humidification (30–40% RH) compared with the non-humidification phase (20–30% RH). However, the perception of stuffy air increased significantly during humidification, which also included unpleasant odor and dustiness perceptions (not significant).
Reinikainen et al. (1997) Offices	Steam humidification up to 30–40% RH compared with non-humidified units. Cross-over trial, use of naïve panel (n = 20) to assess the perceived IAQ, weekly.	Humidification caused a decrease of the perceived IAQ, strongest among women.
Reinikainen and Jaakkola (2001) Offices	Same office workers as in 1992 study. Cross-over trial in two wings. One wing humidified and the other non-humidified for one week (constant temperature), then switch for a total of 6 weeks. Daily questionnaire.	High temperature conditions increased dryness symptoms and sick-building syndrome symptoms during non-humidified conditions. Increase of RH from about 25–35% resulted in fewer sick-building syndrome symptom complaints. Synthesis of studies: high temperature conditions increased sick-building syndrome symptoms in 4 out of 7 studies; high temperature resulted in an increase of perceived dryness. Humidification reportedly decreased sick-building syndrome symptoms or dryness in 5 out of 11 studies and in 3 studies an increase. Present study showed lower sick-building syndrome symptoms than in non-humidified conditions and alleviation of perceived dryness during humidification. Dryness increased more acutely under non-humidified conditions.
Reinikainen and Jaakkola (2003) Offices	Office workers (n = 368; 71%) returned baseline questionnaire and diaries with information about symptoms or perceptions; 342 diaries from non-humidified (25–26% RH) and 233 from humidified conditions (21–49% RH). Temperature from 21 to 26 °C.	Eye dryness was alleviated, but not significant. Humidification decreased nasal dryness. High temperature increased nasal congestion significantly (especially for AH). Odor perception increased at elevated RH; slightly stronger for AH. "Stuffiness seemed to be associated with humidification". Humidification alleviated nasal congestion.
Sato et al. (2003) Factory	Comparison workers (n = 12) in ultra-low RH (2.5%) with workers (n = 143) at normal RH.	33% versus 18% reported eye symptoms in ultra-dry and normal RH, respectively, but not significantly. Skin complaints were significantly higher at ultra-low RH.
Singh and Jaiswal (2013) Cochrane review	Only two selected double-blind studies.	Conclusion: Little (scanty evidence) benefit from use of dehumidification by use of mechanical devices on the clinical status of asthma patients' sensitive to house dust mites.
Wiik (2011) Offices	Comparison of responses from office workers (n = 484) and green house workers (n = 21).	Deteriorated productivity in offices at dry conditions based on calculating the "indoor productivity index" from questionnaire data.
Wright et al. (2009) Homes	Double-blind placebo control (ventilation) study; intervention in about half of the homes of adults (n = 120) with asthma (dust mite): 54 active with mechanical-heat-recovery-ventilation and 47 placebo. RH went from 45% to 21%.	Carpets were steam-cleaned, new bedding and mattress before activation of the mechanical heat-recovery-ventilation. The addition of mechanical-heat-recovery-ventilation to house dust mite eradication strategies did not reduce mite allergen levels, but did improve evening peak expiratory flow.

AH = absolute humidity. NBUT = non-destructive break-up time of PTF (same as SBUT). RH = relative humidity. SBUT = subjective break-up time of PTF. PTF = precorneal (eye) tear film.

that an increase of RH may alleviate the perception of dry air and symptoms of dry eyes and upper airways, i.e. the longer-term IAQ reduces the symptom reporting; for example, see Hashiguchi et al. (2008) and other intervention studies shown in Table 1.

3.1.2. Perceived air quality

Perceived IAQ is an umbrella of reported descriptors like temperature, draft, odor/smell, stuffy air, and dry and wet (humid) air, and where "dry air" is a common and among the most abundant, e.g. Bluyssen et al. (2016). The perception of "dry air" can be associated with mucous membrane irritation of the eyes (e.g. dry eyes) and upper airways in presence of strong sensory irritants (Doty et al., 2004), which is an important component included in the classic "sick-building syndrome" in non-industrialized buildings. For further discussion of the semantic validity of this terminology, see Wolkoff (2013).

There is some inconsistency about the perceived IAQ by humidification. Thus, the immediately (snapshot) perceived IAQ, not to be confused with symptoms, appears more acceptable in laboratory settings at low RH and low temperature from the assessment of VOC emission from building materials (Fang et al., 1998). However, the thermodynamic condition (i.e. the influence of temperature and RH (Zhou et al., 2017)) and altered VOC emission profiles influences the perception of IAQ (Cain et al., 2002; Fang et al., 1998). For instance, the emission profile of polar VOCs from building materials may alter markedly by increase of the RH, e.g. Fang et al. (1999), Fechter et al. (2006), Huang et al. (2016), Markowicz and Larsson (2015), Wolkoff (1998), but also the temperature including competitive adsorption mechanisms and water solubility (Zhou et al., 2017).

The immediate perception of odor and "stuffy air" increased slightly upon increase of RH in offices (Reinikainen et al., 1997; Reinikainen and Jaakkola, 2003), see Table 1. Thus, the perceived stuffiness may, in part, be caused by the altered VOC (odor) emission profile combined with the thermodynamic effect. However, at the same time, alteration of the inhalable particle chemical composition, the deposition and resuspension that occur from surfaces may differ at different RH, see below. This is especially for particles that predominantly deposit in the nostrils and upper airways, i.e. particle sizes > 2.5 μm, that also may influence the perception of the IAQ, cf. Bottcher (2001). The particle surface-active properties may also influence the nature of perception of IAQ, if the mucus membranes are susceptible, i.e. desiccated or denaturized; for instance, one may speculate whether reporting of "dry air" reflects "slightly irritating" air that is triggered by odor, while desiccated mucus membranes or eyes may interact more readily with active particle surfaces or sensory irritants.

3.1.3. Particles

Particles impact the IAQ and health by their chemical and physical properties, but they may also be carriers of influenza virus. Particle concentration, chemical composition, particle size (diameter) and shape, particle deposition and resuspension, and hygroscopic growth appear to depend on RH, however, the picture is far from complete; the mechanisms behind resuspension are by nature complex that depend on many factors and their interaction (Qian et al., 2014). For instance, larger particles, in general, show larger resuspension by walking at low RH in laboratory settings (Kivistö and Hakulinen, 1981; Qian et al., 2014) and low deposition of particles < 1 μm (Han et al., 2011). This agrees with a 6.4 $\mu g/m^3$ decrease of $PM_{2.5}$ per 10% increase of RH in schools during winter; however, an opposite trend was observed during summer time (Fromme et al., 2007). Increase of RH 3–10% from very low RH in long-haul flights significantly lowered the concentration of respirable particles from 6 to 1 $\mu g/m^3$; similar observation was seen for mold and bacteria (Lindgren et al., 2007). Modeling indicates that shorter people may be exposed to higher concentrations of resuspended particles and pathogens, than taller people, but experimental confirmation is needed (Khare and Marr, 2015).

The resuspension of particles depends on walking style and density; further, particle-substrate interaction and substrate interactions like the microscopic surface roughness (Qian et al., 2014; Qian and Ferro, 2008; Tian et al., 2014). For example, Tian et al. (2014) observed that course particles (3–10 μm) resuspend with a 2–4 higher concentration from carpets in comparison with hard floorings, while no difference was observed for fine particles; however, elevated humidity caused enhanced resuspension on high-density carpets, while hard surfaces showed the opposite effect. Furthermore, the water solubility of the particles is important, thus, resuspension was higher for hydrophobic (e.g. cat and dog fur) respirable particles than hydrophilic ones (e.g. dust mites) (Salimifard et al., 2017). This is in some contrast to observations reported about human emissions of course particles from frictional interaction between human skin and clothing. For instance, Bhangar et al. (2016) reported an increase of emissions of fluorescent particles from human subjects at elevated RH in a climate chamber; however, differentiation between resuspension from the floor and body envelope emissions was not possible. This is further complicated by use of skin moisturizer, where mean emission rates of fluorescent particles differed insignificantly at low and high RH, but lower humidity was associated with smaller emission peak amplitudes of the fluorescent particles (Zhou et al., 2016).

Overall, laboratory experiments indicate more resuspension of large particles and less for smaller particles at low RH, however, surface dependent. More experience from field studies is warranted to understand the mechanisms and chemical nature of the particles that influence the resuspension by indoor air humidity.

3.1.4. Work performance

The "indoor productivity index" in "normal" and well-ventilated offices in buildings, characterized as "not sick", has been assessed by a questionnaire study of 484 office workers and 21 green house employees (Wiik, 2011). The self-assessed productivity depended equally on psychosocial and environmental factors, and RH was identified as important. This agrees with the observation of a few percent reduced visual data acquisition for certain office tasks among young students that were exposed to low RH for 4 h (Wyon et al., 2006); an effect that is expected to become more pronounced among elderly office workers, cf. Wolkoff (2017).

Overall, the immediately perceived IAQ appears more acceptable at low RH and low temperature, which reflects altered VOC emission profiles from material surfaces or altered surface reactions with oxidants. The common reported "stuffy or dry air" may thus be affected not only by alteration in the VOC emission profile, but also at the same time by alteration of the dynamics, composition, deposition and resuspension of inhaled particles; possibly in concert with susceptible eyes or mucus membranes in the upper airways at low RH. This contrasts the outcome of many intervention studies which show the beneficial effects by increase of the indoor air humidity from low RH as shown in Table 1.

3.2. Sensory irritation in eyes and upper airways and odor

3.2.1. Rodents exposed to sensory irritants at different relative humidity levels

The only standardized and validated animal bioassay, which predicts sensory irritation in the airways in humans from airborne chemicals, is the Alarie test (Nielsen and Wolkoff, 2017). It is a mice bioassay, which uses the trigeminal reflex-induced decrease in the respiratory rate, where the 50% decrease (**RD_{50}**) has been correlated with occupational exposure limits (threshold limit values) caused by sensory irritation in the upper airways; furthermore, no-observed-adverse-effect-levels may be predicted according to Kuwabara et al. (2007). Since sensory irritation in the eye and upper airways is mediated by the same nerve system (Trigeminus), the predicted limit is similar for both targets, although eyes may generally show a slightly lower limit as shown in human exposure studies (Doty et al., 2004).

Data from animal inhalation studies about sensory irritation in the upper airways are summarized in Table 2. The studies indicate that sensory irritation in the upper airways is unaffected by low RH; however, o-albumin-sensitized mice appeared to be less affected than normal mice regarding bronchoconstriction at very high formaldehyde levels (Larsen et al., 2013). This observation is compatible with slightly less sensory irritation in nose and throat in asthmatic subjects in comparison to healthy subjects, when exposed to a steady-state reaction mixture of ozone (max 37 ppb) and limonene (36 ppb) [resulting in < 10 ppb formaldehyde (Atkinson and Arey, 2003)] for 3 h in a controlled and blinded chamber study (Fadeyi et al., 2015). It has been proposed that the excess mucus in the airways of asthmatics and in the sensitized animals has a scrubbing (protective) effect, thus explaining the difference between the healthy and asthmatic subjects and similarly in normal and sensitized mice exposed to formaldehyde or a reaction mixture of ozone and limonene (Hansen et al., 2016; Larsen et al., 2013).

No major influence on sensory irritation was observed in mice exposed to ammonia at dry versus humid conditions; however, a minor effect was seen in rats (Li and Pauluhn, 2010). This effect should be considered cautiously due to the breathing parameter, RD_{50} used for comparison, which reflects the combined effect of sensory irritation and time of inspiration, while "time of break" (not reported) before

Table 2
Animal studies: airway (sensory irritation) and ocular surface effects.

Study	Method	Rel. hum. %	Observation
Barabino et al. (2005)	Normal mice (5 for each condition) exposed to dry air in controlled environmental chamber and compared with control mice (n = 30) at room temperature. Ocular surface examined after 3, 7, 14 and 28 days of exposure.	18.5 50–80	Low RH caused a decrease of tear production and increase of fluorescein corneal staining in normal mice compared to control mice exposed at 50–80% RH. A significant drop ingoblet cells after 7 days was observed in mice exposed to low RH.
Chen et al. (2008)	Mice (5 for each condition)) were exposed to controlled dry environment. The ocular surface was examined after 3, 7, 14, 28, and 42 days of exposure at room temperature.	15	Aqueous tear production decreased, while an increase was observed for corneal fluorescein staining, thinning, and accelerated desquamation of the apical corneal epithelium. Upregulated apoptosis was observed on the ocular surface.
Larsen et al. (2013)	Mice (5 for each condition) were exposed to formaldehyde (4–5.7 ppm) for 1 h. Respiratory parameter, time of break, was measured.		Sensitization of mice did not cause increased sensitivity to sensory irritation of formaldehyde at dry conditions.
	Non-sensitized mice Non-sensitized mice Sensitized (ovalbumin) mice Sensitized (ovalbumin) mice.	< 5 85 < 5 85	At humid conditions, sensitized mice were more sensitive to pulmonary effects at high formaldehyde concentrations, while under dry conditions the non-sensitized animals were more sensitive.
Han et al. (2017)	Normal and evaporative dry eye induced rats (6 in each condition) were exposed for 24 h to titanium dioxide particles (< 75 nm; 0.5 mg/ml) by installation and compared with sham condition; corneal clarity and tear samples were measured.	30 50	Evaporative dry eye induced rats were more susceptible (e.g. inflammatory cell infiltration on the ocular surface) to titanium dioxide particles than normal rats.
Li and Pauluhn (2010)	Mice and rat (male) bioassay. Animals (4 per condition) were exposed to ammonia and respiratory rate RD_{50} was measured.	 0 95 0 95	Reduction of RD_{50} (%) 582 ppm, mice 732 ppm, mice* 972 ppm, rat 905 ppm, rat
Lin et al. (2009)	Guinea pigs (7–9 for each condition) exposed to hot (40.5 °C) humidified air for 4 min via a tracheal tube to the lung and compared with control group exposed to humidified room air. Pulmonary resistance was measured.	Not known	(Expiratory airway temperature is significantly higher in asthmatics, 2.7 °C). Elevated tracheal temperature from 36.4 to 40.5 °C induced immediate transient airway constriction mainly mediated through cholinergic reflex, probably elicited by the activation of the TRPV1 temperature-sensitive receptor − water is believed to be a critical factor in delivery of the heat load. Further, increase of total pulmonary resistance. In contrast, hyperventilation with humidified air at room temperature did not alter pulmonary resistance.
Nakamura et al. (2010)	Female rats were exposed in a swing to dry air for 6 h daily period. Lacrimal function and morphology were evaluated after undergoing 10 days of the swing procedure.	25	It was shown that not only excess evaporation of tear fluid but also hypofunction of the lacrimal gland contributes to the pathogenesis of visual display unit-associated dry eye in humans.
Suhalim et al. (2014)	Mice (n = 10) exposed to a controlled drafty dry air environment. After 5 and 10 days eye samples were analyzed.	30–35	Dry air environment has a direct effect on the Meibomian gland function − a 3-fold increase in basal acinar cell proliferation after 5–10 days and abnormal meibocyte differentiation and altered lipid production.
Wilkins et al. (2003)	Mice (4 at each condition). Respiratory rate (RD_{50}) reduction by exposure to ozone/limonene mixture (16 s old) and ozone/isoprene mixture (90 s old) at different RH.	 0 32 0 32	Reduction of RD_{50} (%) By ozone/limonene: 33 22* By ozone/isoprene: 56 42*
Xiao et al. (2015)	Mice (60 for each condition) were exposed for 1, 2, 4, and 6 weeks to controlled dry environment at room temperature, and air velocity 2.2 m/s. Further, mice were housed in normal laboratory conditions. The ocular surface was analyzed.	13 vs 60	Dry environment induced corneal epithelium damage (apoptosis) and stimulated inflammatory cytokine production in conjunctiva and lacrimal gland. Further, lacrimal gland structural alterations were observed.

RD_{50} = concentration that causes 50% reduction of the respiratory rate.
* Statistically significant.

initiation of exhalation is a more specific measure of sensory irritation, cf. (Wolkoff et al., 2012). The animal data agree with statistically unaltered lateralization thresholds for sensory irritation at humid and dry conditions among eight volunteers (Monsé et al., 2016).

Many rodent studies have shown adverse effects on the eye physiology by exposure to low RH, see Table 2. Thus, less tear production and dry spot formation in the (precorneal) eye tear film has been observed (Barabino et al., 2005; Chen et al., 2008) and epithelial damage (Xiao et al., 2015). All in all, the studies show that low RH aggravates the stability of the eye tear film, which becomes more susceptible and consequently initiates a cascade of adverse inflammatory reactions (Wolkoff, 2017). For instance, a destabilized eye tear film relative to a stable one may be more susceptible to inflammatory reactions by exposure to titanium dioxide nanoparticles as shown in a rat model (Han et al., 2017).

3.2.2. Sensory irritation and odor in humans

Induction of sensory irritation in the upper airways (nose) by strong sensory irritants (chemicals) appears independent of the RH in animal studies, see above. This is contrary for odor thresholds in humans. For instance, a lower threshold was found for butanol than at dry conditions (80% vs 30% RH), at least in comparison at hypobaric conditions (Kuehn et al., 2008), while no effect on RH was found for pyridine (Callado and Varela, 2008), which in part agrees with clinical experience (Philpott et al., 2007). The studies, however, are not directly comparable and the contradictory data does not allow for a generalization.

One study at three different geographical locations and humidity indicated a trend of "a higher overall skin irritation level at dryer climatic conditions for both positive (0.1% sodium lauryl sulfate) and negative controls (0.9% saline) (Trimble et al., 2007). Asthmatics may be less sensitive to inhalation of strong water-soluble irritants, like formaldehyde, than non-asthmatics. However, individuals with allergic diseases (e.g. allergic rhinitis) may perceive IAQ and 'dry air' differently than normal subjects and possibly react differently to other pollutants, e.g. unpleasant odors. Thus, more secure and standardized information is warranted about the influence of humidity on odor thresholds.

3.2.3. Ophthalmological investigations of the precorneal tear film and ocular comfort in humans

An intact and stable eye tear film is essential for visual acuity and ocular comfort, in general. The prevalence of external eye symptoms continues to be high in European and Japanese offices (Bluyssen et al., 2016; Yokoi et al., 2015). Retrospectively, the prevalence has not declined substantially during the last decades, despite lower emitting building materials and modern buildings (Bluyssen et al., 2016; Wolkoff, 2013).

Many ophthalmologic studies have demonstrated how fast low RH aggravates the stability of the eye tear film, i.e. break-up or thinning of the eye tear film resulting in less tear production or exacerbation of water loss, see Table 3. This leads to desiccation and hyperosmolarity in the eye tear film and initiation of a cascade of inflammatory reactions

Table 3
Human exposure and field studies at different humidity conditions − ocular surface.

Study	Approach	Rel. hum.%	Observation
Abelson et al. (2012)	Dry eye patients (n = 33) exposed for 1½ h	Low	Decrease of mean break-up area induced by low RH; correlation with other measures of dry eye diseases and demonstration of compensatory mechanisms in dry eye patients.
Abusharna and Pearce (2013)	Healthy subjects (10 men, 2 women) were exposed for 1 h followed by tear and ocular measurements	40 vs 5	Evaporation rate of water, lipid layer thickness, ocular comfort, low RH significantly adversely affected precorneal film stability and production. Tear film parameters became like dry eye patients after 1 h at low RH.
Alex et al. (2013)	Normal subjects (n = 15) and dry eye patients (n = 10) were exposed for 1½ h.	15–25	Significant increase of corneal and conjunctival dye staining (dry spot formation) in both groups, but greater staining in superior cornea in dry eye patients. Eye blink frequency between 30 and 90 min was higher in dry eye patients.
Gonzales-García et al. (2007)	Contact lens-wearers (n = 10) with minimum of symptoms were exposed for 2 hours without contact lens and with contact lens at 2 RHs. Dry eye signs were evaluated before and after each exposure	19 (22 °C) 35 (24 °C)	Without contact lens: Significant changes were observed in comfort, noninvasive BUT, conjunctival hyperemia, and phenol thread test at low RH as opposed to normal conditions (no changes). With contact lens: Same changes were observed in both conditions. These returned to normal after about 1 month, i.e. reversible.
Galor et al. (2014)	United States veteran study. All patients seen in a veteran administration eye clinic between 2005 and 2011; retrospective analysis	National Climatic Data Center and NASA adm	The most important risk factors of dry eye symptoms were shown to depend primarily on air pollution (optical measurement of aerosols) and pressure (high altitude). Furthermore, higher RH and wind speed was inversely associated with the risk of dry eye symptoms.
Hirayama et al. (2013)	Dry eye patients (n = 10) were exposed during minimum 4 h daily visual display unit (VDU) work to Moist Cooling Air Device (MCAD; 100–300 µm droplets) for 5 working days; similarly, patients (n = 10) carried VDU work without MCAD	+/− MCAD in offices	MCAD significantly improved functional visual acuity, lowered BUT and symptom score (less dryness). Strip meniscometry and evaporation rate of water significantly improved. No significant changes in lipid layer stability or corneal staining between the 2 groups. Blink frequency was significantly increased without MCAD.
Lan et al. (2011)	Subjects (n = 12; male/female = 1:1) doing office work at 23 °C and 30 °C	21–22	Ferning test showed an increase of type III and IV patterns that indicate substantial alteration of the precorneal tear film “composition”, i.e. lower tear film quality, at the high temperature.
López-Miguel et al. (2014)	Mild to moderate dry eye patients (n = 19) and asymptotic controls (n = 20) were exposed in climate chamber for 2 hours. Single-item score dry eye questionnaire and diagnostic tests were performed before and after the exposure period	5	Significant increase in corneal staining and significant decrease in fluorescein break-up time were observed in patients and controls. Also, a significant increase in matrix metallopeptidase. In controls: significant decrease of epidermal growth factor and significant increase of interleukin-6 levels were observed after exposure.
Melikov et al. (2013)	Subjects (n = 30) were exposed for 4 h by personalized ventilation (PV) or without at different temperatures and 15 min video recording and analysis of eye blink frequency and Ferning test of tear liquid	+PV 70–26 °C, 28 °C -PV 40–23 °C	Increase of T and RH without PV reduced blink frequency. Only significance at 26 °C/70% RH, not at 28 °C. Use of PV, i.e. 23 °C/40% RH decreased blink frequency significantly in comparison with 26 °C/70% RH, indicating that temperature perhaps is more important than RH. Ferning test showed a decreasing trend in precorneal film quality, by disappearance in Grade I quality going from neutral condition to higher temperature and RH. Use of PV slightly improved the quality of the precorneal tear film. Data, however, should be interpreted with caution. Ferning test should be compared at comparable conditions, thus interpretation of data is difficult.
Madden et al. (2013)	Dry eye patients (n = 3) and normal subjects (n = 3) were exposed in controlled climate chamber. Tear evaporation rate was measured after 0, 5, 10, 15, 20 and 25 min. Noninvasive BUT and tear evaporation rate were determined at 5% to 70% RH in dry eye patients (n = 10) and normal subjects (n = 10); T = 72 °F (22.2 °C)	40	Ten min required for reaching steady-state of the tear evaporation rate (peak after 5 min) and no chance in noninvasive BUT. Dry eye patients had higher evaporation rate and shorter noninvasive BUT than normal subjects at 5% and 40% RH, but not at 70%. Emulsion drops helped.
Nakamura et al. (2010)	Cross-sectional survey of tear film characteristics in 1025 office workers during VDU work.		VDU users have less tear secretion (impaired lacrimal function), less the more VDU use, both on a yearly duration and daily basis. Dry conditions cause less tear secretion. “Human and rat studies provided the evidence that not only excess evaporation of tear fluid but also hypofunction of the lacrimal gland contributes to the pathogenesis of VDU-associated dry eye.” The study suggests that a proper number of eye blinks is required for healthy lacrimal gland function to occur. Since VDU use suppresses the blink frequency, modifications, such as the use of bigger and clearer characters, should be considered when trying to increase the blink frequency, in addition to modifying daily working conditions or lifestyles.
Norbäck et al. (2006)	Aircraft cabin crew (n = 70–79) were exposed to low or elevated (blind) humidity for 8 hours transatlantic flight.	10–14 21–25	Significant improvement of precorneal tear film stability (i.e. longer subjective BUT) and decrease of perceived eye dryness and fatigue.

(*continued on next page*)

Table 3 (*continued*)

Study	Approach	Rel. hum.%	Observation
Paschides et al. (1998)	Three geographically and climatically different groups (n = 55–57, each) were tested for eye tear film stability.	• Dry, warm and heavy pollution • Dry, warm, and low pollution area • Cool, humid and low pollution	The precorneal tear film stability (Schirmer-1 test and BUT) was influenced by low RH and high temperature. The outdoor pollution (traffic) may have impacted the tear film quality differently.
Sunwoo et al. (2006a)	Healthy students (n = 16) were exposed to different RH for 90 min.	10, 30, 50	Significant increase in eye blink frequency below 30% RH.
Takahashi et al. (2010)	Eye steaming after VDU work at different humidity.		Increase of RH at the periocular region improved subjective amplitude of accommodation and near vision.
Tesón et al. (2013)	Dry eye patients (n = 20; 6 males) and dry eye control patients (n = 15: 5 males; 45% RH) were exposed in simulated in-flight condition for 2 hours at 23 °C.	5 45	Tear IL-6 and matrix metalloproteinase increased significantly, while epidermal growth factor decreased significantly. Dry eye patients suffered significantly by lower BUT, tear volume, and an increase of corneal staining. A mild increase of corneal staining was seen in the control patients.
Uchiyama et al. (2007)	Dry eye patients (n = 18) and healthy subjects (n = 11) were exposed to different RH.	20–25 40–45	Evaporation rate increased 100% from normal to low RH in both dry eye patients and healthy subjects.
Um et al. (2014)	Korean adults (n = 16431; age > 30) were analyzed for the spatial epidemiological pattern of dry eye disease prevalence.		Lower RH, sunshine exposure, and degree of urbanization (air pollution) were suggested to be associated with increase of dry eye disease.
Walsh et al. (2012)	Cross-sectional design assessment of patients (n = 111; 56 males; age = 77 ± 8) admitted to acute unit. Dry eye questionnaire, dryness (VAS), noninvasive BUT, hydration, and tear osmolarity.		Dry eye patients showed higher plasma osmolarity, thus indication of suboptimal hydration in comparison to non-dry eye patients. Whole-body hydration appears to be important.
Wang et al. (2017)	The RH was randomly elevated by use of a desktop USB-powered humidifier in a masked crossover study with VDU users (n = 44) for 1 hour. The eye tear film quality was measured, and the eye comfort was assessed by the users.	45–50	BUT increased from 6.4 to 9.0 sec at 50% RH. The lipid layer thickness and tear meniscus were unaltered. The users (36%) of humidifier reported a significant improvement in eye comfort versus 5% without humidifier at 50% RH. 7% of the users reported less comfort at 50% RH and 48% reported less comfort at 45% RH.
Wyon et al. (2006)	Young subjects (n = 30; 13 males) were exposed for 5 hours to different RH.	5, 15, 25, 35	Increased eye blink frequency and eye discomfort and reduced visual data acquisition at low RH.

BUT = break-up time. MCAD = moisture cooling air device. NBUT = noninvasive break-up time. PV = personal ventilation. RH = relative humidity. T = temperature. VDU = visual display unit.

(Wolkoff, 2017). For example, one-hour low RH exposure to healthy subjects resulted in tear film parameters like in dry eye patients (Abusharna and Pearce, 2013).

The instability of the eye tear film may increase the formation of (local) dry spots, which enhances direct exposure of the corneal epithelium to pollutants; thus, the eyes may possibly become more susceptible and react faster to external stimuli like sensory irritants (e.g. formaldehyde) and other aggressive pollutants, e.g. oxidants like ozone and particulate matter (Wolkoff, 2017).

Attempts have been carried out to reduce dry symptoms among office workers by various techniques that locally elevate the humidity. For example, even a modest increase from 45% to 50% RH for one hour showed a significant increase of the eye tear film stability by increase of the non-invasive break-up time followed with a significant dry eye relief (Wang et al., 2017). Similar positive effects have been shown for the use of glasses with moist inserts, e.g. Korb and Blackie (2013); Ogawa et al. (2017); Waduthantri et al. (2015).

Overall, the human eye tear film is susceptible to low RH, which aggravates its stability, and likely the susceptibility to aggressive chemicals and particles, and which potentially may initiate a cascade of reactions like hyperosmolarity leading to inflammatory reactions; however, even modest local increase of RH may be beneficial by dry eye relief. Further studies are necessary to explore the interplay between low humidity, tear film stability and exposure to aggressive indoor air pollutants.

3.3. Human climate chamber studies – airway effects and sleep quality

3.3.1. Airway effects

The major function of the nose and nasal cavity is to humidify and warm inhaled air; thus, the anterior part of the nasal cavity contributes within a short nasal passage to air conditioning of inspired air (Keck et al., 2000). The temperature of the nasal cavity strongly depends on feet temperature; for instance, the conditioning capacity in response to cold-dry-air is significantly higher at 40 °C feet temperature than 30 °C, i.e. the ability of the nose to condition inspired air without concomitant change of volume of the nasal cavity (Naclerio et al., 2007).

Mucous membranes lose water by evaporation and heat in the humidification and warming processes (Cruz and Togias, 2008; Naclerio et al., 2007). Thus, the mucosal function depends strongly on the humidity and heat in the inhaled air, the exposure time, and the health of the individual (Williams et al., 1996). Hundred percent RH at core temperature is moisture neutral, “and preserving maximum mucociliary transport velocity” (Williams et al., 1996); either lower or higher RH will alter the mucous viscosity and the mucociliary activity.

The respiratory epithelium plays an important role by evaporation of water from its surface (desiccation). This continuous need for evaporation may lead to a hyperosmolar environment on the surface of the epithelium. Increased ventilation may result in a larger hyperosmolaric surface that moves more distal, and this may stimulate the epithelial cells releasing inflammatory mediators. Cold-dry-air led to significantly higher osmolarity than methacolin or histamine, thus confirming that the osmolarity in nasal secretions has increased after cold-dry-air challenge (288 to 306 mOsm/kg H_2O) (Naclerio et al., 2007). “Desiccation (dehydration) of the epithelium includes desquamation, leukocyte infiltration, vascular leakage, and mast cell degranulation, all of which may worsen inflammation”. Thus, the epithelial cells may be stimulated to release inflammatory mediators if the hyperosmolaric surface is not restored (Naclerio et al., 2007). Further, hyperosmolar challenge may cause histamine and leukotriene (C4) release. It is concluded that the histamine release is probably caused by hyperosmolar stimuli in mast cells and the release is greater among those responding to cold-dry-air (e.g. asthmatics) than non-responders. Furthermore, in the end, dryness of the epithelium may increase bacterial adherence and allows for greater penetration of foreign species, like particles (Naclerio et al., 2007).

Table 4 shows studies about the impact on lung function in normal and asthmatic subjects exposed to different humidity. For example, asthmatic patients appear to be more sensitive to cold dry air than normal subjects (Hanes et al., 2006; Naclerio et al., 2007). However, for thermally induced asthmatics the issue of airway desiccation, i.e. hyperosmolarity, per se, does not appear to be important; further, there is indication that the "cooling-rewarming gradient, rather than desiccation is important" (McFadden Jr. et al., 1999). The observation that humidity is of less importance among asthmatics is compatible with the studies by Larsen et al. (2013) and Fadeyi et al. (2015). These studies showed that ovalbumin-sensitized mice ("asthmatic") and asthmatics were less affected than non-sensitized mice or normal subjects, respectively, from exposure of formaldehyde or an ozone-limonene initiated reaction mixture.

Nasal mucociliary transport (an epithelial function) is an important factor in exchange of heat and water, and protection of the mucosal interface; this requires an periciliary fluid layer of a certain height (thickness) for an efficient mucociliary transport (Naclerio et al., 2007). Thus, the saccharin mucociliary clearance time in the upper airways was significantly lower in elderly subjects at low RH in comparison with younger subjects, which appear to be less sensitive (Sunwoo et al., 2006a, 2006b). This could be interpreted that the upper airways of elderly are less efficient in achieving moisture neutrality and maximum mucociliary transport. However, young subjects also showed longer clearance time below 30% RH, experienced sensation of dry eyes at entering the exposure chamber, while the sensation of dry nose and throat became significant after 90 min (Sunwoo et al., 2006a). Subjectively, the elderly group had difficulty in feeling dryness in the upper airways (nose), despite longer clearance time, but the young subjects did feel dryness after 180 min. In general, subjects felt greater dryness in the throat. This agrees with a previous study that showed a significant increase in clearance time from 11.9 min at 40–43% RH breathing air for 30 min to 18.5 min at 0.1% RH among healthy subjects (Salah et al., 1988). Sunwoo et al. (2006a, 2006b) recommended RH > 30% to avoid dry eyes and RH > 10% to avoid nasal dryness. At the same time, nasal patency is lower at dry and/or cold air in comparison to room air (Zhao et al., 2011); furthermore, the forced expiratory volume within 1 s (FEV_1) was shown to reduce by increase of water loss from extended dry air exposure (McFadden Jr. et al., 1999).

Overall, except for longer saccharine mucociliary clearance time among elderlies, asthmatics appear to be more susceptible to cold dry air and at the same time more robust to exposure to strong (water-soluble) sensory irritants than non-asthmatics at low RH. While it is well established that RH less than 30% aggravates the eye tear film leading to eye symptoms like "dry eyes", the sensation of dry nose and throat also occurs in the nose and throat after some latency and without pollution, but more pronounced at RHs below 10%. Further studies are necessary to clarify the interplay between clearance time, humidity, and indoor pollution, e.g. particles.

3.3.2. Continuous positive airway pressure in patients

Table 5 shows studies with patients suffering from obstructive sleep apnea. Humidified (heated) air appears to reduce nasal symptoms in the patients, but not quality of life and sleepiness (Ryan et al., 2009; Nilius et al., 2008, 2016), but methodological issues may obscure the result, e.g. sleepiness and quality of life, according to Ruhle et al. (2011) and Ugurlu and Esquinas (2016).

Benefits of an increase of RH in bedrooms is controversial in view of the consensus that elevated humidity (water activity) in moisture-damaged building constructions is associated with adverse health effects, e.g. by increase of the exposure risk to fungi, mildew, dust mites, etc. (World Health Organization, 2009); however, increase of bedroom RH has been proposed to have a beneficial effect (Myatt et al., 2010).

Overall, based on the studies, humidified breathing air appears to be beneficial for high-risk patients with nasopharyngeal complaints (Ryan et al., 2009; Nilius et al., 2008, 2016). However, effects on sleepiness and quality of life are unclear and need further documentation. More controlled field studies are necessary to identify the effects of temperature and humidity in bedrooms and associated ventilation for further substantiation.

3.4. Influenza virus survival and transmission

Table 6 shows influenza virus survival and transmission studies at different air humidity. Cold temperature and low RH has been associated with increased occurrence of respiratory tract infections, in line with increased survival and transmission efficiency of influenza virus, e.g. from coughing. Thus, RH > 40% greatly reduces the infectivity of virus, e.g. Lowen et al. (2007); Mäkinen et al. (2009); Noti et al. (2013); Myatt et al. (2010). For instance, Myatt et al. (2010) estimated that an increase of RH to 47% reduced the influenza survival by 17–32% with an operating humidifier in a bedroom. Furthermore, it has been modeled that low temperature and low AH prevents disruption of the influenza virus as opposed to higher temperature and humidity (Koep et al., 2013; Ud-Dean, 2010).

Several studies indicate favorable survival conditions for some influenza viruses at cold and low RH (see Table 6). Experimental inadequacy of the studies should be considered carefully together with the overall complexity of transmission and survival, and associated mechanisms of infection (Memarzadeh, 2012; Yang and Marr, 2012). At least three mechanisms have been proposed, cf. Memarzadeh (2012); RH interacts with the host's airways, i.e. desiccation of mucus membranes in nose and upper airways may cause epithelial damage and reduced mucociliary clearance (an important defense mechanism), thus the airways may become more susceptible to viral infection. Second, RH impacts the virus-aerosol stability that depends on the physical-chemical properties; thus, virus with a lipid envelope are more stable in dry air as opposed to a non-lipid virus envelope (Morawska, 2006). For instance, high RH decreases the survival of lipid-enveloped virus, like influenza A and influenza b (Schaffer et al., 1976; Tang, 2009; Teller, 2009). Third, RH impacts virus/droplet dynamics, i.e. size, surface properties, water content, and consequently transmission and deposition, etc. Probably, all three mechanisms act in a concerted manner. Perhaps, more important is the strong association identified between AH and influenza survival and transmission as reviewed by (Lipsitch and Viboud, 2009). Finally, it has been hypothesized that disease transmissions could depend on resuspension of floor dust, thus shorter people may be exposed to higher levels of infectious particles than taller ones (Khare and Marr, 2015); for resuspension of particles, see the subsection "Particles".

Overall, many studies have shown that survival and transmission potential of influenza viruses are inversely associated with AH rather than RH in wintertime, e.g. Lipsitch and Viboud (2009); Metz and Finn (2015); Shaman and Kohn (2009); Shaman et al. (2010). This, in part, agrees with a large cross-over study among military conscripts (Jaakkola et al., 2014). Thus, indicating that cold and low RH conditions favor survival and transmission for some influenza virus, which also include viruses like RS virus, human rhinovirus, and avian influenza virus, e.g. Ikäheimo et al. (2016) and Davis et al. (2016b). However, the opposite has been observed for other virus types (Morawska, 2006; Weber and Stilianakis, 2008). Thus, the mechanisms of survival and transmissions are far from fully understood and generalization about viral transmission and survival, due to the complexity, is not applicable, but should be dealt with virus-by-virus, cf. (Morawska, 2006; Weber and Stilianakis, 2008). Clearly, ventilation rates of fresh and adequately humidified air and temperature play an important role that needs more research attention for substantiation about the

Table 4
Human exposure studies at different relative humidity conditions – the airways.

Study	Approach	Number of subjects	Age years	Observation
Baroody et al. (2008)	Double-blind, placebo- controller, cross-over, clinical trial of patients.	20		Nasal allergen challenge probably initiates nasal and a nasal ocular reflex.
Cruz and Togias (2008)	Review paper about upper airway reactions to cold dry air in context of cold-air rhinitis.			It is proposed from that cooling and water loss/hyperosmolarity are key candidates for a clinical response. However, it is argued that water loss/hypertonicity is more important, but the two stimuli work in concert. Hyperosmolarity stimulates the sensory nerves that generate a central reflex (contra-lateral secretory response), but can also release inflammatory biomarkers (neuropeptides) by the same nerves.
Freed and Davis (1999) animal	Canine exercise-induced model to investigate hyperventilation at warm humidified air vs dry air.			Dry air challenge increased peripheral airway resistance, the airway surface volume, and the surface osmolarity. Data support that changes in airway osmolarity during hyperventilation initiate peripheral airway constriction.
Hanes et al. (2006)	Comparison of the response of subjects with allergic rhinitis (AR) and asthma (ARA) and subjects with only AR to cold dry air.	24 (ARA) vs 17 (AR)		Patients with ARA were more responsive to cold dry air than subjects with AR alone.
Hashiguchi et al. (2013)	Young healthy male subjects were exposed for 6 h to 10% and 60% RH and pressure (sea level and 2000 m altitude (= low pressure), independently.	14	23	Body fluid loss was significant at low pressure, but combined low pressure and low RH increased the loss even further. Blood viscosity increased also, but low RH alone did not alter the blood viscosity significantly; this, however, cannot be excluded as a possibility, i.e. more subjects required.
Kalhoff (2003)	Review paper about patients with asthma and chronic bronchitis and dehydration.			Still unclear about mild dehydration as risk factor of broncho-pulmonary disorders.
Khosravi et al. (2014)	Allergic rhinitis (AR) patients and healthy subjects (HS) were exposed for 4 min to hot (49 °C; 75–80% RH) humid air and room air (21 °C; 65–75% RH), respectively, during hyperventilation.	7 (AR) 6 (HS)	49 21	Coughs/min in AR patients increased from 0.1 before challenge to 2.4 during and 1.8 first 8 min after end of challenge, for hot air exposed, only. The hot air challenge also caused respiratory discomfort (throat irritation) among AR patients. No effects seen among healthy subjects. Bronchoconstriction was not seen in both groups. Upper airways seem to be triggered by hot air.
Kim et al. (2007)	Prospective trial of 2 groups of adult patients under general anesthesia: controls did not receive warm and humidified air (27 °C; 76% RH), while another group received warm and humidified air (36 °C; 99.5% RH).	200		No appreciable differences in complaints after active warming and humidification of inspired gases (air) after 2 h.
Kuehn et al. (2008)	Male volunteers exposed to 30% or 80% RH and butanol.	27	22 ± 6	High RH showed lower odor threshold for butanol, i.e. enhanced sensitivity.
Lindemann et al. (2003)	Nasal airway resistance was measured in healthy subjects by active anterior rhinomanometry and compared with intranasal RH at different locations.	15	30 (25–42)	Degree of water saturation did not correlate with active anterior rhinomanometry, i.e. no correlation between nasal resistance and water vapor saturation at different anterior nasal segments during the nasal daily cycle.
McFadden Jr. et al. (1999)	Thermally induced asthma was investigated by mucosal dehydration in subjects carrying out isocapnic hyperventilation of dry air at constant level for max 8 min. Lung functions (FEV_1) were investigated at cold (− 12.5 °C) and ambient (24.3 °C) T. Water loss in intrathoracic airways was calculated.	8	28 ± 2	● Less water loss at cold temperature and FEV_1 decreases as water loss increases. ● The effect of water loss increases with time. ● $\%\Delta FEV_{1cold8min}$ = 30%, water loss = 4.7 mg ● $\%\Delta FEV_{1warm8min}$ = 16%, water loss = 7.1 mg The issue of airway dehydration, i.e. hyperosmolarity, per se, does not appear to be of major importance for thermally induced asthma. "When respiratory heat exchange increases in asthmatics the intensity of obstruction follows suit"; a "cooling-rewarming gradient, rather than airway desiccation".
Melikov et al. (2013)	Students (n = 30) were exposed to high temperature (26 or 28 °C; 70% RH) for 4 h and compared with baseline (23 °C, 40% RH) and with additional PV (personal ventilation: 24 °C, 40% RH).	15 male 15 female		The exposure to high T and RH results in lower acceptability of the thermal climate. The subjects' controlled use of a PV improved the thermal sensation and acceptance of climate. Performance appeared to decrease at high temperature and RH. Use of PV improved, i.e. the ability to work was higher during PV conditions.
Salah et al. (1988)	Saccharin mucociliary clearance time and nasal breathing were measured after 30 min exposure of non-smoking subjects (n = 11) to dry air (0.1% RH) or room air (40–43% RH).	6 males 5 females	17–38	Saccharin mucociliary clearance time was significantly longer at breathing dry air (18.5 min) versus room air (11.9 min).
Sunwoo et al. (2006b)	Saccharin mucociliary clearance time, hydration state of skin, transdermal water loss were measured in non-smoking elderly and students. Rating of thermal, dryness and comfort. Experimental conditions: Precondition: 25 °C/50% RH (50 min); exposure for 180 min: 25 °C at 10%, 30% and 50% RH.	8 students 8 elders	22 ± 1 71 ± 4	Saccharin mucociliary clearance time was significantly longer in the elderly group at 10% RH after 90 and 180 min of exposure. No change in saccharin mucociliary clearance time in the students at the different RH.
Sunwoo et al. (2006a)	Saccharin mucociliary clearance time, hydration state of skin, transdermal water loss were measured in non-smoking male students. Rating of dryness and comfort. Experimental conditions:	16 students	23 ± 3	The eyes and the skin become dry below 30% RH; below 10% RH nasal dryness as well as eyes and skin. 10% RH, but not 30%, decreases saccharin mucociliary clearance time. Skin hydration state affected at 10% and 30% RH, only.

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Table 4 (*continued*)

Study	Approach	Number of subjects	Age years	Observation
	Precondition: 25 °C/50% RH (50 min); exposure for 120 min: 25 °C at 10%, 30% and 50% RH.			
Zhao et al. (2011)	Nasal patency was rated by subjects (n = 44) when breathing under controlled conditions from 3 different boxes: Room air 24 °C, 49% RH Dry air 25 °C, 27% RH Cold air 12 °C. 59% RH	20 males 24 females		Both temperature and humidity contributed significantly to the perception of nasal patency rating. Nasal mucosal cooling (heat loss) is the underlying stimulus in the individual's perception of patency and trigeminal input.

cHH = controlled heated breathing tube humidifier. PV = personal ventilation. T = temperature.

Table 5
Human chamber studies and sleep quality.

Study	Approach	Number of subjects	Age years	Observation
Nilius et al. (2008)	Patients (n = 19) with obstructive sleep apnea. Effect of controlled heated breathing tube humidifier (cHH) on nasal symptoms and quality of life during continuous positive airway pressure.	14 male 5 female	55 ± 10	cHH improves subjective rating of nasal and pharyngeal symptoms (dry nose, dry mouth, dry throat) during continuous positive airway pressure. After 4 weeks at home the use of cHH also showed lower symptoms, but no effect was seen on sleep quality. In summary, cHH improves side effects (symptoms) of continuous positive airway pressure, but not quality of life, cf. (Ruhle et al., 2011). cHH might be beneficial for patients preferring a cool bedroom temperature.
Nilius et al. (2016)	Patients with obstructive sleep apnea were divided in high risk complaint group (n = 35) and low risk complaint group (n = 37). Effect of controlled heated humidification on nasal symptoms, improvement of sleep, quality of life during continuous positive airway pressure.	72	52 ± 8	Heated humidification in breathing air showed a positive effect by reduction of nasal symptoms, and improvement of sleepiness and quality of life among the high-risk complaint group.
Ryan et al. (2009)	Patients with obstructive sleep apnea syndrome exposed to dry air, humidified air with or without nasal steroid application in nasal continuous positive airway pressure therapy for 4 weeks.	125		Humidified air decreased the reported frequency of nasal symptoms in unselected obstructive sleep apnea syndrome patients (28%), but not in the other groups; compliance, sleepiness, and quality of life remained unchanged.

cHH = controlled heated breathing tube humidifier.

Table 6
Survival of influenza virus.

Study	Approach	Observation
Jaakkola et al. (2014)	Case cross-over study among military conscripts (n = 892); 66 influenza A (57) and B (9) episodes − in a cold climate.	"The risk of contracting influenza was positively associated with mean T and AH. A decrease in both temperature and AH (max change) during the three days prior to seeking medical consultation increased the risk of influenza". "According to these results, a 1 °C decrease and 0.5 g/m^3 decrease in AH increased the estimated risk by 11% (OR1.11; 95%, CI 1.03–1.20)".
Khare and Marr (2015)	Model study of resuspension of dust and influenza virus.	"Shorter people (children) may be more exposed to higher levels of resuspended particulate matter than would taller ones". It is hypothesized that "particle resuspension could be a mode of disease transmission".
Koep et al. (2013)	Automated sensors for humidity and CO_2 levels in two schools and humidification. Estimation of virus survival.	Strong association between outdoor and indoor AH. Estimated decrease of virus survival at elevated AH. "Classroom humidification may be an approach to increase indoor AH to levels that may decrease influenza virus survival and transmission".
Lowen et al. (2007)	Influenza virus transmission studied in guinea pigs as model host in environmental chamber at different temperature and RH.	Both cold temperature (5 °C) and dry conditions (20%) favor spreading of influenza virus (transmission), while no transmission at 30 °C and 35% RH or 80% RH. Transmission efficiency depends on RH and is inversely correlated with temperature. Transmission sensitivity to RH is largely due to virus stability. Cold temperature does not appear to impair the innate immune response. Hypotheses about mechanisms in variation in transmission: 1. Breathing dry air may desiccate nasal mucosa, leading to epithelial damage and/or reduced clearance, render the host more susceptible to virus infection. 2. Stability of virus in aerosols shown to be maximal at low (20–40% RH) and minimal at 50%, and high at 60–80% RH. Stability appears to be a key determinant (except at high RH where transmission is absent). 3. Low RH enhances evaporation from exhaled bioaerosols leading to small droplet nuclei that remain airborne for extended period, thus increasing the opportunity for transmission of pathogens; conversely, high RH causes water uptake in droplet nuclei, increase in size and increase of deposition.
Mäkinen et al. (2009)	Population study (n = 892) where diagnosed respiratory tract infections were compared with outdoor temperature and RH.	Cold outdoor temperature and low RH were associated with increased occurrence of respiratory tract infection. Upper tract infection was associated with AH and 1 g/m^3 of AH increased the risk of infections by 10%. A decrease in temperature and RH preceded the onset of infection.
Myatt et al. (2010)	Model study of survival of aerosolized virus in single-family residences by moisture control. Estimation of emission rates for virus was particle specific. Sleep quality included tidal breathing and coughing.	Output of 0.16 kg/h water increased median sleeping hours AH/RH levels of 11–19% compared to without a humidifier present. The associated decrease in influenza virus survival was 17–32%. Distribution of water through a whole residence increased RH 3–12% and reduced influenza virus survival 8–14%.
Noti et al. (2013)	Infectivity of aerosolized virus was studied in a chamber with a manikin and a coughing simulator emitting influenza virus.	The infectivity was ca. 75% at RH ≤ 23%, but only 15–22% at RH ≥ 43%. "Maintaining indoor air at RH > 40% will significantly reduce the infectivity of aerosolized virus".
Shaman and Kohn (2009)	Reanalysis of previous studies.	AH provides a coherent physical explanation for variability of influenza virus survival and transmission. The transmission of virus decreases with vapor pressure.
Silva et al. (2014)	Correlation of 11953 hospitalizations (adults and children) with respiratory symptoms.	22% of infections in adult patients admitted to emergency departments were caused by respiratory viral infections. Influenza-like illness was associated with AH, use of air conditioning, and presence of mold in home. "Severe acute respiratory infection cases were found to be negatively related to RH."
Ud-Dean (2010)	Model work and prediction of survival (persistence) and transmission of influenza virus.	Example shows that "at lower temperature low AH prevents disruption of the virus. On the other hand, higher temperature and higher RH prevent desiccation of the virus".

AH = absolute humidity. RH = relative humidity.

influence of humidity and associated mechanisms of infection, cf. Yang and Marr (2012); Yang et al. (2012), especially in the field. Jaakkola et al. (2014) hypothesized that "Higher temperature approaching 0 °C may favor transmission and survival of the virus itself, but a decline in temperature and humidity may make the host more susceptibility through body cooling and/or drying of the respiratory tract". It is suggested the combination relatively warmer temperature and higher AH followed by a sudden decline in these meteorological parameters have the strongest impact on the risk of influenza". Air-conditioned cold and dry air in offices, thus would favor survival and transmission for certain airborne viruses, but not others (Morawska, 2006; Tang, 2009; Teller, 2009).

For bacteria, the situation about survival and transmission is even more complex than viruses, thus, likewise requiring individual assessment (Tang, 2009).

3.5. Vocal cord effects

Table 7 shows studies about effects on the vocal cord by humidity. Desiccating challenge may be detrimental to voice production in individuals with vocal fatigue, even in young and vocally healthy males (Hemler et al., 1997; Tanner et al., 2016); further, it has been shown that isotonic saline nebulization decreases the self-perceived effort among the males (Tanner et al., 2016). However, extended daily exposure to high RH should be considered cautiously, because it may for still unknown reason increase the risk of respiratory symptoms (Angelon-Gaetz et al., 2015); this, in contrast to the positive observations about improved sleep quality, see above. Teachers' asthma-like symptoms increased modestly, but not significantly, at both low and high RH in schools (Angelon-Gaetz et al., 2016).

Overall, there are indications that both too high or too low RH may be associated with adverse effects of virus survival and asthma-like

Table 7
Effects on the vocal cord and voice.

Study	Approach	Observation
Hemler et al. (1997)	Subjects (n = 8) exposed to different RH, dry (2%), normal (45%), and high (100%) for 10 min at 23–24 °C. Analysis of voice perturbation during producing repeatedly a sustained/a/of controlled pitch and loudness.	Dry conditions increased voice perturbation compared to normal and humid air. No difference was observed between normal and humid air exposure.
Sivasankar et al. (2008)	Subjects (n = 8) reporting vocal fatigue and (n = 8) matched controls were tested. Phonation threshold pressure was measured during oral breathing in humid environments.	Drying challenge may be detrimental to voice production in individuals with vocal fatigue. It is suggested that short-term oral breathing may cause dehydration to impair compensation.
Tanner et al. (2016)	Young (n = 10; 22 years) male singers and male non-singers (n = 10) underwent double-blinded exposure to oral breathing laryngeal desiccation challenge for 30 min using medical grade dry air (< 1% RH) followed by nebulized isotonic saline (3 or 9 ml).	Self-perceived effort and dryness increased (worsened) after challenge and decreased after the saline nebulization. No consistent changes were observed for phonation threshold pressure and cepstral spectral index of dysphonia for sustained vowels and connected speech, self-perceived vocal effort, mouth and throat dryness. Young, vocally healthy men may not experience physiologic changes in voice production associated with laryngeal desiccation.

symptoms. This should be seen in view some of the reported beneficial effects of reduced virus survival at elevated humidity in contrast to dry and cold conditions; however, generalization is not possible. There are anecdotal reports about "dry air" and problems among art performers (e.g. singers); however, the few studies (Table 7) identified indicate that extreme dry conditions may be detrimental in conjunction with vocal fatigue and saline nebulization may be beneficial. It should be considered that vocal comfort among young healthy subjects may differ from elderly subjects. Furthermore, other pollutants, e.g. with desiccating properties, should be considered.

4. Discussion and conclusion

Reporting of "dry air" or "dryness" continues to be a major complaint in office-like environments, e.g. (Bluyssen et al., 2016; Brightman et al., 2008; Reijula and Sundman-Digert, 2004) and anecdotal reports about detrimental voice performance in dry conditions flourish in the artistic milieu. This is surprising in view of the continued effort to develop and use low emitting building materials and consumer products during the last decades, e.g. by implementation of national labeling schemes for emission testing (Wolkoff, 2003), a change to lower room concentrations of VOCs by lower material emissions (Tuomainen et al., 2003), and use of less volatile organic compounds (Weschler, 2009), if the complaints are associated with indoor VOCs, as re-advocated by Sundell and Lindvall (1993) and Fang et al. (2004). For instance, Qian et al. (2016) argued that parents' perception of both dry and humid air is associated with the presence of sensory irritants, especially dry air, despite an organ of sensing humidity by inhalation is non-existing in humans (Nagda and Rector, 2003; Wolkoff and Kjærgaard, 2007). Thus, from a semantic point of view "dry air" or "humid air", that is different from the symptom "sensing of dryness" (e.g. dry eyes), appears to be composed of different perceptions and associated causes, e.g. rhinitis sicca (Hildenbrand et al., 2011). Further, it is unclear whether perceived "humid or wet air" could be confused by the body sensation of feeling humid (sweaty). Trigeminal nerve endings are known to respond to innocuous cooling via activation of TRPM8 receptors (Lumpkin and Caterina, 2007).

The Qian et al. study does not present data nor RH measurements that support their statement about "dry air" (versus "humid air") caused by sensory irritants. From a toxicological point of view, however, reported concentrations of VOCs in both office and residential environments, in general, are orders of magnitude below thresholds for sensory irritation in the eyes and airways, perhaps with the exceptions of formaldehyde and acrolein (e.g., Huang et al., 2017), known emitters from construction products, combustion, and ozone-initiated reactions (Salthammer et al., 2010).

The prevalence of "dry air" more than doubled from one-man cellular office to open space office; further, both eye and nose irritation doubled (Pejtersen et al., 2006). Pejtersen et al. conclude: "It seems that perceived dry air is something different from humidity and there is a need to validate this question" and Wiik (2011) conclude "real cause of the sensation of dry air is dusty air". One may speculate about the sensation of odor (pungent or moldy) might trigger the sensation of "dry air", possibly in concert with the physiological effects of low RH on the eyes and upper airways. Further, unrecognized pollutants could play a role by themselves or in (synergistic) combination with the former loads, also see below. Furthermore, if the "sense of dryness" is caused by stimulation of trigeminal nerve endings, it is fair to speculate that irritated or dry eyes may cross interact with nerve endings from the nose and vice versa, cf. Baroody et al. (2008). On the other hand, several epidemiologic studies have shown associations between low RH and complaint rates and intervention studies have demonstrated the beneficial effect of elevating the humidity (Table 1). Furthermore, aggravation of the eye tear film stability by exposure to low RH results in desiccation, hyperosmolarity and inflammatory reactions in the eye (Table 2 and Wolkoff (2017)). Thus, the merged information about the impacts of VOCs and particles versus low RH favors the latter as an important parameter to consider for assessment of eye and upper airway complaints in office-like environments.

The overall mechanistic picture is that dry (and cold) air desiccate the airways leading to hyperosmolarity, which stimulates the sensory nerves generating a reflex response and possibly release of inflammatory biomarkers (Cruz and Togias, 2008). Further, dry air challenge may increase peripheral airway resistance, airway surface volume, and increase the osmolarity in the airways, which may initiate airway constriction in canine, in case of no moisture neutralization (Freed and Davis, 1999), and reduced mucociliary clearance time. This may cause dryness of the mucocilia thus compromising its defense mechanism from influenza virus, which for influenza viruses and others has a greater survival time at low humidity and low temperature. Furthermore, the defense mechanism may also be compromised by aggressive air pollutants.

Synergistic effects may occur between low RH and air pollutants. For instance, in a large cross-sectional study low RH and ozone were associated with dry eye symptoms and dry eye diseases (Huang et al., 2016). Further, evaporative dry eye rats were shown to be more susceptible to titanium dioxide nanoparticles than normal rats (Han et al., 2017). It is reasonable to hypothesize that low RH has aggravated the eye tear film stability, thus becoming more susceptible to aggressive chemicals like ozone or its reaction products with chemically reactive VOCs or particles. Surface active compounds like benzalkonium chloride and particles like quartz may also cause compositional changes of mucus membranes (Zhao and Wollmer, 2001), thus becoming more susceptible to low RH and aggressive pollutants and mimic "dry air".

In conclusion, elevated RH may reduce complaint rates and favor work performance in offices in comparison with very dry conditions, but more information is needed to understand how humidity influences symptom reporting and the performance, especially among the elderly population. Low RH aggravates the eye tear film stability and physiology, and the osmolarity of the upper airways; even slightly elevated humidity may be beneficial and relieve dry eye symptoms. Thus, personal adjustment of humidity and temperature appears to be the way forward towards a satisfactory workplace. Furthermore, elevated humidity may improve sleep quality and reduce effects on the vocal cord, but more substantiation is required. Low and cold RH favors the survival and transmission of many influenza viruses, but the issue is complex for generalization of associated mechanisms, thus, more controlled indoor field experiences is warranted. Furthermore, better understanding is required how humidity influences particle dynamics, resuspension, and their physiological impact on the eyes and the airways as function of their surface chemistry.

There is an increasing trend to apply AH rather than RH as a parameter for comparison and identification of associations, also considering sometimes better correlation between outdoor and indoor AH than between RHs. However, most of all, it is pertinent to distinguish between elevated moisture (activity) in construction materials and behind, elevated RH resulting in condensation on surfaces, and RH in the breathing and ocular zone. Furthermore, there is a need to reconsider the causes and physiological meaning of the semantic incorrect and confusing dry/wet air parameter by identification of its causalities.

Declaration of interest

The author declares no conflicts of financial interest. No-one has seen the manuscript before submission.

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