Low-grade systemic inflammation and the workplace

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Abstract

Background: Psychosocial and physical stressors can elicit the stress response, co-ordinated by interactions between neuroendocrine and inflammatory processes. The central role of the immune system, specifically low-grade systemic inflammation, is sometimes overlooked in work-related stress research.

Objective: To review evidence that work-related psychosocial and physical stressors can stimulate a low-grade systemic inflammation which, through interactions with the neurohormonal systems, may impact on the well-being and productivity of workers.

Methods: Literature searches were performed by databases and by hand. Databases used included Interface - EBSCOhost Research Databases; PsycINFO; Academic Search Complete; Africa-Wide Information; CINAHL; E-Journals; MEDLINE and PsycARTICLES.

Results: Psychosocial stressors, infections, poor indoor air quality, musculoskeletal injuries and chemicals can stimulate a low-grade systemic inflammation that may adversely affect workers' mental and physical health, as well as productivity. The psychological and physical effects caused by infection-induced inflammation are generally referred to as sickness behaviour and that caused by poor indoor air quality as sick building syndrome.

Conclusions: Stressor-induced low-grade systemic inflammation can be a causal factor in the physical and behavioural symptoms of work-related stress. It is therefore important that those involved with the health of workers be cognisant of inappropriate or chronic low-grade inflammation as a potential health hazard.

Keywords: inflammatory; psychosocial stress; sickness behaviour; sick building syndrome; musculoskeletal injury; multiple chemical sensitivity.

1. Introduction

The immune system, once seen as an independent self-regulating system driven by antigenic stimulation and regulated by cytokines and other soluble immune cell-derived substances, is now known to be involved in multi-directional communications with the neuroendocrine system, and by implication somatic and behavioural functions [1]. In these psychoneuroimmunological interactions, the immune system acts as a sixth sense organ informing the brain about peripheral events [2], mainly through the influence of immune cell-derived inflammatory mediators on the brain. This not only has short-term somatic and cognitive-behavioural effects, but may induce long-term anatomical changes with consequences for neuroendocrine function [1,3]. In line with the multi-directional nature of these psychoneuroimmmunological interactions, mental processes such as cognition, perception and mood can, in turn, act as biological response modifiers, with marked influences on the immune system and health. In these multi-directional communications, inflammatory mediators represent an essential part of the immune system's response. When the inflammatory process becomes chronic or inappropriate it can lead to physical and/or behavioural pathology. The interactions are not merely present in isolated conditions such as disease or stress, but form part of all normal homeostatic regulatory processes.

Stress has become a major subject of research in the workplace. Potential workplace stressors include physical factors, which may be in direct contact or close contact to the body, or even in the more distant environment [4]; pathophysiological challenges such as infections, tissue injury and pain; as

well as adverse psychosocial conditions, which may be real or imagined [5,6]. Virtually any of these potential stressors could elicit the stress response, co-ordinated by interactions between inflammatory and neuroendocrine processes. Whether the stress response develops or not depends not only on the attributes of the potential stressor, but also on that of the individual. Factors that contribute to inter-individual differences in the vulnerability to stress include genetics, previous life experiences, conditioning, as well as general physical and psychological well-being. In addition, temporal and context-dependent variations generally exist for the same individual [6,7]. Similar inter-individual, temporal and context-dependent variations also apply to inflammatory vulnerability.

Varying degrees of inflammatory involvement have been reported for virtually all physical, as well as psychological, disturbances [1,8]. Furthermore, conclusive evidence exists that not only environmental and physiological stressors, but also psychosocial stressors, can stimulate inflammatory activity and lead to low-grade systemic inflammation and neuroinflammation. Neuroinflammation, in turn, can impact on neuroendocrine systems with effects such as anorexia, fever, fatigue, somnolence, hyperalgesia, psychomotor slowing, malaise, anhedonia, social withdrawal, depressive symptoms, anxiety and subclinical deficits in cognition [9]. This involvement of inflammatory mediators in normal and abnormal physiological processes has become a major subject of interest in both the medical and the psychological sciences. In fact, inflammation has been described as *the common pathway for stress-related disorders* [10]*, the common soil of multifactorial diseases* [11], *the common denominator in neuro-behavioural and somatic symptoms* [12] and as *the intersection between behaviour and somatic symptoms* [13].

1.1 Inflammatory mediators and the central nervous system response to stressors

Activation of the peripheral immune system by environmental and pathophysiological stressors leads to the release of inflammatory cytokines such as interleukin (IL)-1β, IL-2, IL-6, tumour necrosis factor (TNF)-α, and interferon (IFN)-γ, which can elicit a co-ordinated response from the central nervous system (CNS). Peripherally produced cytokines can affect immune and neuroendocrine

components of the central nervous system, and by implication, neuroendocrine and behavioural functions, *via* both neural and circulatory routes. In the neural pathway, peripherally produced cytokines can trigger activity in vagal afferents that relay neural signals from the periphery to the brain, promoting intracerebral production and release of pro-inflammatory cytokines. In the circulatory route, various mechanisms exist by which peripherally released cytokines can upregulate intracerebral cytokine synthesis. For instance, microbial ligands and cytokines can travel through the circulation and enter the central nervous system at areas devoid of an intact functional blood-brain barrier, or, in areas with an intact blood-brain barrier, by specific saturable carrier-mediated mechanisms. Moreover, microbial ligands and cytokines can bind to the cerebral vascular endothelium and facilitate the release of second messengers, as well as the induction of central nervous system cytokine synthesis and release [7,14–16]. In response to this inflammatory signalling from the periphery, central nervous system cells like microglia secrete cytokines such as IL-1β, TNF-α, IL-6, and IFN-γ, which, by binding to their respective receptors, can mediate a number of neuroendocrine and behavioural responses [17]. In addition to the upregulation of central nervous system cytokines by inflammatory signals from the periphery, the levels of pro-inflammatory cytokines in the brain can be increased by emotional and/or cognitive stress.For example, in response to adverse psychosocial stimuli, microglia in the brain can undergo a number of changes including upregulation of pro-inflammatory cytokine production [18].

Pro-inflammatory cytokines can influence neuroendocrine and behavioural functions: through effects on the regulation of excitatory and inhibitory neurotransmission [17,19];the synthesis, release and reuptake of neurotransmitters involved in mood and cognition [20]; the influence on hippocampal kynurenine metabolism which plays a role in depressive behaviours during inflammation [21]; and stimulation of the acute phase response, when stressed by immune challenges such as infection [22]. Several work-related stressors have the potential to stimulate the release of inflammatory mediators which, through effects on central nervous transmission, could have adverse effects on mental and physical well-being of workers. The role of the immune system, and more specifically low-grade

systemic inflammation, on well-being and productivity of workers is often overlooked. This may not only be to the detriment of the worker, but may also hamper relevant research.

2. Aim

In this writing we briefly look at the potential of a number of work-related stressors to stimulate low-grade inflammation which, through interactions with the neurohormonal systems, may impact on the well-being and productivity of workers. Psychosocial stressors and physical stressors such as infections, poor indoor quality, musculoskeletal injuries and exposure to chemicals are used as examples.

3. Methods

A literature search was performed by databases and by hand. Databases used included Interface - EBSCOhost Research Databases; PsycINFO; Academic Search Complete; Africa-Wide Information; CINAHL; E-Journals; MEDLINE and PsycARTICLES.

4. Results

Several psychosocial and physical work-related stressors can stimulate low-grade systemic inflammation that, through interactions with the neurohormonal systems, may impact on the well-being and productivity of workers. We discuss five types of work-related stressors that have the ability to cause low-grade inflammation, i.e., psychosocial stressors, infections, poor indoor air quality, work-related musculoskeletal injury and exposure to chemicals.

4.1 Work-related psychosocial stressors

Several large studies and reviews support the fact that physical and mental health can be negatively affected by work-related psychosocial factors. Probably the best studied example is the association between cardiovascular disorders and work-related psychosocial factors such as job strain, effort-reward imbalance, lack of social support, organizational injustice, small decision latitude, pressing

work, lack of skill discretion, insecure employment, night work, long working weeks and workplace noise [23–27]. The influence of adverse psychosocial conditions on the physical well-being of workers is further evidenced by the negative effects of job dissatisfaction and poor social support from supervisors and co-workers on the quality of life and perceived pain in workers with chronic pain [28] and the fact that work-related psychosocial risk factors such as higher emotional demands, excessive work pace, low justice and lack of respect in the workplace can increase the occurrence of musculoskeletal pain [29]. Furthermore, psychosocial factors such as job insecurity, work-family imbalances, and hostile work environments may contribute to work-related injuries [30], while factors such as negative attitudes and employment variables associated with reduced labour market desirability may result in poor return to work following workplace injury [31]. In addition to the physical effects, work-related psychosocial conditions may also be risk factors for mental distress, with depression, anxiety and burnout amongst the most frequently reported symptoms [32–34]. The interested reader is referred to a somewhat older but more detailed review by the World Health Organisation on the impact of a range of work-related psychosocial hazards on physical and mental health [35]. In support of the association between psychosocial stress and mental and physical health, indications are that appropriate interventions to improve the psychosocial work environment yield health benefits and may reduce the prevalence of psychological stress-related disorders in the workplace [36,37].

An association has long been observed between adverse psychosocial conditions and chronic low-grade inflammation, not only in the periphery, but also in the central nervous system [18,38]. Acute stress can increase the levels of circulating inflammatory markers such as pro-inflammatory cytokines, both in stressful situations and with experimental laboratory stress-induction [38,39]. However, significant inter-individual differences seem to exist with markedly greater inflammatory responses in individuals with low self-esteem, depressive symptoms, high hostility, loneliness, higher work stress, higher state anger and anxiety, lower self-compassion, effort-reward imbalance, negative affective responses to tasks and a decline in physical wellness. Moreover, factors generally seen as health-protective, such as social support, positive affect, self-compassion and compassionate

meditation, are associated with milder inflammatory responses to psychosocial stress [38,39]. The subjective perception of stressors and the type of attention bestowed on the stressors are likely to give rise to further inter-individual differences [5,40]. Indications are that the chronicity of the stress, as well as the influence of adverse early life experiences on the neuro-endocrine and immune systems and on the multidirectional communication between these systems, may potentiate the strength of the acute inflammatory response, and that the intensity of the acute inflammatory response may be predictive of the emotional and physical consequences of stress [1,18,39]. Increases in pro-inflammatory activity, in turn, have the potential to contribute to the prevalence of stress-related somatic and affective disorders [41]. In fact, inflammation is suspected to be the common link between stress and stress-related disorders [10]. This potential of inflammation as a causal factor in the development of a number of stress-related somatic and affective disorders has recently been reviewed by Langgartner *et al* (2019). In line with the favourable influence of health-protecting psychosocial factors and conditions on the pro-inflammatory response to acute stressors, a number of studies found that positive psychosocial factors such as self-esteem, coping, sense of coherence, optimism, emotional vitality, and perceived life enjoyment may have a protective influence against the development of physical disorders. Indications are that the positive effect of health-protecting psychosocial factors on the development of physical disorders may indeed be mediated through their moderating influences on the inflammatory response [42,43].

In a review by Nakata (2012) on work-related psychosocial stress, 56 studies showed a relationship between work-related psychosocial stress and immune function. High job demands, low job control, high job strain, job dissatisfaction, high effort-reward imbalance, overcommitment, burnout, unemployment, organizational downsizing and economic recession had quantifiable effects on functional parameters of the immune system, e.g., declines in natural killer (NK) cell activity, NK and T cell subsets, CD4+/CD8+ ratio, and increases in certain inflammatory markers. Results for pro-inflammatory cytokines were, however, inconsistent as not all studies showed significant effects. Nevertheless, significantly higher levels of either TNF-alpha and/or IL-1β were found in association with low job satisfaction, burnout, high job demands, low job control and low social support at work.

In addition, C-reactive protein (CRP), a non-specific indicator of systemic inflammation, showed significant increases with high job demands, low job control, low social support, high effort-reward imbalance and unemployment stress [44]. Further evidence for a positive association between work-related psychosocial stress and CRP levels is, moreover, described in a review by Johnson *et al* [45]. Based on findings from over 43,000 men and women, it is elsewhere reported that work stress is associated with higher levels of systemic inflammation. However, the conclusions were based on white cell counts only [46]. In short, although an analysis of all available publications is beyond the scope of this paper, indications are that chronic work-related psychosocial stressors could stimulate and maintain low-grade systemic inflammation, and in this way impact on the psychological and physical well-being of the worker. Fortuitously, a protocol for a systematic review and meta-analysis on the associations between psychological factors at work and inflammatory markers has just appeared in BMJ Open [47]. It is anticipated that, once published, the final manuscript may give direction to further studies on this link.

4.2 Infections and sickness behaviour

Infections, even the common cold, may lead to low-grade emotional, cognitive and physical problems that, in the work environment, can impair productivity and safety. Sickness behaviour is an example of infection as an immune stressor that can elicit transient neuroinflammation, resulting in a co-ordinated set of physiological and behavioural changes. The behavioural symptoms are triggered by pro-inflammatory cytokines such as interleukins 1 (IL-1α and IL-1β), IL-6 and TNF-α produced by activated cells of the innate immune system when in contact with the infectious microorganism. Sickness behaviour presents as a combination of any of a number of psychological or behavioural symptoms including somnolence, lack of concentration, loss of interest in food and drink, avoidance of social interaction, a decline in self-care, loss of interest in the physical environment, decreased libido, decreased locomotor activity, depression, irritability, general feelings of discomfort and anhedonia. The behavioural symptoms are generally accompanied by fever and often by one or more physical symptoms such as fatigue, hyperalgesia, nausea, and malaise [15,16].

Sickness behaviour is primarily an adaptive mechanism that optimally allocates the body's resources to fight off infection by changes in feeding, sleeping and activity levels and by redirecting available energy. The accompanying fever is well-known for its ability to make the internal environment less favourable for the proliferation of infectious microorganisms by suppressing microbial growth and by increasing the immune defence through processes like stimulation of the expression of adhesion molecules which favour leukocyte migration and enhancement of neutrophil bactericidal capacity [16]. Sickness behaviour may further, through its antisocial effects such as decreased interest in social interaction, have a more altruistic function by reducing interpersonal contact, thus limiting the spread of infection to the environment [15]. Indications are that psychological and immune stressors may act synergistically to promote inflammation and sickness behaviour [48]. In summary, it can be said that sickness behaviour is a functional homeostatic adaptation caused by the induction of pro-inflammatory cytokine production, rather than a debilitating side-effect of infectious diseases.

There is evidence that working while sick is becoming more common. This could have adverse effects, not only on the worker's health and productivity, but also on co-workers and members of the public with whom the worker may be in contact. The potential danger to co-workers and others when working while suffering from a contagious illness speaks for itself. In addition, evidence shows that the habit of working while sick may, over time, be a risk factor for burnout, and may even have negative consequences for future cardiovascular and mental health. This may influence long-term well-being and in the long-run lead to extended sickness absence [49]. Moreover, various symptoms of sickness behaviour could influence work output. For instance, physical and cognitive slowing, as well as problems in concentration, could lessen the capacity to monitor and respond to environmental demands, and in that way not only cause a decline in productivity, but also increase the likelihood of errors and accidents [49].

4.3 Poor indoor air quality and sick building syndrome

Sick building syndrome develops when physical elements in the indoor environment stimulate the peripheral inflammatory response followed by transient neuroinflammation, neuroendocrine changes

and a co-ordinated set of physiological and behavioural adjustments. The term sick building syndrome describes a condition in which the occupants of a building experience acute physical and behavioural symptoms that seem to be linked directly to the time spent in a building or in a specific part of the building [50]. The concept of sick building syndrome is believed to have had its origin at the time of the 1970's oil embargo when changes were made to building design and construction to limit natural ventilation with outdoor air, and when mechanical ventilation standards for commercial buildings were relaxed, both in an attempt to conserve energy [51]. These adjustments in construction and in ventilation standards had a negative effect on indoor air quality.

A number of behavioural effects are described for sick building syndrome, including difficulty concentrating, lethargy, depression, drowsiness, mental fatigue, memory problems, personality change, and other cognitive and mood disturbances [50,52–54]. Physical symptoms of sick building syndrome can present as a combination of headache, dizziness, nausea, eye, nose or throat irritation, running nose and eyes, dry cough, wheezing, hoarseness or changed voice, dry or itching skin, sensitivity to odours, increased incidence of asthma attacks, allergies, flu-like symptoms, physical tiredness, slowed motor responses and, occasionally, light sensitivity and gastrointestinal distress [50,52–54].

Poor indoor air quality has long been accepted as the main cause of sick building syndrome. Poor indoor air quality may result from inadequate ventilation, contamination introduced by the ventilation system *per se*, the ergonomic characteristics of buildings, activities within the buildings, and inadequate maintenance. What is sometimes overlooked in the work environment is the inflammation-inducing potential of ineffectual cleaning which may result in indoor surface pollution with contaminants such as dust, fibres and micro-organisms deposited on or in surfaces of buildings. It has been shown that settled dust may contain any of at least 20 substances such as fungal spores, dust mites, dandruff, fibres, insect parts and other elements that can contribute to the allergenicity of dust [55]. Areas of dampness, whether it be in the walls, ceilings, floors or due to inadequate maintenance of building hygiene, not only fosters the accumulation of dirt, but increases the potential for microbial growth. A good example is seen in the results of a 10 year follow up study that showed an association

between variations in dampness and moulds in workplace buildings and the incidence and remission of sick building syndrome, as well as the levels of biomarkers of inflammation [56]. Development of the symptoms of the sick building syndrome is, however, not restricted to poorly maintained workplace hygiene and inadequate ventilation. Volatile organic compounds, emitted from sources such as building materials, paints, cleaning agents, furnishings, adhesives, combustion materials, floor and wall coverings, and office equipment are considered important contributors to a decline in indoor air quality and are, amongst others, associated with symptoms of sick building syndrome such as allergies and inflammatory processes [57,58]. In addition to indoor-produced pollutants, indoor air quality can also decline when external pollutants derived from sources such as vehicle exhausts are sucked into buildings via air intake systems [59].

Factors in the psychosocial environment such as organizational stress and lower levels of organizational support have, in addition to aspects of the physical environment, been described as contributors to the development of sick building syndrome [60]. In fact, the question has early on been asked whether we are talking about dysfunctional buildings or dysfunctional people [61]. According to the findings of the Whitehall Study II, the physical environment of office buildings appears to be less important than features of the psychosocial work environment in explaining differences in the prevalence of sick building syndrome symptoms [62]. The most feasible conclusion is that the cause of sick building syndrome, depending on the context, is of multifactorial origin and related to chemical, physical, biological and psychosocial factors that interact or coincide with one another [63].

As a functional somatic syndrome, sick building syndrome shares many symptoms with other functional somatic syndromes, presumably also low-grade systemic inflammation [64]. Associations have been described between causal factors of sick building syndrome such as microbial contamination, especially moulds, volatile organic compounds, exhaust fumes, and a range of particular matter on the one hand, and inflammatory activity on the other [56,58,65–67], but more comprehensive research on the association is required. A relatively recent suggestion [64] is that sick building syndrome be included as part of a group of inflammation-related ailments referred to by

Maoz-Segal *et al* as an "Autoimmune (Auto-inflammatory) Syndrome Induced by Adjuvants" (ASIA) [68]. ASIA is a wide term that describes the role of various environmental factors in the pathogenesis of immune-mediated diseases [68]. The interested reader is referred to a recent review on ASIA that presents evidence in support of the syndrome, as well as reservations regarding its validity [69].

Numerous studies have ascribed reduced work efficacy, increased absenteeism and objective productivity losses of around 6.5% to sick building syndrome [50,70]. Bas *et al* [70] reviewed 34 papers on the association between sick building syndrome and work efficacy and productivity. Productivity losses between 2.8 and 11% were described by the different studies. Improvements in indoor air quality were reported to result in decreases of over 50% in sick building syndrome-associated symptoms, declines of between 12.5% and 61% in the number of sick leave days and increases of up to 6.5% in objectively measured work productivity.

4.4 Work-related musculoskeletal disorders

Work-related musculoskeletal disorders are injuries or disorders of the muscles, nerves, tendons, joints, cartilage, and spinal discs associated with risk factors in the workplace. According to the Centres for Disease Control and Prevention (CDC), work-related musculoskeletal disorders are conditions in which the work environment and performance of work contribute significantly to the condition and/or the condition is made worse or persists longer due to work [71]. Work-related musculoskeletal disorders are especially prevalent in physical work marked by repetitiveness, force, or inadequate body postures and control [72,73] and are occasionally also referred to as repetitive strain injuries, cumulative trauma disorders or overuse injuries [72,74].

Physical symptoms of work-related musculoskeletal disorders include swelling, pain, stiffness, decline in the range of movements, and an inability to function normally [74]. High co-morbidity exists between musculoskeletal and mental disorders in humans. Chronic pain, functional limitations and activity restrictions associated with musculoskeletal conditions are generally assumed to be predisposing factors to frequently co-morbid mental symptoms such as anxiety, depression, feelings

of helplessness, irritability, insomnia, exhaustion and withdrawal from work and social activities [75]. However, results from animal experiments suggest that inflammatory mechanisms may be the underlying cause or at least contribute to symptoms such as depression, anxiety, hyperalgesia, a decline in confidence and problem solving ability, reduced social interaction and pain behaviours [72,76]. What has become evident is the fact that psychological factors may worsen the symptoms of work-related musculoskeletal disorders, and indications are that it may sometimes be the primary cause of the symptoms [72,77]. Although it cannot be sure whether specific psychological traits contribute to, or result from, work-related musculoskeletal disorders there are indications that a number of work-related psychosocial factors are predictors or risk factors for the development, or exacerbation of the associated pain. Implicated psychosocial factors include long-term low decision latitude, high job demands with time pressure, unfavourable demand-control-support ratios, effort-reward imbalance, low job satisfaction, low support from supervisors and colleagues, lack of social support, excessive involvement and perfectionism, adverse interpersonal relationships at work, long hours at work, adverse work content, and workplace bullying [78–82]. It has also been shown that psychosocial risk factors such as harassment, violence, bullying and work pressure have an influence on the reporting of work-related musculoskeletal disorders, as well as a bearing on subsequent workers' compensation claims [83]. Furthermore, individuals with somatising tendencies appear to be more prone to the development of musculoskeletal pain and associated disability [84]. An association between musculoskeletal disorders and the psychosocial disposition of the individual is also implicated by indications that psychosocial/psychological interventions can contribute to the prevention of acute back pain becoming chronic, and to the rehabilitation of chronic back pain [85].

Inflammation invariably plays a role in all forms of musculoskeletal disorders, whether work-related or not [86]. In fact, levels of various biomarkers of inflammation, including pro-inflammatory cytokines, confirmed that inflammatory processes play a part in work-related musculoskeletal disorders *per se* [72,87,88]. Formation and remodelling of musculoskeletal tissues are controlled by the host's genome and by mechanical and biological factors, including the relative amounts of different pro- and anti-inflammatory cytokines and growth factors [89]. The aim of inflammation is to

restore the structural and functional integrity of the injured tissue [86]. However, when the causal work-related physical task is continued, superimposed on the injured and inflamed tissue, a vicious cycle of injury, chronic or systemic inflammation, fibrosis, and even tissue breakdown is said to occur, resulting in pain and a decline in motor function [72].

Work-related musculoskeletal disorders have, for decades, been a major cause of sick leave and workers' compensation claims. By the beginning of the 21st century millions of people were absent from work due to work-related musculoskeletal pain or impairment of function and, in currency, billions were lost as a result of compensation costs, lost wages, and lost productivity [71,90]. It seems feasible to assume that the effects of musculoskeletal pain and impairment of function are exacerbated by the behavioural characteristics often observed with work-related musculoskeletal disorders. Several studies suggest that emotional distress and psychological symptoms such as depression, which accompany not only musculoskeletal disorders, but also other forms of tissue injury, are indeed risk factors for increases in sick leave and reduced work capacity [91].

4.5 Exposure to chemicals and the multiple chemical sensitivity syndrome (idiopathic environmental intolerance)

Multiple chemical sensitivity is a renaming of a condition initially referred to as environmental illness. Although the World Health Organisation recommended the term idiopathic environmental intolerance [92], the term multiple chemical sensitivity still appears to be the one most commonly used. According to a recent review in the Journal of Occupational and Environmental Medicine, multiple chemical sensitivity is currently included in the broader definition of idiopathic environmental intolerance, which also includes physical risk factors such as electromagnetic fields [93]. No one definition is generally adhered to, but it is safe to say that multiple chemical sensitivity is an acquired, chronic condition in which low levels of chemicals can cause symptoms in sensitized individuals that may vary in intensity from mild to disabling. Multiple chemical sensitivity is a

multisystem disorder that manifests as a result of exposure to various environmental contaminants at concentrations below a threshold limit value considered toxic for the general population [93].

A multitude of risk factors have been described, many overlapping with those identified as risk factors in the development of sick building syndrome. Examples of risk factors for multiple chemical sensitivity include: pesticides; paint fumes; smoke; natural gas; petroleum-based solvents like toluene and benzene; volatile organic compounds like formaldehyde; heavy metals like mercury and aluminium; moulds and the potentially dangerous mycotoxins they produce; tobacco smoke; the phthalates and other endocrine-disrupting compounds like the bisphenol A found in plastics; flame retardants like polybrominated diphenylethers; automobile exhaust fumes; newspaper print; scented products like perfumes, air fresheners and other fragrant products; personal care products; laundry detergents and fabric softeners; household cleaners and more [94,95].

There is a striking overlap between symptoms of multiple chemical sensitivity and that of sickness behaviour, sick building syndrome, work-related musculoskeletal disorders, chronic fatigue syndrome and fibromyalgia. The most common physical symptoms reported for multiple chemical sensitivity are sneezing, rashes, dizziness, headache, chronic fatigue, weakness, muscle and joint pain, insomnia, nausea, migraines, difficulties in breathing and swallowing, coughing, gas and bloating, urinary frequency and urgency, visual disturbances, palpitations and chest pain, nasal congestion and sinus pressure, burning of the eyes, nose and skin, musculoskeletal pain, sexual discomfort and gastro-intestinal problems, as well as other painful inflammatory complications. Psychological symptoms include depression and irritability, anxiety and panic attacks, as well as cognitive dysfunction such as impairment of memory and concentration problems [94–96]. Depending on the sensitisation of the individual and the exposure level, the severity of the symptoms can range from mild to disabling and although delayed reactions may occur, symptoms usually occur within minutes to an hour after exposure [94,95,97,98]. Reactions to chemicals are influenced not only by the physical, but also to an extent by the psychological well-being of the individual. Negative moods and emotional distress at the time of exposure to the offending chemical result in stronger reactions against it [99]. This led to the question being asked whether multiple chemical sensitivity should be seen as pathophysiology or

pathopsychology [94]. In fact, multiple chemical sensitivity has, on occasion, been described as a psychosomatic, psychoneurotic disturbance [98]. Although multiple chemical sensitivity was described almost 60 years ago [100] it received renewed public attention when symptoms were recorded following the 9/11 disaster, the 1984 Bhopal industrial catastrophe caused by the explosion in a pesticide plant [94], and especially after the Gulf War when health complaints and symptoms similar to those previously reported for multiple chemical sensitivity, including headache, fatigue, muscle stiffness, joint pain, inability to concentrate, sleep problems, and gastrointestinal issues, were reported by war veterans [101].

Although absolute consensus for an association with inflammation needs further investigation, dysregulation of the peripheral immune system with subsequent induction of neurogenic inflammation is frequently proposed as a mechanism likely to play a role in the aetiology of the disease [93,97]. In addition, pro-inflammatory mediators such as cytokines and chemokines have been reported in plasma from subjects with multiple chemical sensitivity, suggesting a low-grade systemic inflammation in these subjects [102,103]. Evidence supporting the association between chemical sensitivity and inflammation is further indicated by increases in circulating inflammatory biomarkers found in individuals with multiple chemical sensitivity , but not in controls, upon exposure to certain chemicals [98,104].

Multiple chemical sensitivity can have far-reaching effects for the workplace, not only for the affected individual, but also for companies and healthy co-workers. It has in the past not been uncommon for individuals with multiple chemical sensitivity to lose their jobs as a result of environmental effects [105]. Workplace policies have since been introduced to try and protect sensitized individuals and to avoid compensation claims. The Indoor Air Quality Policy of the CDC is of interest as it not only has prescriptions for construction, air conditioning, maintenance and cleaning of buildings, but also for the behaviour of co-workers. In addition to the long-standing prohibition on smoking, it also imposes a fragrance-free policy. Scented or fragranced products are, for instance, prohibited at all times in all interior spaces owned, rented, or leased by the CDC; personal care products (e.g. colognes, perfumes, essential oils, scented skin and hair products) may not be applied at or near actual workstations,

restrooms, or anywhere in CDC-owned or leased buildings, and employees are encouraged to be as fragrance-free as possible when they arrive in the workplace [105,106]. In view of a number of successful worker's compensation claims the question has recently been asked whether multiple chemical sensitivity may become the next big workers' compensation issue [107].

5. Discussion

In this writing we briefly examined how stressors encountered in the workplace can lead to low-grade inflammation with adverse effects on the well-being and productivity of the worker. Five examples of work-related conditions that involve low-grade inflammation were briefly discussed, i.e., psychosocial stress, sickness behaviour, sick building syndrome, work-related musculoskeletal disorders and multiple chemical sensitivity, that were caused by adverse psychosocial conditions, infections, poor indoor air quality, musculoskeletal injuries and exposure to chemical substances, respectively. It was seen that these stressors all have the ability to stimulate a pro-inflammatory response and that the co-ordinated response between the immune system and brain can have somatic and behavioural effects that may negatively impact on workers' productivity and well-being.

The five conditions discussed have many symptoms in common, including mental and physical fatigue, malaise,pain, depression and/or irritability, slowing of motor and/or cognitive function and others . With low-grade systemic inflammation, followed by neuroinflammation, as common causal denominator, an overlap, as seen in the behavioural and certain physical symptoms, is not unexpected This overlap in symptoms is also common to what is traditionally referred to as the functional somatic syndromes, a feature that underlies the discourse on the concept of one general functional somatic syndrome [108].

Another feature common to all five examples is the fact that the expression of the symptoms are influenced bythe general psychological disposition and perceptions of the worker, as well as the psychosocial environment of the workplace. This statement is borne out by observations that adverse factors in the psychosocial environment may contribute to the development of sick building syndrome [60]; that emotional distress and symptoms such as depression, after injury, are risk factors for

increases in sick leave and reduced work capacity [91]**;** that negative moods and emotional distress at the time of exposure to offending chemicals result in stronger immunological stress responses [99]; and that individuals with somatising tendencies appear to be more prone to the development of musculoskeletal pain and associated disability [84]. Such observations gave rise to questions such as whether we are talking about dysfunctional buildings or dysfunctional people when referring to the sick building syndrome [61] and whether multiple chemical sensitivity should be seen as pathophysiology or pathopsychology [94]. In contrast to the detrimental influence of negative psychological characteristics and adverse psychosocial conditions, the reverse also appears to be true. Social support and positive traits such as a sense of coherence, optimism, emotional vitality and enjoyment of life would appear to exert a degree of protection against the development of stress-related physical disorders and indications are that it might be mediated through attenuation of the inflammatory response [38,39,42,43]. .

Throughout this writing reference was made to the potential negative impact of the physical and psychological symptoms of the neuroimmune response on the workplace and on the well-being of the worker. However, the aim of any normal stress response is to protect and help the individual to cope with the stressor by physiological and behavioural adaptations [6]. This also applies to the transient low-grade inflammation with the resultant physical and behavioural symptoms that develop in response to stressors like infection, physical injury and noxious environmental substances. For instance, the neuroinflammation-induced behavioural and physiological components of sickness behaviour represent a highly organized strategy of the organism to fight infection [14,16,109], while the function of early inflammatory processes during musculoskeletal and other forms of tissue injury is known to aid in the restoration and the structural and functional integrity of the injured tissue, including injury to the central nervous system tissue [86,110]. However, although the primary aim of the inflammatory response is adaptive and beneficial it should be tightly controlled and transient in nature. While immune processes are vital for central nervous system homeostasis, as well as cognitive and social abilities [111], and while transient upregulation of microglial inflammatory activity is adaptive and beneficial, continuation or exaggeration of the neuroinflammatory process could become

pathological [112]. Should the inflammation not be resolved and become inappropriate or chronic it can have serious consequences and may give rise to psychopathology and/or pathophysiology. This then would give credence to the description of inflammation as the common pathway for stress-related disorders [10], or even as the common soil of multifactorial diseases [11].

Although substantial agreement was observed between results from different studies, some inter-study variations exist. The cause of such differences is probably multifactorial and could include differences in the type of biomarkers used to assess the inflammatory status; whether the exposure was acute or chronic; previous exposure or sensitisation to the stressor; demographic properties of the study populations; as well as the general psychosocial atmosphere and available support systems in the work environments. A shortcoming of the present paper is the omission of an overview of such confounding factors. It is suggested that an overview focussing on such confounding factors would not only contribute to further clarity in the field, but could be of value in the development of protocols for further studies.

Conclusions:

Overwhelming evidence exists for low-grade systemic inflammation to be a contributing factor to the development of the physical and behavioural symptoms of work-related stress. When tightly controlled and timely resolved the neuroinflammation is adaptive; if not it may negatively affect workers' long-term mental and physical well-being, as well as productivity. Inappropriate continuation of the stressor-induced inflammatory response can, in most cases, be avoided or resolved by early identification of the cause and by appropriate interventions. It is therefore important that those involved with the health of workers be cognisant of inappropriate or chronic low-grade inflammation as a potential health hazard.

Declaration of interest

The authors have no conflict of interest to declare.

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