Session 2 SBS, Irritation, Odours

Perceptions, subjective symptoms and syndromes related to IAQ and their use in guideline settings

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INTRODUCTION

Definitions

Health is a state of complete physical, mental and social well-being and not merely the absence of decease or infirmity (WHO 1948). The effects of interest indoors therefore include both adverse effects and changes of well-being. Building-Related Illness (BRI) is a group of known causalities between symptoms and indoor exposures to air pollutants. Generally, the causalities have a uniform clinical picture and a specific cause of the complaints. Many BRIs´ are low exposure levels manifestations of adverse effects known from high exposures e.g. occupational exposures. The symptomatology is important for diagnoses of adverse effects at low exposure levels indoors. The prevalence of building-related symptoms (BRI) is commonly used to characterize the indoor air quality (IAQ) in office buildings (Niemela et al 2006). An association may exist between BRI and productivity or sick leave (Niemela et al 2006).

Objective health effects are quantifiable changes or signs observed by an independent observer (not the exposed). In contrast, symptoms and perceptions are personal experiences or judgements made by the exposed occupant. Symptoms are unspecific i.e. many exposures may cause each of them. Therefore they do not alone identify the exposure cause. For each symptom multiple response modifiers and multiple biases are possible and different persons may have different spectrum and intensity of symptoms. Also, most indoor exposures may cause a number of different signs and symptoms. Therefore, objective measurements of effects are preferred and subjective ratings should be substituted by objective measurements where possible but few are available. On the other hand, objective measurements are expensive and time consuming, a fact which in many cases prevent their use and in the absence of instrumentation for chemical detection of small amounts of some air pollutants, the senses remain the most sensitive indicator system (Berglund et al 1992). Added to this is that discomfort is subjective by nature and cannot be measured without subjective evaluations. Many symptoms are therefore important *per se*, and cannot be substituted by objective measurements.

Aims

This presentation is aimed at both an update on the biological background for known symptoms and perceptions in IAQ science and practice as well as presenting some of the newest literature in the field. In addition recommendations are given on how to use symptom's and perception's reports in field investigations and IAQ sciences. The paper discusses how substitution of subjective evaluations can be made with objective measurements, and if IAQ guidelines can be defined for signs and subjective symptoms. Finally, recommendations are given on guideline settings for IAQ.

This review includes literature younger than a review made by Berglund et al (1992). It does not pretend to be complete but merely summarizes uses of symptoms and perceptions during the last 5-7 years in IAQ research and managements of buildings. The focus is on symptoms and subjective ratings, not on objective health effects.

BRIEF DESCRIPTION OF SYMPTOMS AND PERCEPTIONS AND THEIR CAUSES

Indoor airborne exposure of humans to indoor pollutants may either affect sensory systems or result in tissue changes. Table 1 summarises some of the biological reactions or processes which may be active in human responses to poor IAQ.

The chemical sense

The chemical senses include specialised receptors for odours and irritants in eyes, facial skin and nose cavity. These senses incorporate n. Olfactorius (odours) and n.Trigeminus (irritants). Most odorous compounds are also irritants and visa versa and the chemical sense acts as a warning system (Berglund et al 1992). Mixtures of pollutants may interact and one odorant may mask other odorants (Pan et al 2000). The time course of effects may show adaptation or accumulation of effects which create problems for the interpretation of causality.

Unspecific pain and irritative receptors

Unspecific pain and irritative receptors in the skin or mucosa of eye, nose, throat, and air ways are other sensory systems active in response to indoor air pollution. These senses detect the status of the tissues including presence of absorbed irritants or initiate release of irritating signalling compounds or reflexes in the exposed tissue.

Visual observations

Visual observations are involved in observations of skin rashes, smog, or dust in the air and thus influence the evaluation of the effects of poor IAQ.

Immunological responses

Immunological responses to IAP include diseases such as allergic asthma and extrinsic allergic alveolitis (hypersensitivity pneumonitis) which are the two most serious allergic diseases caused by allergens in indoor air. Allergic rhinoconjunctivitis and humidifier fever are other important diseases. The biological mechanisms include

immunological specific IgE sensitisation to an airborne allergen. The type of symptoms observed in allergic asthma is characterised by reversible narrowing of the lower airways leading to difficulties in breathing, tightness of breath, respiratory sounds etc. Other symptoms are itching of the eye and/or the nose, sneezing, watery nasal secretion and some stuffiness of the nose. Pulmonary function during an attack shows an obstructive pattern in serious cases together with reduced respiratory ventilation capacity. Many objective measurements are available but may not apply at low indoor exposure levels where the symptomatology becomes more important.

Inflammation

Two types of sensory irritation appear in the literature to be related to indoor climate and air quality: a primary sensory irritation caused by direct stimulation of sensory cells by environmental exposures and a secondary irritation following changes in the skin, mucous membranes, or other tissues (Berglund et al 1992). Each of these may subsequently lead to the other. Often inflammation is a direct effect of chemicals on the tissue cells leading to cell damages. Through release of mediating compounds, the cells may signal the need of activation of defensive responses. Inflammation is characterised by a sensation of heat ("calor'), redness ("rubor"), swelling ("tumor"), pain ("dolor") and a certain loss of function in the tissues affected. Non allergic asthma type of responses may be related to inflammatory responses. Irritative effects on tissues can be a considerable annoyance either in terms of severity of effects on an individual or in terms of the number of persons affected. Irritative effects causing tissue changes in the skin and mucous membranes have been reported in many forms, although they have seldom been seen in an adverse form to follow exposure to normal indoor air (Berglund et al 1992).

The body's signalling systems

Body signalling systems may be activated by biomarkers or neural activity. These reactions follow both from immune and inflammatory type of responses and include biomarker or mediator compounds released in the tissues and neural activity in the form of reflexes. Both are signaling the status of the body and initiate defensive responses where needed immune responses or weak irritative reactions may lead to release of signalling compounds or biomarkers such as histamine or cytokines. These compounds may by themselves be irritative in the tissue and may thus accelerate the irritative effects. These responses may be observable as rashes, skin reddening etc. Neural reflexes are often defensive reactions. The symptoms are related to watering eyes, secretion of mucosa or tears, increased blood flow in the exposed tissues, bronchial constriction, or cilia movements in the upper airways, or cough. The effects may often but not always appear at the site of contact on the exposed skin or mucosa.

Central nervous system (CNS)

Symptoms or perceptions are reported as processed evaluations incorporating many symptoms or perceptions such as perceived comfort or sensation of air quality. It is not known how this is done in the Central Nervous System (CNS). They are typically reported by the occupant as prevalence or intensity of symptoms or perceptions. It is, however, known that the reports are strongly affected by personal or external biases, and that adaptation and sensitization frequently appear.

THE TWO DIMENSIONS OF SYMPTOMS AND REPORTS

Indoor air pollutants may each activate a multitude of biological mechanisms and subjects are often experiencing many exposures at the same time. Because of this and the complex nature of the resulting subjective reports as described above, no consistent and general agreed classification exists of reports of symptoms or evaluations of IAQ. Here a suggested classification is found in table 2 which shows three groups of perceptions, symptoms, well-being and other subjective health effects in relation to IAQ. The table is a modification of a classification suggested by (Berglund et al 1992). The three groups of symptoms and perceptions are here called "Perceptions of body functions", "Environmental perceptions", and "Processed reports or evaluations". These classes are defined with consideration to whether they can be replaced by objective measurements or not or if the target value for their prevalence in guideline setting is zero or not.

Perceptions of body functioning

Perceptions of body functioning are reported as symptoms of mal-functioning body systems, inside the body or on the body surface. These may be caused by immune or inflammatory reactions. Focus of the occupants' reports are on the type of organs affected such as eyes, nose, mouth, or throat (exposed mucosa), skin, respiratory malfunction, allergic asthma responses, non-immune responses, bronchial constriction, CNS changes (e.g. reaction time and errors), and increased responsiveness (e.g. hyper reactivity, allergy). Many of the biological mechanisms mentioned above may be involved in each reported symptom. Typical symptoms are dryness, increased secretion, perceived irritation, soreness, cough, tightness of breath, headache, rashes, stinging, itching, burning. Although biologically different, subjective reports of irritation of mucous membranes in eyes, nose, and throat caused by inflammatory or immunological responses cannot be separated from responses of the chemical sense n.Trigeminus. In principle, objective measurements can be used for most if not for and objective measurements exist for many of the physiological effects reported by these body perceptions but not for all. These body perceptions are characterized by a target value for guideline settings and recommendations of zero prevalence.

Environmental perceptions

Environmental perceptions include perception of the environment including the presence of any air pollutants. Typical reports include odours as response to odorants in the air (n. Olfactorius) and irritation (n. Trigeminus and the chemical sense) in mucous membranes, nose and eyes, and facial skin (unspecific censors in the skin may be included). Other important IAQ senses relate to air temperature, humidity, and vision. The environmental senses also include hearing, taste, noise, draught, and illumination. These will not be dealt with in this summary. Adverse perceptions are unwanted changes of life quality and thus full value health effects (Berglund et al 1992). However some level of perceptions is required to allow persons to follow changes in the status of their environment. It follows that these perceptions may have a D-R relation of U-form i.e. in guideline settings the prevalence target is non-zero.

The detection of ocular and nasal sensory irritation increases as a function of vapour concentration at much higher rate than that for the detection of odour. However the odour intensity of mixtures of odorants cannot presently be predicted (Cometto-Muniz et al 2004). Although biologically different, subjective reports of activation of the chemical sense and n.Trigeminus cannot be separated from responses caused by irritation of mucous membranes in eyes, nose, and throat following inflammatory or immunological reactions in the tissues. Recent work in this area is therefore summarized above.

Processed evaluations and syndromes

The processed evaluations are based on multiple symptoms or perceptions. They are interpersonal dynamic interactions expressing the person's emotional content of body and environmental perceptions.
Processed evaluations are important indicators of IAQ. By definition they are based on psychological processes and thus cannot be documented without using subjective reports. However, they are difficult to use in scientific research and in investigation of buildings with poor IAQ.

They include many symptoms´ complexes such as syndromes (a spectrum of related symptoms) and overall evaluations of many symptoms combined into one evaluation. An example is the "Sick Building Syndrome" (SBS) in which the affected workers report non-specific symptoms only during the time at work, most often with no known cause (Berglund et al 1992). Symptoms reported in SBS have typically included mucous membrane and eye irritation, cough, chest tightness, fatigue, headache, and malaise. The criteria for the definition of SBS are summarised in Table 3. More details on the SBS can be found in a monograph prepared by a group of experts for the Committee of the COST 613, and the reader is referred to that document for further information (EU 1989, Berglund et al 1992). The use of SBS should be discouraged and replaced by multi-symptom questionnaires such as MM 40 (Lahtinen et al 2004).

Other examples are "Perceived air quality" which is a mixture of odour, irritation, stuffiness, feeling of heavy head, stuffy or stale air resulting from stimulation of both the nerves Trigeminus and Olfactorius, "Comfort" or "Well-being" which seem to be a mixture of body symptoms or body perceptions. Discomfort and general well-being are in many investigations used as independent evaluations. "General Well-being" or "General Symptoms" in many publications seem to be a mixture of body symptoms or body perceptions, etc. Finally, productivity and absenteeism report a mixture of the perceptions, or body reports seem to be processed evaluations and a mixture of the perceptions or reports mentioned above.

Productivity and learning capacity are also integrating CNS changes. Results from a preliminary study yield a significant association between classroom-level ventilation rate and test results student performances on standardized aptitude tests that are administered to students on a yearly basis (Shaughnessy et al 2006).A review of 23 studies suggests that a linkage exists between typical BRIs and productivity indicators such as task or work performance or absence from work. Quantitative associations between BRS and productivity were demonstrated in two office environments (Niemela et al 2006).The existing literature indicates that ventilation has a significant

impact on several important human outcomes including task performance and productivity among occupants or sensory panels (Seppanen et Fisk 2004). It has now been shown that poor indoor air quality in buildings can in addition to causing visitors to express dissatisfaction. The size of the decrease of productivity in most aspects of office work performance appears to be as high as 6-9%, the higher value being obtained in field validation studies (Wyon 2004).In an intervention study the performance of four simulated office tasks improved monotonically with increasing ventilation rates, and the effect reached formal significance in the case of text-typing. For each two-fold increase in ventilation rate, performance improved on average by 1.7% (Wargocki et al 2000).Another intervention study indicated that the indoor air quality improved productivity by 11%, compared with a 4% reduction of productivity among the control group of workers (Menzies et al 1997).Recent studies show that improvement of IAQ by a factor of 2-7 compared with existing standards increases office productivity and school learning significantly, while decreasing the risk of allergic symptoms and asthma in homes (Fanger 2006).

IDENTIFICATION OF THE MAIN INDOOR AIR POLLUTANTS AND RELATED SOURCES CAUSING THE DISEASE

Symptoms are unspecific i.e. many exposures may cause each of them. Therefore they do not alone identify the exposure cause. The relevant IAPs are those which can stimulate our senses or may cause tissue changes i.e. all known indoor airborne chemicals at some level (maybe excluding radon and CO). The pollutants may be gasses, vapours, viable or non-viable aerosols or particulate matter, allergens, etc. The risk factors also include technical causes such as ventilation, humidity and temperature. The sources of IAP are found indoors and outdoors and include humans, their activities, processes, maintenance, furniture, etc.

Perceptions of body functioning

In recent investigations symptoms related to mucous membranes in eyes, nose, mouth, and throat are symptoms frequently related to poor IAQ (Skyberg et al 2003, Peitersen et al 2006). These symptoms are reported from office buildings (Reijula et al 2004, Wolkoff et al 2006). or buildings with low ventilation (Wargochi et al 2000). Symptoms have been related to house or office dust exposures (Pan et al 2000; Skulberg et al 2004, Chao et al 2003), chemical contaminants from the sewer system and damp construction materials (Putus et al 2004), and with mould exposure (Ebbehøj et al 2005; Hirvonen et al 1999; Park et al 2006). Pharyngeal dryness increased when temperatures rose and was alleviated with a rise in relative humidity (Reinikainen et al 2003). Symptoms related to skin areas are frequently reported from field surveys (Skyberg et al 2003). Recently reported or suggested causes are exposures to mould (Ebbehøj et al 2005), storing of organic waste in the home (Herr et al 2004a,b), and house,or office dust (Skulberg et al 2004). Examples of respiratory symptoms are cough, tightness of breast, asthmatic symptoms, phlegm, wheeze, chest tightness, attacks of shortness of breath, and attacks of cough. These symptoms are reported from buildings with low ventilation (Wargochi et al 2000). Chemical contaminants from sewer system and damp construction materials (Putus et al 2004) exposures to house or office dust (Pan et al 2000; Herr et al 2004b), mould exposures

(Hirvonen et al 1999; Putus et al 2004; Chao et al 2003) have been suggested as cause. Significantly increased lower respiratory symptoms were associated with Endotoxin in floor dust (Park et al 2006). In field surveys, symptoms related to CNS and performance are frequent (Skyberg et al 2003). Examples are difficulty in thinking clearly, concentration difficulty, headache, feeling of fatigue, heavy-headedness, sluggishness, sleepiness, nausea, etc. These symptoms are reported from buildings with poor ventilation (Wargochi et al 2000). The symptoms are often work-related (Reijula et al 2004). Occupants in open-plan offices more frequently complain about CNS symptoms than occupants in multi-person and cellular offices (Peitersen et al 2006). Some reported or suggested causes are house or office dust (Pan et al 2000), and moulds in the indoor environment (Hirvonen et al 1999; Ebbehøj et al 2005).

Environmental perceptions

Dampness in dwellings, with emissions of odorous compounds, is associated with an increase in symptoms (Engvall et al 2002). The indoor climatic conditions seem to influence the perception of odours. Any kind of humidity seems to increase odour sensation (Reinikainen et al 1997, 2003). A combination of odours and signs of high humidity in buildings was related to an increased occurrence of all symptoms (Engvall et al 2002). Increasing ventilation decreased the percentage of subjects' odour reports, and increased the perceived freshness of air (Wargochi et al 2000). N.Trigeminus and the chemical sense for irritation are found in mucous membranes of nose and eyes, and facial skin.

Processed evaluations and syndromes

Occupants in open-plan offices are more likely to perceive poor air quality than occupants in multi-person and cellular offices (Peitersen et al 2006, Reijula et al 2004, Wargochi et al 2000). The recently reported or suggested causes are chemical contaminants from the sewer system and damp construction materials (Putus et al 2004), with mould exposure (Ebbehøj et al 2005), lack of office cleanliness, and low job satisfaction (Chao et al 2003). Processed ratings such as perceived "Air Quality" may be significantly correlated with other responses (Pan et al 2000). Recently several groups have discussed a prioritising of the most IAQ relevant compounds (WHO 2006, 2007, Cochet et al 2006, Kotzias et al 2005, Anonymous 2006).

EPIDEMIOLOGY: INCIDENCE/PREVALENCE OF THE DISEASE, RISK ATTRIBUTABLE TO IAQ, TIME TREND

The most frequent effects related to indoor air quality (IAQ) seem to be acute physiological or sensory reactions, psychological reactions, and subacute changes in sensitivity to environmental exposures (Berglund et al 1992). Objective, adverse health effects of poor IAQ are well known but rare compared to the prevalence of unwanted symptoms and perceptions (Berglund et al 1992). Because of the unclear and subjective nature of evaluations and complaints no clear definitions exist for the unacceptable prevalence and no reference values or golden standards exist on which conclusions can be based. In the literature, the levels of prevalence, which have been called abnormal range from 10% to 100% depending on the symptom or perception in

question. There is good and substantial evidence for the relation between Indoor Air Pollutants (IAP) and symptoms and perceptions (Berglund et al 1992).

IDENTIFICATION OF SUSCEPTIBLE POPULATION SUBGROUPS

It is well documented that risk groups exist and many response modifying factors affect the occupants' responses. Examples of known risk factors are health status (atopy, sick persons, skin temperature), demographic data (age groups incl. children, occupation, job function, gender), life style (smoking), psycho-social loads (low social support or satisfactions, psychosocial and personal biases), exposure scenario (previous exposures, competing sensory stimulation, interactions between concurrent exposures, adaptation, accumulation, duration of exposure). Interactions between concurrent exposures and adaptation processes are characteristic of the sensory systems involved in the perception of odour and mucosal irritation, further the duration of exposure influences the perception (Berglund et al 1992).

Women report symptoms more often than men (Ebbehøj et al 2005; Reijula et al 2004; Skyberg et al 2003; Bullinger et al 1999; Runeson et al 2003, 2006). This may be an effect of less favourable working conditions under which women are employed (Bullinger et al 1999). Responding women may have a lower sense of coherence (SOC) value, a psychological measurement of a life attitude (Runeson et al 2003). Individuals experimentally given a harmful bias reported significantly more health symptoms following exposure indicating induction of a strong personal bias (Dalton 1999). Therefore psychosocial and personal reasons may dominate general symptoms (Ebbehøj et al 2005). Sick Building Syndrome (SBS) may be more common in younger subjects (Runeson et al 2003). Atopic disposition is a possible risk factor for skin irritation (Herr et al 2004a,b, Chao et al 2003, Runeson et al 2003, 2006, Reijula et al 2004, Skyberg et al 2003). Lifestyle including passive smoking and psychosocial load are also predictors of symptoms (Skyberg et al 2003). Also occupation, job functioning, low social support or satisfactions are risk factors (Skyberg et al 2003, Chao et al 2003, Runeson et al 2006).

GUIDELINE SETTINGS

Challenges of the use of symptoms in IAQ science and practice

From the previous chapters it appears that indoor air pollutants cause unspecific effects and that these do not unambiguously identify the exposure. A multitude of biological mechanisms are involved in the responses to multiple exposures indoors and only few objective measurements are available. Some types of responses can not be replaced by objective measurements and often the effects and exposure cannot be quantified. Added to this, the resulting subjective reports are affected by bias and response modifiers. It follows that traditional toxicological procedures to the establishment of guidelines seem impossible to use for these subjective responses and evaluations.
In IAQ guideline settings three types of DR relations must be considered. These are perceptions and symptoms with known causality, based on quantifiable effects and exposures, unspecific symptoms with unknown causality, and hypothetical causalities waiting for further investigations.

Guidelines for perceptions and symptoms with known causality

As described in the introduction, a BRI is characterized by a known causality between health and a certain exposure. At low exposure levels only unspecific symptoms may be present and often symptoms are the most sensitive effect of IAP. It follows that most IAQ guidelines for BRI will be defined from such symptoms. At low exposure levels the presence of these unspecific symptoms does not by themselves identify the causal exposure. This must be identified by other means e.g. measurements. Formaldehyde is an example for which a threshold for irritation/odour could be defined in the lab. Another example is asthma or COPD caused by many types of air pollutants. For these diseases the symptomatology is important for the diagnoses.

Because of the known causality behind a BRI, thresholds and guideline values can be defined following traditional procedures using symptoms in controlled lab settings and quantifiable exposures. In this way thresholds, NOEL, and LOEL can be defined where interactions from other types of exposures can be excluded.

For most of the health effects for which objective measurements are available D-R relations and thresholds are not available and few of the thousands of relevant chemicals have been examined at low exposure levels. Despite this some progress has been seen. Recently several groups have discussed guideline settings for the most IAQ relevant compounds (WHO 2006, 2007, Cochet et al 2006, Kotzias et al 2005, Anonymous 2006). Several procedures for prioritizing are available by which the most important pollutants can be identified. However, no consensus exists. While we are waiting for missing data, substitute measures might be helpful. At low IAQ exposure range a lowest concentrations of interest (LCI) type of estimates may be useful. Recommended low and a higher action levels may also apply (Bluyssen et al 1997). Again no consensus exists for such procedures. Under all circumstances an ALARA principle should be followed.

In IAQ guideline settings apportionments between allowable contributions from different sources must be discussed. We do not know how to deal with it. A special case of this is how indoor/outdoor fractions are coordinated in I/O guidelines.

Guidelines for unspecific symptoms with unknown causality

Assuming that all BRI with known traditional mono-factorial causality are dealt with as described above, it can also be assumed that all causalities which in higher exposure ranges might cause more adverse and irreversible health effects in occupants are under control. However, a group of causalities remain to be dealt with. These typically include effects with multifactor relationships following mixtures of exposures (cocktail effects). For the reasons mentioned above, many such symptoms and perceptions in mixed real life exposures do not qualify for traditional guideline settings. A broad spectrum of causes is possibly contributing to the prevalence of individual symptoms or perceptions in any particular building and to SBS. Because of the ill-defined causality, lack of quantifiable effects and exposure measurements etc. no strict traditional guidelines can be established. However, the importance of such complaints is well documented and guidance, recommendations, labelling systems, and emission control become the tool of prevention. These less strict guidelines are acceptable only for discomfort and SBS etc. and only if averse health effects can be excluded e.g. because all relevant exposures are under guideline regulation as mentioned above. Also the combined effects of cocktail exposures are unsolved both scientifically and administrative. Some additive procedures may be taken over from occupational guideline settings.

It follows that a set of good practices for construction, maintenance, and building usage should be developed which covers all relevant risk factors (a healthy building's regulations). The risk factors include technical causes such as ventilation, humidity and temperature, IAP sources, maintenance etc. In any case an ALARA principle should be followed.

An example of the complex nature of such guidelines is Endotoxin in building dust which may indicate dampness and possible microbial growth and thus increased risk of building-related symptoms including building-related asthma, respiratory, and systemic symptoms (Park et al 2006). Building type especially open-plan offices may be a risk factor for adverse environmental perceptions and symptoms (Peitersen et al 2006). Indoor air temperature and humidity may be important for the perceived air quality and SBS symptoms (Fang et al 2004). Perceived indoor environments, non-specific symptoms, and their associations are associated with the season (Mizoue et al 2004).

Guidelines for unknown or hypothetical causalities

An example of an unknown or hypothetical causality is multiple chemical sensitivity (MCS). This is presently hypothetical and more research is needed before guidelines can be defined. In any case an ALARA principle should be followed.

DISCUSSIONS AND CONCLUSIONS

Use of symptoms and perceptions as indicators of indoor air quality

This review shows that not much has changed since the report of Berglund et al. (1992). The poorly defined symptoms remain poorly understood. The disability associated with IAQ symptoms and syndromes still generates controversy (Hodgson 2002).

Three types of subjective evaluations or reports related to IAQ are identified. They are "Perceived Body Functions", "Environmental Perceptions", and "Processed Reports or Evaluations". "Perceived Body Functions" describes changes in body functioning and are focussed on individual organs or tissues. "Environmental Perceptions" addresses exposure factors in the environment. Subjective evaluations are essential for these two last types of evaluations and they can probably not be replaced by objective measurements. The science of psychophysics offers a variety of sensory models for studying indoor air quality effects and for indoor air quality characterization (bio-assays).

No simple causal D-R relation can be expected for subjective symptoms and perceptions and unknown biases make it difficult to use occupants' reports in science and investigations as their personal biases can be strong. In real life situations, the symptoms or subjective reports prevalence's should not be used as exposure measurements and subjective reports from buildings may only qualify as screening tools. It is concluded that the use of SBS should be discouraged and replaced by

multi-symptom questionnaires. Personality and personal vulnerability such as gender, age, atopy, and asthma, as well as indoor exposures, should be considered in both indoor environmental epidemiology and in practical handling of buildings with suspected indoor problem, especially when the technical investigations fail to identify any obvious technical malfunction (Runeson et al 2003, 2004, 2006). It is important to combine technical measurements or inspections with a longitudinal evaluation of occupant reactions (Engvall et al 2005) and indoor air temperature and humidity may be important for the perceived air quality and SBS symptoms (Fang et al 2004).

A WHO expert group has recommended that odours can be measured through the immediate response of the non-adapted olfactory system (visitor situations). It should be noted that odour intensity measured by visitors does not necessarily correlate with the perceptions of the occupants (WHO 1987, Berglund et al 1992). Therefore occupants' reports are also needed. Regulatory agencies now require sensitivity, validity, reliability, and biological meaningfulness of sensory methods applied for indoor air quality control (Berglund et al 1992). Therefore, investigators should use a strong quality assurance policy in IAQ evaluations based on subjective reports. However, to reduce bias a trained external panel may have to be included in IAQ investigations. Control groups and norm values in reference groups are difficult or even impossible to use in relation to IAQ. Taking this into consideration, the search for norm values or a framework seems to be of limited value (Neuner & Seidel 2006).

Objective methods may only apply for body perceptions and some environmental perceptions, and suggested indicator of activated defence mechanisms include indicators of inflammation and immune system responses, changed biomarker values in lavages, condensed exhalation, blood, and tear liquid (e.g. cytokines, cells), reddening eyes and skin, skin irritation, and rashes. Recent indications of new biomarkers for changed body functions caused by poor IAQ have appeared. Inflammatory markers may predict high prevalence of respiratory symptoms (Hirvonen et al 1999). Lu et al indicated that the urinary 8-hydroxydeoxyguanosine (8-OHdG) level was significantly associated with SBS complaints (Lu et al 2007). This is also that case for matrix metalloproteinase 9 (MMP9), leptin, and alpha melanocyte which may stimulate hormone (MSH), vascular endothelial growth factor (VEGF), immunoglobulin E (IgE), and pulmonary function (Shoemaker & House 2006). Neurological functioning may in the future be monitored objectively through *v*isual contrast sensitivity (VCS), an indicator of neurological function, which was abnormally low in SBS patients (Shoemaker & House 2006) and performance measurements may be used as processed measurements of CNS function. Examples are errors made while typing, number of calls made in call centres, and absence from work. Physiological changes may in the future be registered objectively through blinking frequency (Nøjgaard et al 2005). Peak flow and respiratory measurements are available for respiratory effects and allergy-asthmatic changes. An interesting observation is that Shoemarker et al indicated that cholestyramine (CSM) therapy may be an effective therapy against SBS (Shoemaker & House 2006). The indicated objective methods can only be used for body perceptions, but many are themselves not real health effects but merely biomarkers which in addition also are strongly influenced by biases.

Guideline settings based on symptoms reports and perceptions in IAQ

Several working groups have shown that principles for setting of IAQ guidelines can be defined based on combinations of existing procedures. The WHO has initiated a working group to define such guidelines and recommendations. The future guidelines may include both traditional guidelines for single compounds and a set of guidance and recommendations for healthy buildings covering situations with only minor adverse health changes or discomfort.

Many suggested objective measurements (e.g. mediators) which are in progress to be used in guideline setting are not real health effects but merely biomarkers of ongoing changes, and are strongly influenced by biases. It is often questionable if they can be used as substitute measurements. In IAQ guideline settings three types of DR relations must be considered. These are perceptions and symptoms with known causality, based on quantifiable effects and exposures (BRI), unspecific symptoms with unknown causality, and hypothetical causalities waiting for further investigations. It is concluded that future guidelines for ventilation rate based on comfort and health should no longer be independent of indoor air temperature and humidity.
Because of the known causality behind a BRI, thresholds and guideline values can be defined following traditional procedures using symptoms in controlled lab settings and quantifiable exposures. In this way thresholds, NOEL, and LOEL can be defined where interactions from other types of exposures can be excluded. Some progress has been seen recently in approaching guidelines for IAQ. Several procedures for prioritizing are available by which the most important pollutants can be identified. In guideline settings apportionments between allowable contributions from different sources must be discussed. A special case of this is how indoor/outdoor fractions are coordinated in I/O guidelines.

The combined effects of cocktail exposures most be dealt with both scientifically and administratively. Some additive procedures may be taken over from occupational guideline settings. Symptoms and perceptions in such mixed real life exposures do not qualify for traditional guideline settings and guidance; instead recommendations, labelling systems, and emission control become the tool of prevention. These less strict guidelines are acceptable only for discomfort and SBS etc and only if adverse health effects can be excluded e.g. because all relevant exposures are under guideline regulation as mentioned above.

Guidelines for undocumented or hypothetical causalities are presently hypothetical and more research is needed. No rational guidance except an ALARA principle can be recommended.

OPEN QUESTIONS AND RESEARCH NEEDS

There is a strong need for research on:

- How humans report symptoms and perceptions.
- On biological mechanisms involved in human responses to IAQ.
- Replacement of some of symptoms and perceptions with objective measurements.
- A quality assurance policy in IAQ evaluations based on subjective reports.
- Toxicological data for IAQ relevant compounds.
- The interactions between multiple exposures (cocktail problems).

A consensus is required on:

- Procedures for prioritizing among the most important IAQ pollutants.
- Interim procedures for estimation of substitute data until more accurate toxicological data become available.
- A set of good practices for construction, maintenance and building usage should be developed for all non industrial building types which cover all IAQ relevant risk factors (a healthy building's regulations).
- Apportionments and coordination of I/O guidelines.

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Table 1. Biological processes involved in response to poor IAQ

- The chemical sense for odorants and irritants in face, eyes, and nose
- Unspecific pain/irritative receptors in skin
- Vision
- Immune responses
- Inflammatory responses
- Body signalling systems
- Mediators
- Neural reflexes
- Interpretation in CNS

Table 2. Perceptions, symptoms, well-being, and other subjective health effects in relation to IAQ

Perceptions of body functioning, symptoms of malfunction of body functioning

- Eyes, nose, mouth, throat
- Skin
- Indicators of respiratory malfunction, asthma, allergic responses, non immune based responses, bronchial constriction
- Indicators of CNS malfunction, performance, and productivity

Environmental perceptions

- Odours, n. Olfactorius, odour masking, adaptation.
- Irritation n. Trigeminus

Processed reports or evaluations

- General well being
- Indoor Air Quality
- Sick Building Syndrome (SBS)
- Productivity and learning

Table 3. The Sick Building Syndrome (Berglund et al 1992)

A high proportion of the occupants of the building must be reacting, and the symptoms, and reactions observed belong to the following groups:

A. Acute physiological or sensory reactions
- Sensory irritation of mucous membranes or skin
- General malaise, headache, and reduced performance
- Unspecific hypersensitivity reactions, dryness of skin
- Odour or taste complaints

B. Psychosocial reactions
- Decreased productivity, increased absenteeism
- Contacts to primary health care
- Initiatives to modify the indoor environment
- Sensory irritation in eyes, nose, and throat must be dominating
- Systemic symptoms (e.g. from stomach) must be infrequent
- No obvious causality can be identified e.g. in the form of high exposure to single agents.