Environmental Sciences Europe

DISCUSSION

Open Access

Toxicant-induced loss of tolerance for chemicals, foods, and drugs: assessing patterns of exposure behind a global phenomenon

Shahir Masri[1†], Claudia S. Miller[2†], Raymond F. Palmer[2*] and Nicholas Ashford[3]

Abstract

Background: Despite 15–36% of the U.S. population reporting Chemical Intolerances (CI) or sensitivity, the condition has been overlooked in medicine and public health. CI is characterized by multisystem symptoms and new-onset intolerances that develop in a subset of individuals following a major chemical exposure event or repeated low-level exposures. While Toxicant-Induced Loss of Tolerance (TILT) is a two-stage disease mechanism proposed to explain CI, less is known about the exposures that initiate the disease, than about the intolerances that have been documented.

Methods: We reviewed eight major exposure events that preceded onset of chemical intolerance in groups of individuals sharing the same exposure. Our goal was to identify the chemicals and/or groups of chemicals that were most pervasive during each exposure event as well as identify the concentrations of key chemicals involved in each exposure event and the proportions of exposed individuals who ultimately developed TILT following exposure. Case studies we selected for review included (1) workers at U.S. Environmental Protection Agency (EPA) headquarters during renovations; (2) Gulf War veterans; (3) pesticide exposure among casino workers; (4) exposure to aircraft oil fumes; (5) the World Trade Center tragedy; (6) surgical implants; (7) moldy environments; and (8) tunnel workers exposed to solvents.

Results: Mixed volatile and semi-volatile organic compounds (VOCs and SVOCs), followed by pesticides and combustion products were most prevalent across TILT initiation events. As a broader category, synthetic organic chemicals and their combustion products were the primary exposures associated with chemical intolerance. Such chemicals included pesticides, peroxides, nerve agents, anti-nerve agent drugs, lubricants and additives, xylene, benzene, and acetone.

Conclusion: A select group of exposures were predominant in several major initiating events, suggesting their potential role in TILT initiation. Such insights are useful to public health scientists, physicians, and policymakers seeking to minimize harmful exposures and prevent future disease.

Keywords: Chemical intolerance, Multiple chemical sensitivity, TILT, Environment, Exposure

Introduction

Toxicant-induced loss of tolerance

Toxicant-induced loss of tolerance (TILT) is a two-stage disease mechanism first described in the 1990s [1, 2] and characterized by multisystem symptoms and new-onset intolerances that develop in a subset of individuals

*Correspondence: palmerr@uthscsa.edu
†Drs. Masri and Miller share equal effort and are co-first authors.
[2] Department of Family and Community Medicine, The University of Texas Health Science Center at San Antonio, San Antonio, TX, USA
Full list of author information is available at the end of the article

following major chemical exposure events or repeated low-level exposures. Unlike the well-recognized multi-step damage processes known in the causation of some cancers and in endocrine disruption, the worldwide observations of the TILT mechanism fit under neither classical toxicology nor classical allergy. Stage I of TILT, called Initiation, begins upon exposure to a particular chemical or mixture of chemicals that commonly affect the immune system and/or nervous system. For initiation to occur, this chemical exposure must interact with one (or both) of these systems in a way that renders individuals intolerant to subsequent triggering events.

Triggering marks Stage II of TILT, in which (following initiation) affected individuals no longer tolerate everyday exposures to a wide range of structurally diverse substances (including but not limited to the chemical responsible for initiation) at levels that never bothered them previously and do not bother most people. Triggering exposures may include chemically unrelated substances, including ingestants, inhalants, implants, and skin contactants which may take the form of fragrances, cleaning solvents, cigarette smoke, as well as certain foods, drugs/medicine, and other exposures. Following initiation, exposure (even at low levels) to such "triggers" results in symptoms that include fatigue, headache, weakness, rash, mood changes, difficulties with memory and concentration (often described as "brain fog"), and respiratory problems. Many previously tolerated foods and drugs may trigger symptoms (once initiation from a prior exposure has occurred). In Fig. 1, we have provided a schematic—an analogy to observations only at the tip of an iceberg—to help illustrate the two stages of TILT. Often, initiation is not observed or reported, and the phenomenon of masking sometimes obscures triggering of sensitivities suppressing their observation.

Figure 1 shows illness that appears to develop in two stages: (1) initiation, i.e., loss of prior, natural tolerance resulting from an acute or chronic exposure (pesticides, solvents, indoor air contaminants, etc.), followed by (2) triggering of symptoms by small quantities of previously tolerated chemicals (traffic exhaust, fragrances), foods, drugs and food/drug combinations (alcohol, caffeine). The medical doctor (MD) sees only the tip of the iceberg—the patient's symptoms—and formulates a diagnosis based on them (e.g., asthma, chronic fatigue, and migraine headaches). Masking hides the relationship between symptoms and triggers. The initial exposure event causing breakdown in tolerance also may go unnoticed (©UTHSCSA, 1996).

Although TILT was described only recently, reports of TILT-like illness date back much earlier [3, 4]. Initially, the condition appeared restricted to North America. However, a study of nine European countries supported

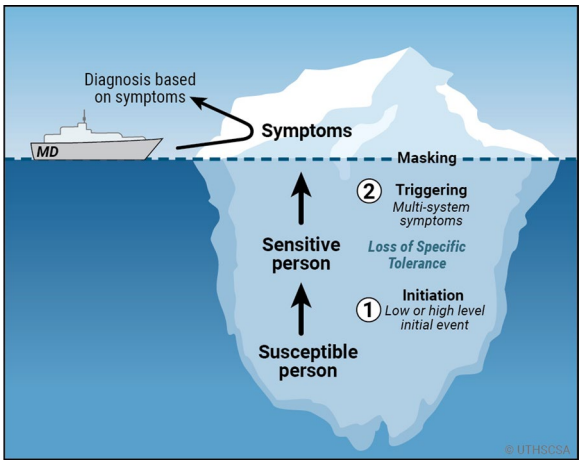

Fig. 1 Phenomenology of TILT

by the European Commission documented parallel observations in 1995 [5, 6]. Interestingly, this cross-country study comparing different presentations of "chemical sensitivity" also revealed different initiating events for chemical sensitivity in each of the nine countries, providing evidence for the two-step disease process that Miller [7] described as TILT. Given the abundance of acronyms that accompany the description and discussion of chemical intolerance and environmental chemical exposures that appear in this paper, a list of acronym definitions can be found in Table 1.

Background and evolution of chemical intolerance

The sharp growth in reports of TILT appears to coincide with the post-WWII expansion of the petrochemical industry and widespread growth in the production of petrochemicals such as organophosphate pesticides, solvents, dyes, and fragrances. U.S. production of the so-called "synthetic organics," which had been less than 1 billion pounds per year, soared to over 460 billion pounds per year by 1994 [8] (of note, while the term "synthetic" can be interpreted differently, its use in this paper is in reference to compounds whose chemical structures do not appear in nature). The same pattern can be seen for pesticide use in U.S. agriculture, which grew from 200 million pounds of active ingredient in 1960 to over 600 million pounds by 1980 [9]. Assuming that exposure to synthetic pesticides and other chemicals is a function of their production and use in everyday society, it is reasonable to assume that these trends have led to increased human exposure over time. Importantly, given their absence prior to modern history, such chemicals can be considered evolutionarily novel and may present particular challenges as it relates

Table 1 List of abbreviations in alphabetical order

Abbreviation	Meaning
4-PCH	4-Phenylcyclohexene
AChE	Acetylcholinesterase
BFR	Brominated fire retardants
BII	Breast implant illness
CI	Chemical intolerance
CYP	Cytochrome P450
EI	Environmental illness
EMU	Environmental medical unit
ENT	Ear, nose, and throat
EPA	Environmental Protection Agency
IEI	Idiopathic environmental intolerance
IgE	Immunoglobulin-E
MCS	Multiple chemical sensitivity
mVOCs	Mold VOCs
OP	Organophosphate
OSHA	Occupational Safety and Health Administration
PAHs	Polycyclic aromatic hydrocarbons
PB	Pyridostigmine bromide
PCBs	Polychlorinated biphenyls
QEESI	Quick Environmental Exposure and Sensitivity Inventory
SVOC	Semi-volatile organic compounds
TILT	Toxicant-induced loss of tolerance
TMJ	Temporomandibular jaw-joint
VOC	Volatile organic compounds
WTC	World Trade Center

to the body's ability to process them through detoxification or elimination pathways. Furthermore, while the human toxicity of pesticides is widely recognized [10], regulations to safeguard the public are likely insufficient given their focus on the toxicity of individual chemical ingredients, as opposed to complex mixtures of multiple chemicals [11], the latter being more reflective of commercial chemical products and other environmental exposures.

Following the 1973–74 U.S. oil embargo, increased energy conservation efforts led to the construction of more energy-efficient, air-tight buildings with reduced fresh air ventilation. This shift toward the increased airtightness of buildings combined with the fact that Americans today spend roughly 90% of their day indoors resulted in an overall increase in exposures to indoor chemical pollutants (e.g., out-gassing chemicals from construction materials and furnishings). By the late 1970s, a phenomenon known as "sick building syndrome" emerged. Eventually, terms such as "multiple chemical sensitivity" (MCS), "environmental illness" (EI), and "idiopathic environmental intolerance" (IEI) entered the popular press to describe the myriad symptoms reported internationally.

In 1906, von Pirquet coined the term "allergy," defining it as "altered reactivity." In 1925, European allergists redefined allergy in terms of antibodies and antigens. However, other forms of heightened reactivity did not fit this new definition, and in 1967, the discovery of the key biomarker immunoglobulin-E (IgE) solidified the field of allergy in medicine and its focus on antibody-mediated responses. Meanwhile, for the many patients showing no biomarkers of exposure, doctors largely dismissed their problems as psychosomatic.

The situation is similar today as a growing number of patients fit this category yet remain unaided by physicians, in some cases being referred to psychiatrists or psychologists for treatment for alleged psychosomatic disorders. In effect, the field of allergy defined chemically intolerant patients as being out of its sphere of study, despite the fact that these patients have "altered reactivity" per von Pirquet's original definition of "allergy" and fit diagnostic criteria for chemical intolerance.

Dismissal and disease unfamiliarity by physicians often leave chemically intolerant patients having to consult ten or more physicians in search of relief. Furthermore, persistence of symptoms in the face of dismissal by doctors leads to skepticism by family, friends, and employers, ultimately leaving patients destitute without emotional support, employment, or medical insurance.

TILT as a disease category

Today, "Chemical Intolerance" and "TILT" are increasingly used instead of "MCS," "EI," and "IEI." Importantly, however, these should not be considered separate diseases, but rather different descriptive phrases that attempt to characterize the same constellation of allergy-like symptoms (triggered by low-level exposures) that do not fit under the classical definition of allergy yet still plague large portions of the population both domestically and abroad. As terminology has evolved, TILT has become a preferred term since, in contrast to these other terms that only describe symptoms, TILT refers to a general disease mechanism that embodies this entire category of disease, thus paralleling other modern disease mechanisms that scientists have come to understand, such as infectious diseases or immunological disorders. The latter categories began as theories: the germ theory and immune theory of disease, respectively. Now, we understand these theories as broad categories that encompass a wide variety of medical conditions that impact any and every system of the body. With the discovery of specific germs and specific immune markers, scientists understood these conditions to be components of broad classes of diseases that share a general

mechanism (see Table 2). Currently, a growing number of observations worldwide in addition to concurrent advances in our understanding of chemical intolerance provide a framework for yet another novel category or class of disease, namely TILT.

Historically, allergy and allergists have been the home for "untoward" altered reactivity of variable origin. Since the discovery of IgE and the redefinition of allergy in 1967, however, words such as "sensitivity" began to take on restricted use. Since the conditions associated with TILT do not appear to involve IgE, allergy tests (e.g., skin tests, blood tests for IgE) often are not helpful except to rule out "true" allergic conditions; that is, allergies to natural antigens such as pollen, dust, mold, animal dander, and food reactions involving anaphylaxis, hives or eczema (atopic dermatitis). In general, the term "intolerance" is preferable for describing non-IgE-mediated reactions. Thus, for instance, adverse reactions to most drugs are labeled as "drug intolerances." This nomenclature can confuse patients, who commonly refer to their recurring exposure-related symptoms as an "allergy" or "sensitivity," resulting in a communications gap between patients and practitioners. The situation is only exacerbated by the complexity of patient symptoms and complaints, as well as their time-intensive nature, which many doctors are unable to treat and prefer to avoid.

Currently, the diverse symptoms resulting from triggering exposures (Stage II of TILT) often lead affected individuals to see medical specialists based on their most troubling symptoms. When such persons with chemically caused damage present themselves to, or are studied by, various specialists of medicine or toxicology, these practitioners group individuals according to such symptoms and are understandably bewildered by the variety of responses that are often manifest at very low levels of exposure of presumed causation. This symptom-based approach results in patients with breathing problems often being referred to pulmonologists; those with nasal symptoms sent to ear, nose, and throat (ENT) doctors; those with stomach and intestinal disorders to gastroenterologists; and those with mood difficulties to psychologists or psychiatrists. It is only when groups are identified and separated for study or treatment according to their initiating events that the nature of the pathology becomes clearer. Examples of such initiating events are the focus of the present analysis.

To date, attempts to characterize TILT are often focused on triggers—such as fragrances or organic solvents—rather than initiators, which can contribute to confusion about the condition [12]. However, to prevent TILT and the triggers that often lead to disruptive and/or incapacitating symptoms, scientists must better understand the first stage of TILT—initiation. At present, although numerous cases of chemical intolerances are well documented in the medical literature, little is known of the factors and exposures involved in TILT initiation. In an effort to improve this understanding, the aim of the present study was to review eight major exposure events that led to the development of TILT among groups of individuals who shared the same underlying exposures to (1) identify the chemicals and/or groups of chemicals that were most pervasive during each exposure event, (2) identify, to the extent possible, the concentrations of key chemicals involved in each exposure event, and (3) determine, to the extent possible, the proportion of both exposed and symptomatic individuals who ultimately developed TILT following each exposure event. By examining these case studies as a whole, and identifying which exposures are most associated with TILT initiation, this analysis provides insights that can aid in TILT intervention, and could help guide patients, physicians, and policymakers as it relates to the future prevention and treatment of TILT.

Table 2 Historical perspective

	Germ theory	Immune theory	TILT theory
Awareness began	~160 years ago	~85 years ago	~30 years ago
Hallmark symptom	Fever	Anaphylaxis	New-onset intolerances to structurally diverse chemicals, foods, and drugs
Causative agents	Bacteria, viruses, rickettsia, etc.	Naturally occurring proteins	Acute or chronic chemical exposures, e.g., sick building, pesticides
How long have we been living with this?	Co-evolved with humans	Co-evolved with humans	Evolutionarily novel
Principal treatment	Antibiotics, vaccines	Antihistamines, steroids, immunotherapy	Unknown
Susceptibility factors	General health, genetics, developmental stage	General health, genetics, developmental stage	General health, genetics, developmental stage
Prevention	Avoidance of sources	Avoidance of sources	Avoidance of sources

Methods

We selected for study eight major events that preceded onset of TILT in groups of individuals who shared the same initiating exposure. To our knowledge we have not excluded any other initiating events in this country, although a nine-country study in Europe conducted by one of the authors revealed other initiating events, such as exposure to chemically treated wood in Germany [5]. Our goal was to determine whether certain classes of chemicals were more apt to initiate TILT in susceptible individuals. The eight exposure events that we selected for analysis included (1) employment in the U.S. Environmental Protection Agency (EPA) headquarters during renovation; (2) participation in the Gulf War; (3) pesticide exposure among casino workers; (4) exposure to aircraft oil fumes; (5) the World Trade Center tragedy; (6) surgical implants; (7) moldy environments; and (8) exposure to solvents among tunnel workers. In the absence of widespread awareness of and widely used diagnostic criteria for TILT, particularly for cases dating back multiple decades, the inclusion of a given exposure event into our analysis was: (1) a well-documented occurrence of chemical intolerance and (2) one that occurred in a group of people (as opposed to an individual), with an inclusion preference toward larger groups.

We selected these eight events as case studies given their well-documented occurrences of chemical intolerance that developed among groups of individuals who shared the same underlying exposures. In our analysis, we reviewed primary literature that pertained to each case study so as to identify common themes relating to the specific chemical exposures underlying each event. We explore these events, their chemical components and their exposed and affected populations in the following sections.

Results

The following text describes the circumstances surrounding eight key exposures/events that led to the development of chemical intolerance among groups of individuals who shared the same underlying exposures, paying special attention to the specific chemicals and/or groups of chemicals that were most pervasive during each exposure event.

EPA building renovation

In October 1987, approximately 27,000 square yards of new carpet were installed in the U.S. EPA headquarters building in Washington, D.C. Health complaints began shortly thereafter, and increased as more carpet was laid. By January 1988, several employees had suffered severe symptoms requiring hospitalization. An industrial hygienist and emergency response team compiled complaint reports and measured indoor air quality.

By April 1988, about 60 employees reported feeling sick at work and experiencing symptoms triggered by a variety of chemicals (not only by those associated with new carpet), consistent with the second stage of TILT—triggering. An estimated 124 of 2000 EPA employees eventually fell ill. Of these, eight acquired chemical intolerance, most prominently triggered by fragrances, traffic exhaust, and tobacco smoke. Several employees quit their jobs due to illness. Though not the first evidence of TILT, this episode represents the first widely acknowledged episode of chemical intolerance acquired in a building. The event attracted national attention to "sick building syndrome," in part because some of those affected were EPA employees with extensive backgrounds in exposure assessment.

The substance most implicated in these illnesses was 4-phenylcyclohexene (4-PCH) an undesirable byproduct from the manufacture of styrene-butadiene rubber (SBR) latex—an adhesive used to attach carpets to their backing. 4-PCH is among the most frequently occurring semi-volatile organic compound (SVOC) emitted by SBR-backed carpets and gives carpet its "new" smell. In the months following the EPA building renovation, indoor air concentrations of 4-PCH were measured to be as high as 6.7 ppb, with concentrations at the time of initial exposure estimated in the range of 1–15 ppb, depending on the room [13, 14]. Since the EPA outbreak, subsequent studies in humans and animals have shown mixed results regarding the toxicity of 4-PCH [15]. One German study found that 4-PCH was associated with headaches, eye irritation, and nausea (NIEHS, 2002) [15]. Despite the potential role that 4-PCH might play in toxicity, it should be noted that numerous other chemicals can outgas from new carpeting, resulting in complex low-level mixtures that may work in an additive or synergistic fashion to elicit toxicity.

Gulf War Illness

Following the 1990–1991 Persian Gulf War, veterans reported numerous multisystem symptoms consistent with TILT [16, 17]. According to a national 1993–1995 survey of Gulf War-era veterans conducted by the U.S. Department of Veterans Affairs, approximately 30% of 700,000 deployed personnel met the CDC case definition of multi-symptom illness (resembling TILT), approximately twice the rate of non-deployed veterans (IOM, 2017). Although the exact cause of illness is uncertain, numerous studies have shown that stress and psychological features are insufficient explanations. As noted by Golomb [18] (2008), post-traumatic stress disorder rates are not systematically higher among Gulf War veterans

compared to soldiers deployed in other conflicts, yet the rates of chronic illness are substantially higher among soldiers deployed to the Gulf [18]. The Institute of Medicine noted that increased symptoms were also reported by veterans from other countries who participated in the Gulf War [19].

Research on wartime exposures has identified chemical weapons released or otherwise present near military personnel during the Gulf War as risk factors. When U.S. forces blew up an Iraqi weapons depot at Khamisiyah, 100,000 U.S. troops were exposed to the organophosphate (OP) nerve agents sarin and cyclosarin, which inhibit the enzyme acetylcholinesterase (AChE). Even minimal OP exposures can elicit acute symptoms, which may herald the onset of TILT [17]. To prevent vector-borne disease among U.S. troops, OP pesticides also were applied widely in the Gulf. The U.S. Department of Defense estimates that at least 40,000 service members may have been overexposed to OPs [17, 20].

An estimated 250,000 U.S. soldiers received pyridostigmine bromide (PB) pills as a pre-treatment drug to protect against possible nerve agent exposure [18]. PB is a carbamate compound resembling OP pesticides in its action on the central nervous system. Except for combat, PB in the U.S. was approved only for treatment of a chronic muscle disease known as myasthenia gravis, in which affected individuals have antibodies to their cholinergic receptors. PB had never been approved for individuals with normal nervous system function, much less chemically susceptible individuals.

Other major Gulf exposures included combustion products from burn pits and oil well-fires [21]. One study determined that Gulf War Illness was closely associated with taking PB tablets, being within one mile of an exploding Scud missile, using pesticides on the skin, and exposure to oil well fire smoke [22].

The most striking symptoms reported by Gulf War veterans involved the central and peripheral cholinergic nervous systems (which require the neurotransmitter acetylcholinesterase) [16, 23–25]. Golomb [18] attributed excess illness in Gulf War veterans, in part, to exposure to acetylcholinesterase inhibitors, including PB, pesticides, and nerve agents. Just after the Gulf War, one of the authors [CSM] served as environmental consultant to the VA Regional Referral Center in Houston, Texas, where she evaluated approximately 60 Gulf War Veterans with unexplained illness. In a 1995 paper, Miller and Mitzel [26] described 37 chemically intolerant individuals who developed TILT following OP pesticide extermination, and were first to point to organophosphates as probable initiators of Gulf War Illness. Miller subsequently coined the term "Toxicant-Induced Loss of Tolerance" [2] based in part on these observations.

Casino workers

Several hundred casino workers developed a "mystery illness" extending over a 1-month period [27]. Responding to complaints of a "Raid-like" smell, an Occupational Health and Safety Administration (OSHA) industrial hygienist investigated and noted an unusual odor and experienced similar symptoms. According to the OSHA report, carbamate and pyrethroid pesticides applied in the employee café and basement walls coincided with the outbreak, with concentrations of the pesticide ingredient coumaphos (and solvent carriers such as 1,1,1-trichloroethane, methylene chloride, acetone, and xylene) being measured at 7–8 ppb (and up to 250 ppm). Nine months later, 12 of 19 workers referred for medical evaluation developed TILT, describing new-onset "sensitivities" to perfumes, gasoline, newsprint, cleaning materials, pesticides, and various solvent-containing materials.

In an effort to determine whether a pattern of illness existed and whether it might be explained by workplace exposures, particularly pesticides, Cone and Sult [27] conducted a detailed analysis of the episode. They identified the likely culprit as a carbamate pesticide called Baygon and its organic solvent carriers, and concluded that the outbreak represented acute and chronic poisoning with a cholinesterase-inhibiting pesticide. As supporting evidence, they pointed to a measurable decrease in mean red blood cell cholinesterase levels among affected employees compared to the laboratory mean.

Aerotoxic syndrome

Pilots, cabin crew, and some frequent flyers have reported episodic poor cabin air quality, with strong odors and sometimes visible smoke or fumes, often referred to as "fume events," followed by TILT-like symptoms. The term "aerotoxic syndrome" has been coined to describe these exposures and symptoms. In some cases, pilots have quit their jobs to avoid worsening illness. One potential explanation regarding exposure arises when we consider that airplane engine compressors typically supply cabin air. Sporadically, synthetic jet oil leaks over the oil seals and enters the cabin ventilation system. Hydraulic and deicing fluids may also enter. These fluids contain triaryl phosphates and organophosphate anti-wear additives such as tricresyl phosphate. High temperatures in the compression chamber cause pyrolysis, producing complex mixtures of combustion products and hydrocarbons.

Michaelis [28] surveyed British pilots about their health and personal experiences with contaminated air aboard aircraft. Of 274 pilots who responded to the survey, 88% were aware of contamination, with 34% reporting "frequent" exposures, 18% reporting "one to two big exposure events," and 7% reporting visible smoke or mist [28]. Of these pilots, 63% reported immediate-to-long-term

adverse health effects, with 53% describing neurological symptoms, including "chemical sensitivity."

World Trade Center tragedy

The 2001 World Trade Center (WTC) tragedy in New York City dispersed clouds of smoke, fuel, and debris into the surrounding area, engulfing streets and infiltrating homes and other structures [29]. Airborne particles and their re-suspension during clean-up activities resulted in heavy and prolonged exposures for first responders and nearby residents. Many developed respiratory symptoms including a new syndrome with persistent cough and severe breathing difficulties, dubbed "WTC cough" [30–32]. According to the U.S. Government Accountability Office, almost all responding firefighters developed persistent respiratory problems, ending the careers of hundreds.

Dr. Steven Levin of the Mount Sinai School of Medicine noted that some of his patients, "once away from Lower Manhattan have noticed a general improvement in their symptoms but find that exposure to cigarette smoke, vehicle exhaust, cleaning solutions, perfume, or other airborne irritants provokes reoccurrence of their symptoms in ways they never experienced before 9/11."

Pollutants associated with the WTC tragedy include combustion products and chemicals used in construction materials, furnishings, and maintenance. Analysis of dust samples from the wreckage revealed a complex mixture including polycyclic aromatic hydrocarbons (PAHs), pesticides (e.g., organochlorides), asbestos, polychlorinated biphenyls (PCBs), dioxins, phthalates, and brominated fire retardants (BFR) [33, 34].

Implant patients

Following surgical implant operations, numerous physicians have reported multisystem symptoms among a subset of patients closely resembling chronic fatigue syndrome and chemical intolerance [35]. Importantly, silicone may leach slowly from intact breast implant membranes [36], producing inflammatory and immunological responses [37, 38]. The chemical composition of implants varies greatly and may include metals that migrate into surrounding tissue [39]. Processing aids and peroxides also have been used to aid the curing process for implant gels. A causal link between breast implant illness (BII) and symptoms is supported by reports that implant removal can reverse symptoms in 40–60% of patients [40].

Brawer (2017) [41] summarized his observations of over 500 breast implant recipients by stating that "Prior to implantation these patients manifested no adverse reactions to perfumes, room fresheners, deodorants, hairsprays, cleaning agents, cigarette smoke, exhaust fumes, carpeting, fabric dyes, adhesives, caulking, glues, stain removers, detergents, dry cleaning products, paints, lacquers, insecticides, pesticides, and printing resins." After their systemic illness became established, they subsequently began to experience nausea, dizziness, and headaches on exposure to nearly all of the above. Brawer [41] also noted a "profound similarity" between TILT and four decades of his own observations.

Although the use of silicone for cosmetic breast implants was banned in 1992, use of silicone persisted in implants designed to correct temporomandibular jaw-joint (TMJ) dysfunction. Materials used in such procedures included silicone rubber and Teflon film laminated to plastic composite. Repeated friction from chewing can liberate microscopic particles from these implant materials into surrounding tissue [41].

Moldy environments

Important evidence of mold-related TILT occurred when Finnish family members moved into a moisture-damaged house and subsequently developed chemical intolerance [42, 43]. Initial symptoms included intense eye irritation, cough, congestion, sinus and throat infections, and shortness of breath, which flared whenever they were home. Among nine family members, all experienced skin symptoms, many had headaches, six had functional abdominal symptoms, at least four suffered muscle and joint pains, and some had fevers. Four children developed asthma requiring medical treatment. Ultimately, seven developed food and pollen allergies. A relative who visited the home suffered a migraine attack upon arrival, requiring subsequent hospital care. Family members' symptoms resolved only after moving to a different home.

Finland is located in a subarctic region where mold damage and mold-related health complaints occur in homes, workplaces, and schools. Occupational health physicians conducting a cross-sectional study of symptoms associated with workplace moisture damage used the validated Quick Environmental Exposure and Sensitivity Inventory (QEESI) to determine how many patients fulfill criteria for chemical intolerance [44]. Based on clinical experience with more than 1000 patients with "Dampness and Mold Hypersensitivity Syndrome," Finnish physician Ville Valtonen reports that approximately half of those patients will ultimately develop chemical intolerance, with some subsequently reporting electromagnetic sensitivity [45].

Kilburn [46] compared 105 symptomatic adults exposed to indoor mold in their homes (where concentrations of mold spores in indoor air were at least four times higher than outdoor air) to 100 individuals exposed to hydrogen sulfide and formaldehyde as well as various synthetic chemicals (by our definition) including diesel

exhaust, organophosphate insecticides, glutaraldehyde, and cleaning agents. These patient groups were compared with 202 community controls not reporting problems following mold or chemical exposure. At the time of Kilburn's study, there was no way to assess mold/mycotoxin in dozens of homes or to document histories of past chemical exposures. Employing a comprehensive battery of 26 neurobehavioral tests, nonetheless, Kilburn found 6.1 abnormalities among those reporting mold exposure, 7.1 among those reporting synthetic chemical exposures versus 1.2 among controls. Cognitive and memory difficulties were similar in both exposed groups. He concluded that the neurobehavioral and pulmonary impairments in persons exposed to mold and mycotoxins did not differ significantly from those who became ill following various synthetic chemical exposures.

Molds can irritate any exposed part of the body, including the skin, eyes, and respiratory tract, and act as allergens. Although mold spores and particles contain mycotoxins that can be toxic via ingestion or inhalation, it may be mold VOCs that play a role in initiating TILT [47]. During development, fruit flies exposed at concentrations of 2.8–14.7 ppmv (in air) to the types of mold VOCs released by Aspergillus fumigatus exhibited neurological impairment. In particular, 1-octen-3-ol concentrations of 2.8 ppmv adversely affected the dopaminergic neurons resulting in Parkinson's-like symptoms [48, 49]. Importantly, the VOC concentrations used to expose flies were low doses in the range of concentrations reported in mold-infested buildings [50].

Water intrusion and/or indoor air humidity greater than 50% fosters growth of mold and other microorganisms including dust mites and bacteria. The saying, "water it and it shall grow" applies to any organic material that gets wet, e.g., carpets, fabrics, paper, plywood, compressed wood, and gypsum board. If not removed or thoroughly dried within 48–72 h, these materials can place occupants' health at risk. Also, when wet, the resins in these materials can degrade, releasing formaldehyde and various VOCs indoors. Subsequent remediation, that is, the removal of moldy materials and/or applying chemicals such as cleaning solvents to control mold growth, may also contaminate indoor air.

Fungi emit multiple VOCs including hydrocarbons, acids, alcohols, aldehydes, aromatics, ketones, terpenes, thiols, and their derivatives. They have characteristic odors and compositions which depend on substrate, temperature, moisture, and pH [50–52]. Where indoor conditions favor mold growth, and where ventilation is poor, levels of mold and accompanying mold products (i.e., spores and VOCs) can build up to higher and more toxic concentrations than outdoors [50, 53]. Fungi that prefer the same temperatures that we prefer in our homes rapidly grow or "amplify" indoors. This helps explain why fungus-related TILT and its complex symptomatology generally are reported from indoor exposures [54].

Tunnel workers

Davidoff et al. [55] described the development of chemical intolerances in workers excavating a subway tunnel beneath a former gasoline station. For 2 months, they were exposed to soil contaminated with gasoline vapors (benzene: 60 ppm) as the tunnel was being dug. The authors interviewed a random sample of 30 out of 70 workers and assessed their health and chemical intolerances after the tunnel was closed due to high benzene levels, and did so a second time 10–13 months later. The authors compared them to a general population sample of 24 matched individuals. Approximately one-fourth (26.7%) of the exposed workers reported new chemical intolerances and other characteristics that fit criteria for TILT.

Besides benzene exposure from gasoline, other potentially relevant exposures in such a confined tunnel space would include particulates, soil micro-organisms, diesel exhaust, and carbon monoxide. The authors noted that these workers were males of low socioeconomic status who had not previously reported symptoms related to CI and were not litigious.

Comparing case studies

Table 3 presents a summary of the eight case studies examined in this analysis according to the chemicals and chemical groups most pervasive in each exposure event and the numbers and percentages of people (where data was available) who were exposed and subsequently developed illness and TILT. As shown, the number of people exposed across the various events ranged from fewer than a dozen (moldy home case) to several hundred thousand (Gulf War Illness).

For the cases ($n=4$) in which both the number of people exposed and the number of people who developed TILT-like symptoms was reported, the proportion of those who developed TILT-like symptoms ranged from 0.4% (EPA Building Renovation) to 44% (moldy home case), with an average of 25%. This average decreased to 20% when excluding the moldy home case where the sample size was low and individuals were genetically similar (same family).

For the cases ($n=4$) in which both the number of people who reported any illness/symptoms (not just chemical intolerance) and the number of people who developed TILT were reported, the proportion of those who developed TILT-like symptoms ranged from 5% (Casino Workers case) to 44% (moldy home case), with an average

Table 3 Initiating events described according to the chemicals and/or chemical groups most pervasive in the event and the number of people who experienced exposure, illness, and the development of TILT-like symptoms

Case study	Initiating event	# of People (% of exposed, % of ill)	Exposure type	Key chemical exposures	Chemical concentrations
EPA building remodel	Carpet installation	Exposure: 2000 Illness: 60 TILT: 8 (0.4%, 13%)	Mixed VOCs	4-PCH Formaldehyde Xylene	1–15 ppb 6–59 ppb 0.9–4.2 ppb
Gulf War Illness	Vehicle and burn pit emissions, pesticide use, and nerve and anti-nerve agents	Exposure: 700,000 Illness: 210,000 TILT: ~ 200,000 (~ 29%)	Nerve agents	Sarin, cyclosarin	NA
			Nerve agent (anti-)	PB	NA
			Pesticides	Organophosphates	NA
			Combustion products	PM_{10} $PM_{2.5}$ PAHs Mixed metals	104–9576 μg/m^3 [a] NA-2889 μg/m^3[a] 5–500 μg/m^3 [a] NA
			Mixed VOCs	Benzene, acetone, toluene, xylene, etc.	2–55 ppb
Casino workers	Pesticides and solvent carriers	Exposure: NA Illness: ~ 250 TILT: 12 (5%)	Pesticides	Carbamates	7–8 ppb
			Mixed VOCs	Xylene, acetone, etc.	240 ppb (max)
Aerotoxic syndrome	Pyrolysis products of lubricant oil and additives from airplane engine	Exposure: NA Illness: 142 TILT: 16 (11%)	Mixed SVOCs	Triphenyl phosphate and Tricresyl phosphate	NA[c]
WTC disaster	Structure fire and "WTC dust" from building collapse	Unknown	Mixed SVOCs	PCBs, dioxin, phthalates and BFRs	NA[c]
			Combustion products	PM, PAHs, metals, etc.	
			Pesticides	Organochlorides	
Implant syndrome	Surgical implants and processing aids	Unknown	Silicone	Poly-dimethylsiloxane Mixed metals	NA
			Peroxides	2,4-Dichlorobenzoyl peroxide	
Tunnel workers	Outgassing of gasoline vapors	Exposure: 30 Illness: NA TILT: 8 (27%)	Mixed VOCs	Benzene	60 ppm
Mold case in Finland	Mold spores, mVOCs, cleaning solvents	Exposure: 9 Illness: 9	Fungi	Mycotoxin	NA
			Mixed mVOCs	1-octen-3-ol, geosmin, etc.	nd-0.9 ppb[b]
		TILT: 4 (44%, 44%)	Mixed VOCs	Unknown	NA

[a] Since measurements were not available for this exposure event, concentration values are those from a similar combat zone in a nearby geographic region (Iraq) [21]

[b] Since measurements were not available for this exposure event, concentration values were drawn from measurements in other homes that were sampled following mold-related complaints (nd=non-detect) [50]

[c] While on-site air sampling was not conducted during the events, the presence of visible smoke/fumes (reported by some pilots in Aerotoxic Syndrome case and well known for WTC case) suggests potentially high exposure

of 18%. This average decreased to 9% when excluding the moldy home case.

Figure 2 presents the number of initiating events for which each group of chemicals was identified as a potential contributor to TILT-related illness, as described by the case reports we analyzed. As shown, the category of mixed VOCs and SVOCs was the most prevalent exposure (6 of 8 events) that was implicated for potential TILT initiation across exposure events, followed by pesticides (3 of 8 events) and combustion products (2 of 8 events). The mixed VOC/SVOC group of chemicals included such VOCs as benzene, acetone, toluene, and xylene as well as SVOCs including BFRs, PCBs, dioxin, phthalates, and triphenyl and tricresyl phosphates. Among this groups of compounds, xylene was identified most frequently across exposure events, followed by both benzene and acetone.

Pesticides included carbamates, organophosphates, and organochlorides, the latter of which consisted of pesticides that were federally banned in the 1970s (e.g., DDT) yet still linger in the environment. Each pesticide type was equally identified across exposure events. Of

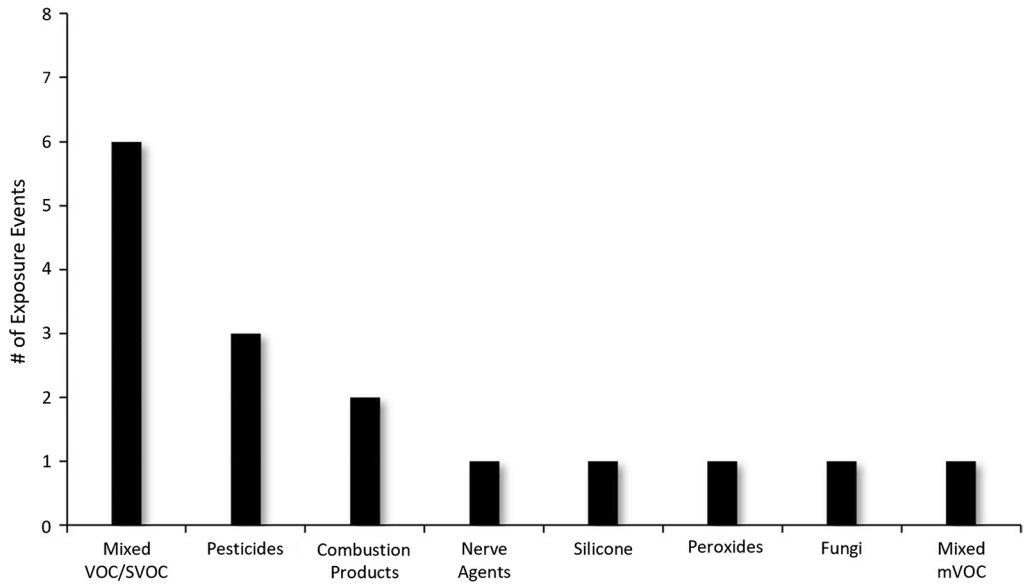

Fig. 2 The number of initiating events for which each group of chemicals was identified as a potential contributor to TILT-related illness

note, while pesticides could also be considered in the VOC/SVOC category, the division of these into separate categories allowed for a more nuanced examination of exposure. And importantly, this grouping did not underweight the VOC/SVOC category, since there was no case of pesticide exposure that was not accompanied by separate chemicals in the VOC/SVOC category. The combustion products identified through our case studies included $PM_{2.5}$, PM_{10}, PAHs, and mixed metals. Combustion products are known to contain other products as well; however, these products are among the most important as it relates to health effects at ambient levels [56, 57].

Discussion

Identifying potential initiators

The purpose of this paper was to examine eight major exposure events associated with TILT to better understand the often-misunderstood pathology of toxicant induction (the initiation step) followed by loss of tolerance (the second and often only observed step). We found that mixed VOCs/SVOCs, followed by synthetic pesticides and combustion products, were the primary exposures associated with TILT initiation. In many instances, such as exposure to pesticides, mixed VOCs/SVOCs, nerve agents, anti-nerve agent pills, lubricants and additives, and WTC exposures could be housed under the phrase "synthetic organics," as defined earlier. That such exposures were predominant in several major initiating events suggests that they may play a role in TILT initiation and provides further evidence for TILT as a new, two-step disease mechanism.

As a broader group, synthetic organic chemicals were a primary source in five cases (Gulf War, building remodeling, aircraft oil fumes, casino workers, tunnel workers) and a secondary source in three cases (WTC tragedy, moldy environment, implants). Four of eight initiating events (Gulf War Illness, WTC tragedy, Aerotoxic Syndrome, tunnel workers) involved decomposition of synthetic organics by burning or pyrolysis, producing secondary exposures. Such combustion products consist of variable mixtures of organic and inorganic gases and particles. The fact that these exposures were pervasive in several major events suggests their relevance to TILT initiation.

Although the proportion of exposed and/or ill individuals who later developed TILT fluctuated considerably depending on the exposure event, the proportions across all cases were far from trivial, supporting the potential magnitude of this public health problem on a global level. The largest proportion of exposed individuals to develop TILT occurred in the case involving the family in a moldy home, potentially due to gene-related similarities between individuals with heightened susceptibility. The lowest proportion occurred surrounding the EPA building renovation, still resulting in nearly a dozen cases among just 2000 exposed.

To date, the identification of TILT initiators stems from observational reports and studies of major exposure events, as highlighted in this analysis. Noteworthy, however, is a study undertaken for the European

Commission [5, 6] that revealed other initiators including wood-preservative chemicals (pentachlorophenol), organic solvents, anesthetic agents, carpets and glue, and formaldehyde.

The case of the EPA building renovation was the first large-scale event to demonstrate TILT. The fact that numerous employees developed chemical intolerance following this exposure served as early evidence for TILT as a new medical problem that can evolve in some sick building occupants.

Miller and Prihoda [58], who surveyed Gulf War veterans, chemically intolerant patients, surgical implant patients, and a control group, used the QEESI to identify individuals who reported developing multisystem symptoms and new-onset intolerances for structurally unrelated chemicals, foods, and drugs which they had previously tolerated and are tolerated by most people. This recurrent pattern of illness following major exposure events occurring in unrelated individuals seen by different doctors in different countries supports a shared underlying mechanism.

Exposures and associated symptoms reported by individuals involved in the WTC collapse closely parallel symptoms of the Gulf War veterans, EPA workers, and others reporting TILT following exposures to combustion products and synthetic organics from building and furnishing materials. Dust samples from the WTC wreckage contained complex mixtures including PAHs (combustion products), pesticides, PCBs (building materials), polychlorinated dibenzodioxins, phthalate esters, and brominated diphenyl ethers (used as fire retardants) [33]. It remains unclear which specific chemicals or chemical combinations are responsible for TILT initiation.

Pesticides were implicated in at least two of the initiating events explored in this analysis, namely, the Gulf War and casino workers examples. As early as the 1960s, occupational health practitioners observed that some individuals who "recovered" from acute pesticide poisoning experienced protracted multisystem symptoms [3]. In the same report, 20 of 114 victims stated that even 3 years later they could no longer tolerate pesticides and became symptomatic from merely a "whiff" of pesticides. Among a group of Nicaraguan agricultural workers, Rosenstock et al. [59] noted decrements in neuropsychological performance that persisted years after accidental organophosphate intoxication. Various studies have similarly shown persistent memory difficulties, cognitive problems, motor impairment, mood alteration, fatigue, and other symptoms following organophosphate pesticide exposure [3, 60, 61].

In a study by Miller and Mitzel (1995) [26], 112 individuals reported TILT-like symptoms following either a well-documented pesticide exposure or building remodeling. The reason this study was not included in the eight events documented in this paper was because unique initiating exposures were difficult to document, a ubiquitous defect of many studies of exquisitely sensitive persons. Despite having had entirely different exposures, both groups exhibited remarkably similar symptom patterns and subsequently reported near-identical triggers (chemicals and specific foods) for their symptoms. Not unexpectedly, the pesticide-exposed group reported somewhat more severe neuromuscular, affective, airway, gastrointestinal, and cardiac symptoms. This study, coupled with Miller's detailed evaluations of Gulf War veterans, led to the development of the QEESI (detailed described later).

Numerous studies have linked chronic multisystem symptoms and new-onset chemical intolerances to organophosphate and carbamate pesticide exposures. Such studies include the case of the casino workers explored in this analysis, as well as farmers, an attorney whose home was exterminated, and others [27, 62, 63]. Ashford et al.'s nine-country European study likewise identified TILT-like cases following various pesticide exposures [5, 6]. Furthermore, in addition to contamination from air bleeding off of the engines, aircraft cabins are often treated with pesticides [64].

While vehicle exhaust and other combustion products are commonly reported triggers, this analysis also points to these pollutants as potential initiators (e.g., the WTC disaster, Gulf War veterans' exposures to oil well fire smoke, diesel exhaust, and incineration of human waste, plastics, and other battlefield materials). More recently, soldiers deployed to Iraq and Afghanistan have reported persistent pulmonary and multisystem symptoms attributed to exposure to combustion products from nearby burn pits in which a wide range of trash was burned, including, but not limited to, paint, medical and human waste, metal/aluminum cans, munitions, petroleum and lubricant products, plastics, rubber, wood, electronics, and discarded food [65, 66]. Chronic and acute upper and lower airway disease due to combustion products is well documented. Less widely known are studies linking air pollution with psychiatric emergency room visits, psychiatric hospital admissions, family disturbances, and anxiety [67–73]. Whether individuals with these exposures develop new-onset chemical, food, and drug intolerances needs to be further studied.

Research has linked indoor air pollution to reduced cognitive performance and productivity [74, 75]. Others have shown an association between air pollution and autism [76, 77]. We (authors Miller and Palmer) have documented a two-to-three-fold risk for autism and for

ADHD in offspring of mothers who are chemical intolerant, based on the QEESI [78].

Thousands of patients report developing multisystem symptoms and chemical, food, and drug intolerances following a wide variety of surgical implants. Common chemical exposures in these cases include silicone and various metals. In addition, processing aids and peroxides such as 2,4-dichlorobenzoyl peroxide are synthetic organics substances that may initiate TILT [79]. Metals leaching from implants may also play a role [80].

In the U.S., increasing numbers of people report adverse reactions to mold [81]. Molds release not only spores and fragments, but also mold VOCs (mVOCs) that become airborne and have toxic and immunogenic effects. Inamdar et al. [82–84] (2012) demonstrated adverse neurological effects on fruit flies (Drosophila melanogaster) of short-chain mVOCs containing as few as eight carbons (e.g., 1-octen-3-ol). With changing climate and increasing major flood events, mold appears to be placing more people at risk for developing TILT. Repairing or refurbishing wet interiors introduces potential exposures to cleaning chemicals, bleach, paints, and other exposures that can exacerbate illness. Unfortunately, many occupants have little choice but to remain in their homes during clean-up.

TILT-related dose and exposure levels

As it relates to the toxicity of various compounds, it has long been understood by toxicologists that the "dose makes the poison." A more nuanced approach to toxicology, however, is to say that the "dose plus host makes the poison." This latter concept highlights the important role that person-to-person biological variation plays in determining the toxicity of a given xenobiotic to a particular individual. Polymorphisms in the genes that code for various cytochrome P450 (CYP) enzymes have been shown, for instance, to produce different metabolic phenotypes and in turn play a role in such variation. For example, individuals whose CYP2D6 phenotype renders them poor metabolizers of debrisoquin are at risk of various adverse drug reactions, whereas extensive metabolizers are at greater risk of lung cancer, perhaps due to the production of carcinogenic metabolites [85].

As it relates to TILT, our analysis demonstrates that important chemical concentration data are often missing from major exposure events, in some cases due to the hazardous nature of the event (e.g., Gulf War combat zone) or its unexpected and episodic occurrence (e.g., WTC disaster). While improved environmental field monitoring would contribute invaluably to understanding TILT, limited measurement data available for our analysis suggest that TILT initiation may occur within the range of chemical exposure levels typically considered hazardous (e.g., the tunnel workers being evacuated due to high benzene concentrations). While measurement data did not exist to characterize the numerous exposures experienced by Gulf War veterans, evidence from other combat zones in the same general geographic region similarly showed extremely high exposure levels (in this case for PM), as noted by an Institute of Medicine report on Joint Base Balad (one of the largest U.S. military bases in Iraq), stating that "the average of the 51 PM_{10} measurements was 709 μg/m^3 (range 104–9576 μg/m^3) and [that] the NAAQS [National Ambient Air Quality Standard] was exceeded for 49 of the 51 samples [21]. Similar results were shown for $PM_{2.5}$.

While concentration data did not exist for our case study on mold, measurements from related research has shown mVOC levels to range from non-detect to roughly 1 ppb in homes that experience complaints, suggesting that mVOCs may affect individuals at extremely low levels (if in fact they are responsible for the complaints). While this analysis did not focus on TILT triggers, such exposures appear to elicit symptoms at very low levels (below those described here for initiation). More field research is needed to determine chemical exposure levels and internal doses required to both initiate TILT and trigger symptoms in susceptible individuals to aid our understanding of chemical intolerance and help prevent future illness.

TILT prevalence

Chemical intolerance has been overlooked in both medicine and public health, despite 15–36% of the U.S. population reporting being "especially" or "unusually" intolerant to certain chemicals, and ~ 5% reporting physician-diagnosed "MCS," "IEI," or other environmentally or chemically related impairment [58].

A nationally representative U.S. population survey conducted in 2016 ($n = 1137$) found a prevalence of 25.9% self-reported chemical sensitivity and 12.8% reported medically diagnosed "multiple chemical sensitivities" or MCS [86]. Two previous nationally representative U.S. population surveys, conducted in 2002–2003 [87] ($n = 1057$) and 2005–2006 [88] ($n = 1058$), found a prevalence (respectively) of 11.1% and 11.6% self-reported chemical sensitivity and 2.5% and 3.9% medically diagnosed MCS. Based on these data, the prevalence of chemical sensitivity may have increased by over 200%, and diagnosed MCS by over 300%, in the past decade.

In a U.S.-based study, 35% of people reported one or more types of adverse health effects attributed to exposure to fragranced consumer products such as cleaning supplies, air fresheners, fabric softeners, and personal care products [89]. Fragranced consumer products are typically composed of tens to hundreds of compounds,

many derived from petrochemicals [89]. Fragrances are common symptom triggers for most chemically intolerant patients irrespective of their initiating event. It is not always clear whether exposure to a fragrance initiates TILT, or whether an individual associates their symptoms (e.g., headache, brain fog, breathing difficulties) to a distinctive odor for the first time.

Similarly, in Japan, Hojo et al. (2018) [90] reported a 10-year increase in CI in Japan from the 1999–2003 period to 2012–2015, based on QEESI scores for Chemical Intolerances, Other Intolerances, and Life Impact. Construction and renovation, which had been the predominant onset/trigger exposures for CI ten years ago, decreased from 69 to 35%, while electromagnetic fields increased significantly from 0 to 26%, perfume from 0 to 21%, and medical treatment from 2 to 7%. These changes may be attributable to greater exposure awareness, increased exposures to synthetic substances, and perhaps the proliferation and use of electronic devices. Notably, most of these reports from the U.S. and Japan involve triggering, the second stage of TILT, but not necessarily initiating exposures.

It is difficult to estimate TILT's current prevalence and impact for a variety of reasons. First, there is little or no follow-up of exposed workers, families, soldiers or others except in a few countries where detailed, longitudinal data are collected. Even in those countries, few doctors are aware of TILT's two-step mechanism, Initiation and Triggering. Additionally, there are no consistent biomarkers or unique pathology that clearly links illness to particular initiating exposures. For decades, Gulf War veterans fought for recognition of their illnesses. In 2016, Congress declared that Gulf War veterans with medically unexplained conditions that appeared during Gulf War service should be recognized. The Gulf War veterans had such diverse exposures, triggers, and symptoms, that a unifying mechanism has eluded researchers. Scientists and physicians saw no underlying etiology, just as Civil War doctors could not make sense of the fevers and symptoms of soldiers who fell ill. They did recognize one common denominator, fever, but their observations preceded the germ theory of disease and so they knew nothing of the microscopic invaders that were underlying the health crisis. Similarly, doctors today are likely facing another new disease mechanism [2, 7].

Identifying a physiological mechanism

Possible physiological mechanisms to explain TILT are being explored. Any proposed mechanism needs to address the two stages of TILT—initiation and triggering. We have described how this process often begins, citing examples of initiating exposures including employment in the EPA headquarters during renovation, participation in the Gulf War, pesticide exposure among casino workers, exposure to aircraft oil fumes, the World Trade Center tragedy, surgical implants, and damp and moldy environments. Following initiation, even tiny amounts of structurally diverse chemicals, foods, and drugs trigger symptoms and perpetuate illness. It is evident that both the nervous system and the immune system must participate in this process, although a specific biological mechanism and markers have remained elusive.

What we do know, based on worldwide observations by patients and clinicians, is that any mechanism purported to explain TILT must explain the characteristics most closely associated with this illness: (1) symptoms involving virtually any system in the body or several systems simultaneously; (2) differing symptoms and severity in different individuals, even those sharing the same exposure; (3) induction by a wide range of chemicals; (4) subsequent triggering at lower levels of exposure than those involved in initiation; (5) concomitant food intolerances, estimated to occur in a substantial percentage of those with chemical intolerances; (6) the spreading of intolerances to include other, often chemically dissimilar substances, each of which may trigger a different constellation of symptoms; (7) adaptation (masking), that is, acclimatization to incitants including various chemicals, foods and drugs, with continued exposure; withdrawal symptoms and loss of this tolerance with removal of the incitants; plus augmented response with re-exposure after an appropriate interval (for example, 4–7 days), and (8) an apparent threshold effect referred to by some practitioners as the patient's "total load."

When considering the two-stage process involved in TILT, it is useful to recall that multi-stage processes are not absent elsewhere in pathology. For instance, chemically—, or radiometrically—caused cancer proceeds through a mutagenic event, followed by promotion of the mutation to a recognized tumor [91, 92]. Chemicals that initiate mutations can be followed by promotion of the genetic damage by other chemicals that are recognized as promotors. The steps are independent, although some chemicals can be both initiators and promoters. Furthermore, endocrine disruption can cause damage to the reproductive system while not being apparent until puberty when developmental hormone production increases. Hormones are, after all, biochemical catalysts that accelerate somatic processes. TILT can be seen as another example of a multi-step damage mechanism in which the loss of tolerance to certain chemicals (or foods or drugs) is initiated by exposure(s), which later expresses itself as intolerance to specific chemicals—called "triggers." Often the initiators and triggers can be dissimilar chemicals, foods, or drugs whose effects may express themselves at very low levels of exposure.

One promising potential physiological mechanism to explain TILT involves mast cells. Mast cells are the first line of defense involved in our bodies' cellular immunity (as opposed to humoral). They consist of white blood cells that originate in the bone marrow and subsequently migrate to every tissue in our bodies during an immune response, in particular the interface between our tissues and the external environment—the nasal mucosa, the olfactory-limbic tract, lungs, skin, blood and lymph vessels, gastrointestinal tract, and urogenital tract. Mast cells are sometimes regarded as our "primitive immunity," protecting the body against xenobiotics in the form of chemicals, foods, drugs, mold, and viruses. Further details on mast cells as a potential physiological mechanism underlying TILT is the focus of another manuscript currently under preparation by some of the current authors.

Opportunities and challenges in diagnosing TILT

Undoubtedly, personal exposure history, living conditions, nutritional status, and genetic and epigenetic make-up determine TILT susceptibility. Effects of major initiators (e.g., OPs, mold) may persist indefinitely, or even be lifelong. In contrast, symptoms triggered by chemicals, foods, or drugs may be reversible within hours or days. Affected individuals may be unable to link their symptoms to specific exposures if they are heavily "masked." Masking results from overlapping responses to many different chemicals, foods, and drugs, and the normal habituation that occurs with chronic exposures. Until "masked" individuals reduce their overall exposures, it may be impossible to know which if any of their symptoms or health problems may be related to their exposures. For a detailed discussion of masking, see Miller [7].

The ideal way to determine whether an individual is impacted by TILT and how they might modify their diets and environment to reduce their symptoms is through a specially designed hospital facility called an Environmental Medical Unit (EMU). EMUs employ "takeaway medicine" by controlling diet and insofar as possible eliminating all potential problem exposures in a chemically "clean" room. In an environmentally controlled medical unit, patients can be housed long enough (4–7 days) to achieve a clean baseline, free of symptoms, thus enabling double-blind, placebo-controlled challenges and allowing physicians to observe patients prior to EMU entry, after unmasking, and before and after specific exposure challenges, while employing objective measures such as proteomics, pulmonary function testing, or brain imaging. As microscopes enabled scientists to see the "germs" responsible for infectious diseases in the late 1800s, the EMU today is a tool that can enable physicians to see the effects of patients' environments. Such facilities are needed for research, diagnosis, and treatment of TILT. Without these tools, the complex illnesses and exposures involved in TILT will continue to elude us. Currently, no EMU exists in the U.S.

To avoid missing or overlooking TILT, doctors must first understand initiation and triggering, and take detailed exposure histories. Overlooking an exposure that initiates TILT may be missing the only opportunity to intervene and prevent worsening health. Too many people remain in a sick building, a moldy home, or continue to use pesticides or other initiating/triggering chemicals, only to have their symptoms and intolerances spread to other triggers including diverse chemicals, foods, and drugs that never bothered them before. Importantly, if initiating exposures continue, TILT becomes frustratingly complex and nearly impossible to reverse.

The QEESI and BREESI diagnostic tools

The QEESI is a validated diagnostic tool developed by one of the current authors (Miller), which is used internationally by clinicians and researchers to evaluate patients, and to identify research subjects and controls in lieu of a case definition. It is an easy-to-complete and readily accessible questionnaire now used in over a dozen countries to help patients and their caregivers understand this condition and avoid key exposures. The QEESI can also be used to track the emergence of TILT following a major exposure event, to compare patient groups for research, and to document changes in symptoms and intolerances over time with treatment or avoidance [58, 93].

Of note, the QEESI was not the basis for TILT diagnosis or the inclusion of cases in the current analysis for two main reasons. First, the QEESI is a diagnostic tool that must be completed by patients. QEESI reveals triggers, not initiators. In the current analysis, we did not have access to the symptomatic populations who suffered from the described exposure events. Additionally, despite the growing use of the QEESI among medical professionals, it was not deployed to evaluate chemical intolerance by the initial scientists and medical doctors who first documented the exposure events examined in this analysis. In some cases, the exposure events even predated the development of the QEESI tool.

For future research, in addition to helping better understand the more widely documented exposure–TILT relationships, less understood areas such as those involving the intersection between ambient air pollution and psychiatric symptoms as well as the role of surgical implants in initiating TILT could be elucidated (e.g., pre/post-exposure) using the QEESI. Additionally, in the hands of epidemiologists, and perhaps workers or community

groups, the QEESI can serve as a tool to facilitate studies of TILT in the wake of exposures such as:

- Agricultural application of pesticides or herbicides such as glyphosate (now the most widely applied chemical for weed control on farms, lawns, roadways, and golf courses) that may expose workers, nearby residents, or consumers [94].
- A large oil spill such as the Exxon Valdez in Alaska or the Deepwater Horizon spill in the Gulf of Mexico and the accompanied spraying of dispersant [95, 96].
- Fracking, with below-ground injection and release of chemicals that have the potential to contaminate the local environment or pollute groundwater [97].
- First responders, fire fighters, rescue workers, and others in the path of a major fire or explosion such as the destruction of the World Trade Center or the major wildfire that destroyed the city of Paradise, CA, in 2018 [98].
- Military exposures such as combustion products from burn pits (e.g., Afghanistan) or the application of herbicides (e.g., Agent Orange used in Vietnam) [16, 99, 100].
- Implanted devices, [36, 37, 41] procedures, materials, or drugs adopted on a broad scale such as various chemotherapies. Also, dental implants, sealants, intraocular lenses, stents, and other medical devices and procedures [101].
- Adoption of new chemical practices or processes such as automated X-ray developing or cleaning of medical equipment, both of which have exposed hospital personnel to glutaraldehyde [102]. Another emerging concern is ethylene oxide, which is used to sterilize plastics that cannot be autoclaved [103].

The QEESI is a useful tool for patients, researchers, and physicians alike, and is available online where it can be downloaded for free [104]. Additional file 1: Figure S1 presents the so-called "Symptom Star," which is an illustrative example of the type of visual results that the QEESI, once completed, can offer to help patients and physicians understand and diagnose TILT. In addition to the QEESI, the Brief Environmental Exposure and Sensitivity Inventory (BREESI) has been developed as a much shorter 3-item screener for chemical intolerance with excellent predictive validity [105]. The purpose of the BREESI is to serve as a more useful tool for a quick assessment for TILT—ideal for personal or doctor office assessments and epidemiological studies.

Before there were microscopes, doctors could diagnose bacterial diseases only by signs and/or symptoms and patterns of spread. As with infectious diseases, we will need to apply new tools such as the QEESI and BREESI to better understand the exposure-symptom dynamics of TILT as well as the pathophysiology, genetics and epigenetics of TILT. During and following the Civil War, fever was the "hallmark symptom." Today, TILT's hallmark symptom is new-onset intolerances for chemicals, foods, and drugs that never bothered the individual previously and do not bother most people. Frequently, symptoms, and intolerances follow on the heels of recognizable environmental exposure, described herein as TILT initiators. A sick building may initiate TILT gradually over a period of weeks or months. In contrast, an organophosphate exposure may initiate TILT in as little as 2 weeks.

In the present paper, we examined a variety of important exposure events to help identify key exposures that may underlie TILT initiation. While results demonstrated several noteworthy associations, it is important to clarify that this study cannot confirm causation between the initiating exposures and TILT. Future research on exposure events and the underlying mechanism of TILT is needed to demonstrate causality.

Conclusion

TILT is a two-stage disease process characterized by new-onset intolerances to certain chemicals, foods, and drugs following "initiation" by a major exposure event (or repeated low-level exposures). In this analysis, we described eight major exposure events that preceded the onset of TILT in small-to-large populations of people who shared the same exposures. Mixed VOCs and SVOCs, followed by pesticides and combustion products were most prevalent across these TILT initiation events. As a broader category, synthetic organic chemicals and their combustion products were the primary exposures associated with chemical intolerance, including pesticides, peroxides, nerve agents, anti-nerve agent drugs, lubricants and additives, xylene, benzene, and acetone. The pervasiveness of specific chemicals and/or chemical groups across numerous initiation events suggest a potential role of these substances in initiating TILT.

The proportion of individuals who developed TILT from those who were exposed and/or fell ill during each exposure event supports the existence of a major public health problem, particularly when one considers the wide range of exposures associated with TILT initiation and their prevalence worldwide.

To prevent the initiation of TILT in future populations as well as help afflicted individuals cope with chemical intolerance, practitioners need to use the validated QEESI which has 0–100 rating scales for symptoms, intolerances, and life impact, as well as a 0–10 masking index. Doctors and epidemiologists can readily use these validated measures to glean invaluable insights that can lead to improved patient health by

identifying and avoiding "triggers." Furthermore, they need to understand TILT's two-step process, which appears to involve both the immunological and nervous systems. For doctors, the QEESI may also help predict who is most likely to respond adversely to future exposures, whether they encounter pesticides, drugs, implants, new construction materials, petrochemicals, and also whether their children may be prone to various exposures, and perhaps, even react adversely to immunizations.

It should give us pause that following diverse exposure events, there is a pattern of new-onset illnesses accompanied by chemical, food, and drug intolerances occurring in demographically diverse groups in dozens of countries, where people see different doctors and speak different languages. These collective observations provide prima facie evidence that we are dealing with a new disease mechanism—Toxicant-Induced Loss of Tolerance. In a forthcoming paper, we propose a new, plausible biological mechanism for TILT.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12302-021-00504-z.

Additional file 1: Figure S1. QEESI symptom star illustrating symptom severity in an individual before and after an exposure event (e.g., pesticide application, indoor air contaminants, chemical spill).

Acknowledgements
The authors wish to thank Carlos Jaen, Chairman of the Dept of Family and Community Medicine at the University of Texas Health Science Center, for his support.

Authors' contributions
CSM and NA are responsible for the conception and design of this work; SM and RFP performed the literature search. All authors contributed substantially to the drafting and revisions of the manuscript and approved the submitted version. All authors are responsible for the accuracy and integrity of the manuscript interpretation. All authors read and approved the final manuscript.

Funding
This work was funded by a grant from the Marilyn Brachman Hoffman Foundation, Fort Worth, Texas (TX).

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Program in Public Health, University of California, Irvine, CA, USA. [2]Department of Family and Community Medicine, The University of Texas Health Science Center at San Antonio, San Antonio, TX, USA. [3]Sociotechnical Systems Research Center, Massachusetts Institute of Technology, Cambridge, MA, USA.

Received: 22 February 2021 Accepted: 8 May 2021
Published online: 27 May 2021

References

1. Ashford N, Miller CS (1998) Chemical exposures: low levels and high stakes, 2nd edn. Wiley, New York
2. Miller CS (1997) Toxicant-induced loss of tolerance–an emerging theory of disease? Environ Health Perspect 105(Suppl 2):445–453
3. Tabershaw IR, Cooper WC (1966) Sequelae of acute organic phosphate poisoning. J Occup Med 8:5–20
4. Randolph TG (1961) Human ecology and susceptibility to the chemical environment. Ann Allergy 19:518–540
5. Ashford N, Heinzow B, Lütjen K, Marouli C, Mølhave L, Mönch B, Papadopoulos S, Rest K, Rosdahl D, Siskos P, Velonakis E, et al (1995) Chemical sensitivity in selected european countries: an exploratory study. A report to the European Commission. Ergonomia, Athens, Greece, 1995
6. Miller CS (1995) Chemical sensitivity: perspectives from North America and Europe. Proceedings of the conference on healthy buildings '95: an international conference on healthy buildings in mild climates, Milan.
7. Miller CS (2001) Toxicant induced loss of tolerance. Addiction 96(1):115–137
8. USITC (1995) Synthetic organic chemicals: United States production and sales, 1994. United States International Trade Commission.
9. Fernandez-Cornejo J, Nehring R, Osteen C, Wechsler S, Martin A, Vialou A (2011) Pesticide use in US agriculture: 21 selected crops, 1960–2008. Agric Pestic Usage Trends Anal Data Sour. https://doi.org/10.2139/ssrn.2502986
10. Roberts JR (2013) J.R. Reigart recognition and management of pesticide poisonings (6th ed.), DIANE Publishing. http://www2.epa.gov/pesticide-worker-safety/recognition-and-management-pesticide-poisonings
11. Nagy K, Duca RC, Lovas S, Creta M, Scheepers PTJ, Godderis L, Ádám B (2020) Systematic review of comparative studies assessing the toxicity of pesticide active ingredients and their product formulations. Environ Res 181:108926. https://doi.org/10.1016/j.envres.2019.108926
12. Sparks PJ, Daniell W, Black DW, Kipen HM, Altman LC, Simon GE, Terr AI (1994) Multiple chemical sensitivity syndrome: a clinical perspective. II. Evaluation, diagnostic testing, treatment, and social considerations. J Occup Med 36(7):731–737
13. Hirzy JW, Morison R (1991) Carpet/4-phenylcyclohexene toxicity: the EPA headquarters case. Anal Commun Percept Risk. https://doi.org/10.1007/978-1-4899-2370-7
14. National Federation of Federal Employees (1989) Indoor air quality and work environment study, Washington DC
15. Masten S, Haneke K (2002) National Institute of Environmental Health Sciences: 4-Phenylcyclohexene [CASRN 4994-16-5]: Review of toxicological literature. NIEHS. https://ntp.niehs.nih.gov/ntp/htdocs/chem_background/exsumpdf/phenylcyclohexene_508.pdf
16. White R, Steele JP, Ocallaghan K, Sullivan JH, Binns BA, Golomb FE, Bloom JA, Bunker F, Crawford JC, Graves A, Hardie N, Klimas M, Knox WJ, Meggs J, Melling MA, Philber RG (2016) Recent research on Gulf War Illness and other health problems in veterans of the 1991 Gulf War: effects of toxicant exposures during deployment. Cortex 74:449–475
17. Hilborne LH, Golomb BA, Marshall GN, Davis LM, Sherbourne CD, Augerson W, Spektor DM, Harley N, Foulkes E, Hudson A, Anthony CR, Cecchine G, Marlowe DH, Rettig RA, Fricker RD, Reardon E, Cotton SK, Hawes-Dawson J, Pace JE, Hosek SD (2005) Examining possible causes of Gulf War Illness: RAND policy investigations and reviews of the scientific literature. Santa Monica, CA: RAND Corporation. https://www.rand.org/pubs/research_briefs/RB7544.html
18. Golomb BA (2008) Acetylcholinesterase inhibitors and Gulf War illnesses. Proc Natl Acad Sci 105:4295–4300

19. Institute of Medicine (2017) Gulf war and health: volume 10: update of health effects of serving in the Gulf War, 2016. Mil Med 182:1507–1508
20. Research Advisory Committee on Gulf War Veterans' Illnesses Gulf War Illness and the Health of Gulf War Veterans: Scientific Findings and Recommendations Washington, D.C.: U.S. Government Printing Office, November 2008
21. Institute of Medicine consensus report (2011) Long-term health consequences of exposure to burn pits in Iraq and Afghanistan.
22. Steele L, Sastre A, Gerkovich MM, Cook MR (2012) Complex factors in the etiology of Gulf War Illness: wartime exposures and risk factors in veteran subgroups. Environ Health Persp 120:112–118
23. Fukuda K, Nisenbaum R, Stewart G, Thompson WW, Robin L, Washko RM, Noah DL, Barrett DH, Randall B, Herwaldt BL, Mawle AC, Reeves WC (1998) Chronic multisymptom illness affecting Air Force veterans of the Gulf War. JAMA 280:981–988
24. Unwin C, Blatchley N, Coker W, Ferry S, Hotopf M, Hull L, Ismail K, Palmer I, David A, Wessely S (1999) Health of UK servicemen who served in Persian Gulf War. Lancet 353:169–178
25. Steele L (2000) Prevalence and patterns of Gulf War illness in Kansas veterans: association of symptoms with characteristics of person, place, and time of military service. Am J Epidemiol 152:992–1002
26. Miller CS, Mitzel HC (1997) Chemical sensitivity attributed to pesticide exposure versus remodeling. Arch Environ Health 50(2):119–129
27. Cone JE, Sult TA (1992) Acquired intolerance to solvents following pesticide/solvent exposure in a building: a new group of workers at risk for multiple chemical sensitivities? Toxicol Ind Health 8:29–39
28. Michaelis S (2018) Aerotoxic syndrome: a new occupational disease? (adverse health effects experienced by aircrew exposed to aircraft contaminated air). Occup Environ Med 75:A15
29. McGee JK, Chen LC, Cohen MD, Chee GR, Prophete CM, Haykal-Coates N, Wasson SJ, Conner TL, Costa DL, Gavett SH (2003) Chemical analysis of World Trade Center fine particulate matter for use in toxicologic assessment. Environ Health Persp 111:972–980
30. Heinrich J (2004) United States. Congress. House. Committee on Government Reform. Subcommittee on National Security Emerging Threats and International Relations., United States. Government Accountability Office. September 11 health effects in the aftermath of the World Trade Center attack : testimony before the Subcommittee on National Security, Emerging Threats, and International Relations, Committee on Government Reform, House of Representatives, Testimony GAO-04-1068 T. U.S. 2004 Government Accountability Office, Washington, D.C.
31. Wheeler K, McKelvey W, Thorpe L, Perrin M, Cone J, Kass D, Farfel M, Thomas P, Brackbill R (2007) Asthma diagnosed after 11 September 2001 among rescue and recovery workers: findings from the World Trade Center health registry. Environ Health Persp 115:1584–1590
32. Lin S, Reibman J, Bowers JA, Hwang SA, Hoerning A, Gomez MI, Fitzgerald EF (2005) Upper respiratory symptoms and other health effects among residents living near the world trade center site after September 11, 2001. Am J Epidemiol 162:499–507
33. Lioy PJ, Weisel CP, Millette JR, Eisenreich S, Vallero D, Offenberg J, Buckley B, Turpin B, Zhong MH, Cohen MD, Prophete C, Yang I, Stiles R, Chee G, Johnson W, Porcja R, Alimokhtari S, Hale RC, Weschler C, Chen LC (2002) Characterization of the dust/smoke aerosol that settled east of the World Trade Center (WTC) in Lower Manhattan after the collapse of the WTC. Environ Health Persp 110:703–714
34. Landrigan PJ, Lioy PJ, Thurston G, Berkowitz G, Chen LC, Chillrud SN, Gavett SH, Georgopoulos PG, Geyh AS, Levin S et al (2004) Health and environmental consequences of the World Trade Center disaster. Environ Health Perspect 112:731–739. https://doi.org/10.1289/ehp.6702
35. Brautbar N, Vojdani A, Campbell AW (1992) Multiple chemical sensitivities—fact or myth. Toxicol Ind Health. 8:5–8
36. Brautbar N, Campbell A (1995) Silicone implants and immune dysfunction—scientific evidence for causation. Int J Occup Med Tox 4:3–13
37. Brautbar N, Vojdani A, Campbell A (1994) Silicone breast implants and autoimmunity: causation or myth? Arch Environ Health 49:151–153
38. Vojdani A (1992) Immune function impairment in immune patients with clinical abnormalities and silicone breast implants. Toxicol Ind Health 8:415–429
39. Gotman I (1997) Characteristics of metals used in implants. J Endourol 11:383–389
40. Campbell A, Brautbar N, Vojdani A (1994) Suppressed natural killer cell activity in patients with silicone breast implants: reversal upon explantation. Toxicol Ind Health 10(3):149–154. https://doi.org/10.1177/074823379401000304
41. Brawer A (2017) Is silicone breast implant toxicity an extreme form of a more generalized toxicity adversely affecting the population as a whole? Int Ann Med. https://doi.org/10.24087/IAM.2017.1.10.347
42. Heinzow HS, Heinzow BGJ (2017) Commentary: severe sequelae to mold-related illness as demonstrated in two Finnish cohorts. Front Immunol 2017(8):1694
43. Tuuminen T, Rinne KS (2017) Severe sequelae to mold-related illness as demonstrated in two Finnish cohorts. Front Immunol 8:382
44. Nynäs P, Vilpas S, Kankare E et al (2019) Observational cross-sectional study on symptoms associated to moisture damage at workplace: the SAMDAW study protocol. BMJ Open 9:e026485
45. Valtonen V (2017) Clinical diagnosis of the dampness and mold hypersensitivity syndrome: review of the literature and suggested diagnostic criteria. Front Immunol 8(951):1–6
46. Kilburn KH (2009) Neurobehavioral and pulmonary impairment in 105 adults with indoor exposure to molds compared to 100 exposed to chemicals. Toxicol Ind Health. 25(9–10):681–692. https://doi.org/10.1177/0748233709348390
47. Bennett JW, Inamdar AA (2015) Are some fungal volatile organic compounds (VOCs) mycotoxins? Toxins 7:3785–3804
48. Inamdar AA, Masurekar P, Bennett JW (2010) Neurotoxicity of fungal volatile organic compounds in Drosophila melanogaster. Toxicol Sci 117(418–26):61
49. Inamdar AA, Hossain MM, Bernstein AI, Miller GW, Richardson JR, Bennett JW (2013) Fungal-derived semiochemical 1-octen-3-ol disrupts dopamine packaging and causes neurodegeneration. Proc Natl Acad Sci U S A 110:19561–19566
50. Korpi A, Järnberg J, Pasanen AL (2009) Microbial volatile organic compounds. Crit Rev Toxicol 39:139–193. https://doi.org/10.1080/10408440802291497
51. Al-Maliki HS, Martinez S, Piszczatowski P, Bennett JW (2017) *Drosophila melanogaste* as a model for studying *Aspergillus fumigatus*. Mycobiology 45(4):233–239
52. Lemfack MC, Nickel J, Dunkel M, Preissner R, Piechulla B (2013) mVOC: a database of microbial volatiles. Nucleic Acids Res 42:D744–D748
53. Nevalainen A, Pasanen AL, Niininen M, Reponen T, Kalliokoski P, Jantunen MJ (1991) The indoor air quality in Finnish homes with mold problems. Environ Int 17:299–302. https://doi.org/10.1016/0160-4120(91)90015-I
54. Zhang J, Zhang J, Chen Q (2002) Yang X (2002) A critical review on studies of volatile organic compound (VOC) sorption by building materials (RP-1097). ASHRAE Trans. 108:162–174
55. Davidoff A, Keyl PM, Meggs W (1998) Development of multiple chemical sensitivities in laborers after acute gasoline fume exposure in an underground tunneling operation. Arch Environ Health Int J 53(3):183–189. https://doi.org/10.1080/00039899809605693
56. Stanek LW, Brown JS, Stanek J, Gift J, Costa DL (2011) Air pollution toxicology-a brief review of the role of the science in shaping the current understanding of air pollution health risks. Toxicol Sci 120:8–27. https://doi.org/10.1093/toxsci/kfq367
57. Masri S, Li L, Dang A, Chung JH, Chen JC, Fan ZH, Wu J (2018) Source characterization and exposure modeling of gas-phase polycyclic aromatic hydrocarbon (PAH) concentrations in Southern California. Atmos Environ 177:175–186. https://doi.org/10.1016/j.atmosenv.2018.01.014
58. Miller CS, Prihoda TJ (1999) A controlled comparison of symptoms and chemical intolerances reported by Gulf War veterans, implant recipients and persons with multiple chemical sensitivity. Toxicol Ind Health 15:386–397
59. Rosenstock L, Keifer M, Daniell WE, McConnell R, Claypoole K (1991) Chronic central nervous system effects of acute organophosphate pesticide intoxication. The Pesticide Health Effects Study Group. Lancet 338:223–227
60. Gershon S, Shaw FH (1961) Psychiatric sequelae of chronic exposure to organophosphorus insecticides. Lancet 1:1371–1374

61. Savage EP, Keefe TJ, Mounce LM, Heaton RK, Lewis JA, Burcar PJ (1988) Chronic neurological sequelae of acute organophosphate pesticide poisoning. Arch Environ Health 43:38–45
62. Rosenthal NE, Cameron CL (1991) Exaggerated sensitivity to an organophosphate pesticide. Am J Psychiatry 148:270
63. Sherman JD (1995) Organophosphate pesticides–neurological and respiratory toxicity. Toxicol Ind Health 11:33–39
64. van Netten C, Leung V (2001) Hydraulic fluids and jet engine oil: pyrolysis and aircraft air quality. Arch Environ Health 56(2):181–186
65. Dursa EK, Barth SK, Schneiderman AI, Bossarte RM (2016) Physical and mental health status of Gulf War and Gulf era Veterans: results from a large population-based epidemiological study. J Occup Environ Med 58:41–46
66. National Academies of Sciences, Engineering, and Medicine (2016) Gulf War and health: Volume 10: Update of serving in the Gulf War, 2016. The National Academies Press, Washington, DC
67. Briere J, Downes A, Spensley J (1983) Summer in the city: urban weather conditions and psychiatric emergency-room visits. J Abnorm Psychol. 92:77–80
68. Evans GW, Colome SD, Shearer DF (1988) Psychological reactions to air-pollution. Environ Res 45:1–15
69. Rotton J, Frey J (1985) Air-pollution, weather, and violent crimes—concomitant time-series analysis of archival data. J Pers Soc Psychol 49:1207–1220
70. Bell IR, Miller CS, Schwartz GE, Peterson JM, Amend D (1996) Neuropsychiatric and somatic characteristics of young adults with and without self-reported chemical odor intolerance and chemical sensitivity. Arch Environ Health Int J 51(1):9–21
71. Khan A, Plana-Ripoll O, Antonsen S, Brandt J, Geels C, Landecker H, Sullivan P, Pedersen CB, Rzhetsky A (2019) Environmental pollution is associated with increased risk of psychiatric disorders in the US and Denmark. PLoS Biol 17(8):3000353. https://doi.org/10.1371/journal.pbio.3000353
72. Strahilevitz M, Strahilevitz A, Miller JE (1979) Air-pollutants and the admission rate of psychiatric-patients. Am J Psychiatry 136:205–207
73. Allen JG, MacNaughton P, Satish U, Santanam S, Vallarino J, Spengler JD (2016) Associations of cognitive function scores with carbon dioxide, ventilation, and volatile organic compound exposures in office workers: a controlled exposure study of green and conventional office environments. Environ Health Perspect 124:805–812
74. Wargocki P, Wyon DP, Sundell J, Clausen G, Fanger PO (2000) The effects of outdoor air supply rate in an office on perceived air quality, sick building syndrome (SBS) symptoms and productivity. Indoor Air 10:222–236
75. Wyon DP (2004) The effects of indoor air quality on performance and productivity. Indoor Air 14(Suppl 7):92–101
76. Roberts AL, Lyall K, Hart JE, Laden F, Just AC, Bobb JF, Koenen KC, Ascherio A, Weisskopf MG (2013) Perinatal air pollutant exposures and autism spectrum disorder in the children of Nurses' Health Study II participants. Environ Health Perspect 121:978–984
77. Kalkbrenner AE, Schmidt RJ, Penlesky AC (2014) Environmental chemical exposures and autism spectrum disorders: a review of the epidemiological evidence. Curr Probl Pediatr Adolesc Health Care. 44(10):277–318. https://doi.org/10.1016/j.cppeds.2014.06.001
78. Heilbrun LP, Palmer RF, Jaen CR, Svoboda MD, Miller CS, Perkinsiller J (2015) Maternal chemical and drug intolerances: potential risk factors for autism and attention deficit hyperactivity disorder (ADHD). J Am Board Fam Med 28(4):461–470. https://doi.org/10.3122/jabfm.2015.04.140192
79. Omotayo OP, Omotayo AO, Mwanza M, Babalola OO (2019) Prevalence of mycotoxins and their consequences on human health. Toxicol Res 35(1):1–7. https://doi.org/10.5487/TR.2019.35.1.001
80. IOM (1999) Safety of silicone breast implants. In: Bondurant, SVESH (ed.) Institute of Medicine, The National Academies Review on mold and health
81. Bush RK, Portnoy JM, Saxon A, Terr AI, Wood RA (2006) The medical effects of mold exposure. J Allergy Clin Immunol 117(2):326–33. doi: https://doi.org/10.1016/j.jaci.2005.12.001. Erratum in: J Allergy Clin Immunol 2066;117(6):1373. Erratum in: J Allergy Clin Immunol. 2014;134(5):1217
82. Inamdar AA, Masurekar P, Bennett JW (2010) Neurotoxicity of fungal volatile organic compounds in *Drosophila melanogaster*. Toxicol Sci 117(2):418–426. https://doi.org/10.1093/toxsci/kfq222
83. Inamdar AA, Bennett JW (2015) Volatile organic compounds from fungi isolated after hurricane Katrina induce developmental defects and apoptosis in a *Drosophila melanogaster* model. Environ Toxicol 30(5):614–620. https://doi.org/10.1002/tox.21933 (**Epub 2013 Dec 5 PMID: 24307503**)
84. Inamdar AA, Bennett JW (2014) A common fungal volatile organic compound induces a nitric oxide mediated inflammatory response in *Drosophila melanogaster*. Sci Rep 10(4):3833. https://doi.org/10.1038/srep03833
85. Richardson JR, Miller GW (2010) Environmental health: from global to local. In: Frumkin H (ed) Environmental health: from global to local. Jossey-Bass, San Francisco, p 65
86. Steinemann A (2018) National prevalence and effects of multiple chemical sensitivities. J Occup Environ Med 60(3):e152–e156
87. Caress S, Steinemann A (2005) National prevalence of asthma and chemical hypersensitivity: an examination of potential overlap. J Occup Environ Med 47(5):518–522
88. Caress S, Steinemann A (2009) Prevalence of fragrance sensitivity in the American population. J Environ Health 71(7):46–50
89. Steinemann A (2016) Fragranced consumer products: exposures and effects from emissions. Air Qual Atmos Health 9:861–866
90. Hojo S, Mizukoshi A, Azuma K, Okumura J, Ishikawa S, Miyata M, Mizuki M, Ogura H, Sakabe K (2018) Survey on changes in subjective symptoms, onset/trigger factors, allergic diseases, and chemical exposures in the past decade of Japanese patients with multiple chemical sensitivity. Int J Hyg Environ Health 221(8):1085–1096
91. Pitot HC (1993) The molecular biology of carcinogenesis. Cancer 72(3 Suppl):962–970
92. Ashford NA et al (2015) Cancer risk: role of environment. Published in Science Express 5 February 2015. http://www.sciencemag.org/content/early/2015/02/04/science.aaa6246.full.pdf
93. Yun M, Kang D, Lee K, Kim YK, Kim JE (2013) Multiple chemical sensitivity caused by exposure to ignition coal fumes: a case report. Ann Occup Environ Med 25:32
94. Swanson NL, Leu A, Abrahamson J, Wallet B (2014) Genetically engineered crops, glyphosate and the deterioration of health in the United States of America. J Org Syst 9(2):6–37
95. Rodríguez-Trigo G, Zock JP, Montes II (2007) Health effects of exposure to oil spills. Archivos de Bronconeumología (English Edition) 43(11):628–635
96. Solomon GM, Janssen S (2010) Health effects of the Gulf oil spill. JAMA 304(10):1118–1119
97. Kovats S, Depledge M, Haines A, Fleming L, Wilkinson P, Shonkoff DS, Scovronick N (2014) The health implications of fracking. Lancet 383(9919):757–758
98. Noji E (ed) (1997) The public health consequences of disasters. Oxford University Press, New York
99. Aurell J, Gullett BK, Yamamoto D (2012) Emissions from open burning of simulated military waste from forward operating bases. Environ Sci Technol 46(20):11004–11012
100. Dobkin C, Shabani R (2009) The health effects of military service: evidence from the Vietnam draft. Econ Inq 47(1):69–80
101. Namikoshi T, Yoshima TT, Suga K, Fujii H, Yasuda K (1990) The prevalence of sensitivity to constituents of dental alloys. J Oral Rehabil 17(4):337–381
102. Nallon AM, Herity B, Brennan PC (2000) Do symptomatic radiographers provide evidence for 'darkroom disease'? Occup Med 50(1):39–42
103. LaMontagne AD, Oakes JM, Lopez Turley RN (2004) Long-term ethylene oxide exposure trends in US hospitals: relationship with OSHA regulatory and enforcement actions. Am J Public Health 94(9):1614–1619. https://doi.org/10.2105/AJPH.94.9.1614
104. Miller, C. The quick environmental exposure and sensitivity inventory (QEESI). https://tiltresearch.org/qeesi-2/
105. Palmer RF, Jaén CR, Perales RB, Rincon R, Forster JN, Miller CS (2020) Three questions for identifying chemically intolerant individuals

in clinical and epidemiological populations: The Brief Environmental Exposure and Sensitivity Inventory (BREESI). PLoS ONE 15(9):e0238296. https://doi.org/10.1371/journal.pone.0238296

Publisher's Note