COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

STATEMENT ON IDIOPATHIC ENVIRONMENTAL INTOLERANCE (IEI)

INTRODUCTION

1. Idiopathic environmental intolerance (IEI) has been defined as an acquired illness characterised by multiple recurrent symptoms that are precipitated by environmental exposures which most people tolerate, and that cannot be explained by any known medical, psychiatric or psychological disorder. When associated with chemical exposures the disorder has also been termed multiple chemical sensitivity (MCS), but a World Health Organisation (WHO) International Programme on Chemical Safety (IPCS) workshop, held in Berlin in 1996, recommended that this name should be discontinued because it made an unsupported judgement about causation.[1] The workshop concluded that IEI was a more appropriate descriptor, and it is the term that we have therefore used throughout this statement, although we have focused specifically on IEI linked to chemical exposures. Other names such as "environmental illness" and "total allergy syndrome" have also been applied to the disorder, but we have avoided them.

2. In 1999, the COT was asked by the Health and Safety Executive (HSE) to consider a review of IEI by the Institute of Occupational Medicine (http://www.iom-world.org/), which has since been published.[2] At that time, the Committee concluded that IEI 'was a condition largely defined by the patient' and that 'there was no consistent pattern of symptoms or exposure data to define the condition.' The Committee also agreed that, on the basis of knowledge at that time, 'there was insufficient evidence to make comments on potential mechanisms or to recommend further research in this area.' In 2000, the COT was asked to consider a further review published by the British Society for Allergy, Environmental and Nutritional Medicine (BSAENM), but agreed that there was no need to revise the conclusion reached in 1999.[3]

3. In June 2004 the Rt Hon Alun Michael, then Minister for Rural Affairs and Local Environmental Quality, asked the Royal Commission on Environmental Pollution (RCEP) to undertake 'a study into the science used to assess risk to people from crop spraying.' In response, the RCEP published a report on crop spraying and health effects in residents and bystanders (http://www.rcep.org.uk/reports/sr-2006-cropspraying/sr-cropspraying.htm) in September 2005. At the start of their inquiry, the RCEP had held an open meeting so that they could take account of a range of perspectives in framing the scope of their investigation and in defining the questions to be addressed. In considering those questions, they reviewed a wide range of evidence including peer-reviewed scientific publications, written and oral statements from stakeholders, and information obtained through visits to individuals and

organisations. Among other things, they noted that some of the individuals who submitted evidence to the inquiry and who had experienced exposure to pesticides, suffered from multi-system and multi-symptomatic disorders, which had been variously grouped under the terms, chronic fatigue syndrome (CFS) myalgic encephalomyelitis (ME) or IEI. After consideration of all the evidence obtained, the RCEP took the view that '*Based on the conclusions from our visits and our understanding of the biological mechanisms with which pesticides interact, it is plausible that there could be a link between resident and bystander pesticide exposure and chronic ill health*'.

4. The COT and the Committee on Carcinogenicity (COC) were subsequently asked by Defra and by the Advisory Committee on Pesticides (ACP) to comment on the RCEP report. The committees' remit was restricted to a review of the contents of the RCEP report as written. They were not, on this occasion, asked to undertake an independent review of pesticide safety and use. In a resulting statement published in 2006, the COT recommended that a further review of IEI should be undertaken.[4]

5. The current statement sets out the findings from that further review. It focuses in particular on toxicological mechanisms that might underlie or have a role in IEI linked to chemicals. In addition, by way of background, it summarises the main clinical features and descriptive epidemiology of the disorder, and considers briefly the evidence for genetic and psychological factors in its causation.

SOURCES OF EVIDENCE

6. Details of the literature searches and the approach used to identify relevant papers are provided in Annex 1 to this statement. In addition to the literature review, the Committee was assisted by a presentation on psychological aspects of IEI, which was given at its June 2010 meeting by Professor Omer Van den Bergh, Research Group on Health Psychology, University of Leuven, Belgium. At the same meeting, the Committee also considered a discussion paper (http://cot.food.gov.uk/pdfs/tox201014.pdf) on the possible role of behavioural conditioning in the development of IEI, together with peer-review comments provided by the Institute of Psychiatry.

BACKGROUND

Clinical features of IEI

Symptoms

7. Individuals with IEI report a range of symptoms after exposure to low levels of environmental chemicals.[5,6] The symptoms relate to multiple organs and systems, and can include headache, fatigue, nausea, chest pain and breathlessness among many others.[6] Lacour and colleagues collated the symptoms of 777 self-reported IEI patients, ascertained from three publications as part of a systematic review of the literature. Among the most common symptoms were those linked to the central nervous system, especially headaches, fatigue and cognitive defects (80.1% of

patients); musculoskeletal (72.7%), gastrointestinal (60.6%), dermal (56.0%), auditory (52.1%), mucosal and respiratory (50.2%) and polyneuropathy-like (13.1%) complaints, and cardiovascular symptoms (5.6%). Other reported symptoms (not ranked) were odour hypersensitivity, allergic diathesis, and food or alcohol intolerance.[7] Hojo and colleagues in the Japanese Diagnostic Criteria Study used the Quick Environmental Exposure Sensitivity Inventory (QEESI) to characterise 106 patients (81 female) with IEI.[8] The predominant symptoms (in descending order) were airway/mucous membrane-related, cognitive, neuromuscular, and head-related. Cognitive symptoms were significantly more common in males than females. The disorder caused important disability, with impacts on attendance at work or school, choice of home furnishings, choice of personal care products, ability to drive or travel, and ability to be around others and enjoy social activities.

8. A German multicentre study of 291 consecutive environmental medicine outpatients, which used a formalised approach to diagnose IEI, was unable to identify a characteristic set of symptoms which could be used to aid diagnosis of the disorder.[9]

Overlap with other disorders and co-morbidity

9. The symptoms of IEI have been observed to overlap with those of chronic fatigue syndrome (CFS) and primary fibromyalgia,[7,10] and also with other conditions such as sick building syndrome, "electro-sensitivity" and Gulf War illness.[5] A study which compared symptoms, trait anxiety, body-related cognitions and symptom attributions in subjects with IEI and somatoform disorder, found similar symptoms and psychological features of somatisation.[11] The authors concluded that IEI is a variant of somatoform disorder. High rates of somatoform disorders, anxiety and depression have been reported in people with IEI.[5,12] A German multicentre study found that environmental medicine patients in general, and IEI patients in particular, suffered from more mental disorders than an age- and sex-matched sample of the general population, and that in most patients, these mental disorders had begun many years before the health complaints attributed to the environment.[9] Reid and colleagues collected information from British Gulf War veterans through a postal questionnaire, which asked about symptoms, psychiatric morbidity and medical diagnoses, and concluded that IEI and CFS accounted for some of the medically unexplained illnesses reported by veterans deployed to the Gulf.[23] There has been debate as to whether disorders such as IEI, CFS and Gulf War illness should be classed as a single functional somatic illness.[5] However, the scope of this statement is limited to what has been labelled as chemical-related IEI.

10. In a study in the USA, Baldwin and Bell identified subjects with moderate or high self-reported intolerance of chemical odours. In comparison with a control group who had never experienced odour intolerance, these individuals were more likely to report cardiopulmonary problems or to have sought treatment for illnesses such as heart disease, asthma and diabetes.[14] In Japan, Hojo and colleagues reported co-morbid allergic disease in 84% of a series of 106 patients with a diagnosis of IEI.[8]

Triggering exposures

11. In 1999, the American Academy of Allergy and Clinical Immunology noted that the list of environmental exposures triggering symptoms in patients with IEI was 'virtually unlimited'.[15] Published studies of IEI patients support this conclusion.

12. In a community-based survey conducted in Atlanta, Georgia, USA during 1999-2000, 199 of 1582 respondents indicated unusual sensitivity to chemicals and 49 reported a medical diagnosis of environmental illness or IEI.[16] A very wide range of triggering exposures was reported, including odours arising from perfume, cleaners, fresh ink, pesticides, chlorine in water, tobacco smoke, new carpets, furniture, hairdressing, and car exhaust. Activities by others which provoked symptoms included laundry, application of lawn pesticides, running a car, smoking, and barbecue grilling. A total of 97 individuals gave information on the exposures which had first caused their symptoms. The most commonly reported initiating exposures were to pesticides and solvents (19 individuals in each case). In another survey of people sampled from the general population in the USA, unusual sensitivity was also reported to fresh paint, petrol-based substances, and fragranced products such as air fresheners.[17] A third study in the USA found that patients with chemical odour intolerance reported being made ill by exposure to environmental tobacco smoke, natural gas, room deodorisers and chlorinated water, as well as by the odorants that were used to identify them as chemical-intolerant (pesticide/insecticide, perfume, drying paint, new carpet and vehicle exhaust)[18]. In addition to there being a wide range of potential trigger exposures for IEI, a process of 'generalisation' has been described, whereby over time, patients respond to an increasing number of structurally diverse chemicals.[2]

13. Information about triggering chemicals comes also from provocation studies in which people with IEI have been challenged experimentally with substances, to test whether they cause symptoms. A systematic review of provocation studies that was published in 2006, covered 37 studies including a total of 784 people with self-reported IEI, 547 controls who did not have the disorder, and a further 180 individuals of whom a subset were chemically sensitive.[6] The authors concluded that people with self-reported IEI do react to chemical challenges, responses occurring only when they can discern differences between active and sham exposures.[6] In one published case-report of experimental exposure to odours, the response of the IEI patient was influenced by prior information on whether the odour should be perceived as harmful.[19]

Clinical course

14. Few studies have explored the clinical course and outcome of IEI. Bailer and colleagues reported findings on 46 patients with clinically diagnosed IEI, whom they had followed for 32 months. Syndrome stability (assessed by outcome measures such as number of symptoms, triggering exposures and associated functional impairments) was high over the follow-up period. Both trait anxiety and somatic attribution predicted persistence of IEI. The authors concluded that IEI was a chronic and disabling condition and that trait anxiety contributes to the maintenance of the disorder. [20]

Descriptive epidemiology

15. Assessment of the epidemiology of IEI is complicated because studies have differed in their diagnostic criteria and methods of case ascertainment. Several case definitions have been published,[21-23] based predominantly on that proposed by Cullen in 1987,[24] but a systematic review published in 2005 concluded that there were no agreed standards for the diagnosis of IEI.[7] In particular, there is no well-established biological or physiological test for the disorder.[5,25,26,] In ascertaining cases, some investigations have relied on self-reported diagnoses, whereas others have defined cases on the basis of a formal clinical assessment. But even physician diagnoses can be inconsistent. Thus, one study found that when physicians assessed patients using the Cullen criteria, they differed in their diagnoses for the same individual.[9] Some research groups have devised self-administered questionnaires[22] or formalised computer-assisted classification approaches for the diagnosis of IEI[9], and a questionnaire-based Chemical Intolerance Index has been developed as a screening tool for chemical sensitivity.[27]

16. Differences in the definition and ascertainment of cases may have contributed to the wide variation in reported estimates of the prevalence of IEI in developed countries, ranging from 6.3% to 66%.[5,28] However, they are unlikely to be the complete explanation.

17. Several papers have indicated that IEI patients are predominantly female, women comprising 69-88% of cases.[9,15,29]

Risk factors

Genetic predisposition

18. Five published studies have investigated the genotypes of patients with IEI.

19. McKeown-Eyssen and colleagues carried out genotyping for cytochrome P450 isoform CYP2D6, N-acetyltransferases1 and 2 (NAT1, NAT2), several paraoxonase isoforms (PON1-55, PON1-192, and PON2-148) , and methylenetetrahydrofolate reductase (MTHFR C677T) in 203 clinically diagnosed female cases of IEI and 194 controls, and found evidence for associations of IEI with CYP2D6 homozygous active (OR 3.36 (95%CI 1.33-8.50) p=0.01) (heterozygotes had intermediate risk) and NAT2 rapid (OR 4.14 (95% CI 1.36-12.64) p=0.01). The authors hypothesised that more rapid metabolism of xenobiotics may confer substantially elevated risk of IEI (the OR for the combination CYP2D6 homozygous active and NAT2 rapid was 18.7 (95% CI 2.9-122.5))[30].

20. Wiesmuller and colleagues conducted a case-control study of 59 patients with self-reported IEI (14 men, 45 women, mean age 48y) and 40 controls (14 men, 26 women mean age 43.9y), in which they undertook genotyping for polymorphisms of serotonin transporter (5HTT), NAT1, NAT2, PON1, PON2, and superoxide dismutase (SOD2). There were no significant differences in the prevalence of these polymorphisms between the IEI patients and controls. [31]

21. In Italy, De Luca and colleagues investigated genotypes in 133 consecutive patients with clinically diagnosed IEI, 93 with suspected IEI, and 218 healthy controls.[32] Allele and genotype frequencies of cytochrome P450 isoforms (CYP2C9, CYP2C19, CYP2D6 and CYP3A5), UDP-glucuronosyl transferase (UGT 1A1) and glutathione S transferases (GSTP1, GSTM1, GSTT1) were similar between cases and controls.

22. Schnackenberg and colleagues carried out genotyping of 521 individuals subdivided into two approximately equal groups according to self-rated chemical sensitivity.[33] Those with chemical sensitivity were more frequently NAT2 slow acetylators and/or homozygous for GSTM1 and/or GSTT1 deletion.

23. In a Danish study, genotypes were compared in 96 patients with clinically diagnosed IEI and 1207 controls from the general population [34]. Associations with CYP2D6 alleles were weak and not statistically significant, but fast NAT2 status was significantly more common in the most severely affected IEI patients (OR=3.1 p=0.04)

24. Overall, no clear and consistent associations with genotype are apparent from these studies. In particular, while two investigations have suggested associations with faster metabolism of xenobiotic chemicals, a third indicated the reverse. Moreover, it is unclear how differences in the rate of metabolism of xenobiotics could give rise to the diverse symptoms associated with IEI.

Psychological risk factors

25. As noted above (paragraph 9), the symptoms of IEI overlap with those of functional illnesses such as CFS, fybromyalgia, sick building syndrome and electro-sensitivity, and like those illnesses, IEI is associated with high psychiatric co-morbidity. Some researchers have proposed a biopsychosocial model for the disorder, in which symptoms are not a direct toxic effect, but are mediated by psychological processes.[5]

26. More specifically, it has been suggested that behavioural conditioning contributes to the development of IEI,[35,36] such that symptoms initially produced by perceived noxious stimuli subsequently occur in the absence of toxic exposures. In his presentation to the Committee, Professor Van den Bergh described experiments in which volunteers were exposed to harmless odours in carbon dioxide-enriched air, the carbon dioxide causing hypercapnic hyperventilation and associated symptoms.[37,38] Subsequently, similar symptoms could be induced by exposure to the odour alone, in the absence of elevated carbon dioxide.[37,38] The nature of the odour, the experiment's context (what the experimenters said about the nature of the odour and the volunteers' expectations), and accompanying neutral or negative imagery were all found to influence the conditioning process.[39-41] Similar findings were observed with hypocapnic hyperventilation (i.e. hypocapnia induced by over-breathing) which often occurs during stress. Harmless odours associated with symptoms experienced during hypocapnic hyperventilation were able to trigger similar symptoms in the absence of hypocapnia.[37-41]

27. A predisposing effect of personality was also observed, reported symptoms being more marked and persistent in subjects with high negative affectivity.[42] Professor Van den Bergh described the process of generalisation, by which responses to 'foul' odours extended to other odours not previously experienced.[42,43] He noted that the threshold for report of symptoms by individuals with high negative affectivity was low, with a tendency to affectively over-evaluate symptoms. A recent study showed that electrosensitivity patients exposed to sham radiation experienced an increase in symptoms associated with activation of the same brain structures as were involved when healthy control subjects experienced painful stimulation by heat.[44] He speculated on neuronal processes that could be involved in IEI, which might entail inhibitory effects on prefrontal processing of information.

28. In a longitudinal study in which participants were followed over five years, environmental "annoyance" (a term which included intolerance of chemicals and also electrical hypersensitivity) was more likely to develop in those who at baseline had more subjective health complaints, higher levels of stress, more dissatisfaction with work and lower personal social support [45].

Implications for pathogenesis

29. Given the background information that has been summarised above, a full explanation for IEI would need to account for:

- The wide and diverse range of chemicals that can trigger symptoms
- The occurrence of symptoms appearing to depend on the triggering exposure being discernible (e.g. by an odour or irritancy), and being more likely when the chemical is perceived as harmful
- The variety of symptoms that are produced, relating to multiple organs and physiological systems
- The triggering of symptoms, in some cases severely disabling, in people who suffer from IEI by levels of exposure to chemicals well below those that are tolerated by the large majority of the population.
- The progressive increase that can occur over time in the number and diversity of chemicals that cause symptoms in an affected individual
- The association of the disorder with psychiatric co-morbidity (although psychiatric illness could occur in some cases as a consequence of the distress caused by IEI)

TOXICOLOGICAL MECHANISMS THAT MIGHT UNDERLIE IEI

Altered odorant threshold or perception

30. One explanation that has been proposed for unusual sensitivity to diverse chemicals in a minority of individuals is a reduced threshold for sensation of olfactory stimuli.[46,47] Many studies have found that individuals with clinically diagnosed IEI perceive odours as more intense, irritant, annoying, unpleasant, pungent or nauseating than other people.[48-53] However, studies of odour detection in IEI patients have not shown any differences in odour threshold or odour identification in comparison with control subjects.[47-52,54-56]

31. Alternatively, some investigators have hypothesised that the heightened olfactory response in IEI patients results from differences in cognitive processing.[47,55] Thus, among subjects recruited by newspaper advertisement in Philadelphia, USA, reported odour intensity and irritancy following a 20 minute exposure to acetone was influenced by prior information about the expected consequences of exposure. The highest perceived irritancy was reported by subjects who were given negative information about the consequences of exposure, while the lowest perceived irritation was associated with a more positive description of the expected effects of exposure[57]

32. Three studies have investigated Chemosensory Event Related Potentials (CSERPs) in response to olfactory stimuli in subjects with IEI. In the first, Papao and colleagues measured CSERPs in 23 clinically diagnosed IEI patients, 21 controls who described themselves as sensitive to odorants, and 23 healthy controls without odour sensitivity. Their findings did not support a role of altered cognitive processing in IEI, although the IEI patients perceived olfactometry more negatively than the control groups.[51] In the second study, Hummel and colleagues measured CSERPs in 23 IEI patients (defined according to Cullen's criteria).[55] Subjects were exposed (double-blind) to 23 mg/m^3 2-propanol (expected to produce olfactory symptoms in around 50% of individuals) or air. CSERPs in response to hydrogen sulphide and carbon dioxide were recorded before and after each exposure. Subtle changes in CSERPs (decreased latencies) were observed following 2-propanol, and were considered to reflect alterations in the early stages of information-processing relevant to perceived stimulus intensity or the attention that it receives. However, no data were collected on the effects of exposure in healthy subjects. The third study measured chemosensory, olfactory and auditory event related potentials in 21 subjects with self-reported chemical sensitivity and 17 controls, who were exposed to CO_2, amyl acetate or a 100Hz auditory tone at 70 dBA [58] Patterns of event-related evoked potentials indicated that chemical-sensitive subjects did not habituate to the same extent as controls, and had difficulty ignoring chemical exposures.

33. Positron Emission Tomography (PET) was undertaken in 12 female IEI patients (diagnosed according to WHO consensus criteria) and 12 age-matched controls, who smelt a range of odours including vanillin (an olfactory stimulant), acetone (a trigeminal stimulant), four odorants (cedar oil, lavender oil, eugenol, and butanol) and two putative pheromones. The researchers commented that IEI patients showed reduced rather than enhanced activation of cerebral regions processing odour signals, which was inconsistent with the theory that these regions were sensitised. However, during several of the exposures, IEI patients showed activation of the anterior cingulate cortex and cuneus-precuneus that was not seen in controls. This finding was considered to be consistent with altered odorant processing by IEI patients in the cingulate cortex. It has been suggested that this may have represented a 'harm avoidance' reaction in IEI patients – i.e. a learnt avoidance response.[49]

34. In another study using single photon emission computed tomography, there was evidence of altered regional blood flow with hypoperfusion of odour-processing areas in 8 IEI patients with clinically diagnosed IEI, as compared with controls, following exposure to chemicals previously reported to induce symptoms in the patients.[59]

COT conclusions on odorant thresholds and perception

35. Provocation studies have consistently failed to demonstrate differences in odour thresholds between individuals with and without a diagnosis of IEI. While some studies using CSERP measurements or PET scanning have indicated differences in brain activity in IEI patients relative to controls when they were challenged with olfactory stimuli, these differences may simply reflect a subjective emotional response, and do not necessarily point to a toxic process.

Trigeminal irritancy of the upper airways

36. Trigeminal irritancy is a sensory-parasympathetic response of the upper airways to a wide range of chemicals, which is mediated via the trigeminal nerves.[60,61] The response occurs when certain receptor proteins are bound by irritant chemicals. These include the transient receptor potential (TRP) family of proteins – for example, the TRPV1 (capsaicin or vanilloid) receptor and the TRPA1 (ankyrin1) receptor.[60] Heightened sensory irritation has been suggested as a possible mechanism for IEI.[62-66]

37. Unblinded exposure of IEI patients (diagnosed according to Cullen's criteria or from self-administered questionnaires) to various chemicals, including odorous substances such as hydrogen sulphide and phenyl ethyl alcohol, has been found to cause more frequent reports of annoyance[50-53] and sensory irritation[48,49] than in controls. Van Thriel and colleagues exposed 24 volunteers (12 of whom had self-reported IEI) to combinations of two solvents (2-butanone and ethyl benzene) at levels below their occupational exposure limits for periods of 4 hours. Sensory irritation was assessed during nine exposure periods on separate days separated by intervals of at least two days. The severity of sensory irritation increased with successive exposures in the IEI patients but not in the controls.[67] Osterberg evaluated complaints of mucous membrane irritation in IEI patients and controls exposed to either toluene or n-butyl acetate at progressively increasing concentrations. A stronger build-up of mucous membrane irritation was found in IEI patients.[62]

38. In comparison with controls matched for sex and age, an increased cough response was observed in 12 clinically diagnosed IEI patients following provocation with capsaicin, supporting the concept of up-regulated sensory response to irritants in IEI patients.[68] In another study, the concentration of capsaicin that was required to induce five or more coughs was compared in patients with IEI, patients with eczema who had symptoms in response to odorous chemicals, and controls.[69] Increased sensitivity to capsaicin was observed in both the IEI and eczema patients. In a further study, 25 patients with self-reported IEI (13 women/12 men, mean age 33y), 25 patients with atopic eczema/dermatitis syndrome (AEDS) (13 women/12 men, mean age 33y), and 25 controls (13 women/12 men, mean age 31y) were exposed to a mixture of volatile chemicals derived from painted surfaces of a room.[70] Plasma substance P, vasoactive intestinal peptide and nerve growth factor were measured before and after 15 minutes exposure whilst the individuals watched a video. Increased levels of these pro-inflammatory neuro-peptides were reported in the IEI patients compared to patients with AEDS and controls.

COT conclusions on trigeminal irritancy of the upper airways

39. It is conceivable that trigeminal irritancy could lead to the development of IEI in some individuals. However, not all of the odours that trigger symptoms in IEI patients are irritant.

Immunological mechanisms

40. One of the more widely discussed theories is that IEI results from chemically mediated immune dysfunction.[2,71] In 2000, Mitchell and colleagues reviewed the evidence that was then available on possible immunologically-mediated mechanisms for IEI, noting variation between studies in diagnostic criteria, use of controls, choice of immunological tests, provision of data on normal ranges for indices, and quality control, and also inadequate description of statistical analyses.[72] Immunological mechanisms that had been proposed included allergies to a variety of chemicals,[72,73] and dysregulation of T lymphocytes with damage to T lymphocytes or alteration of the normal balance of T lymphocyte subsets. Mitchell and colleagues considered these hypotheses and concluded that the idea that a wide variety of dissimilar chemicals could induce a common and subtle pathway of immune dysregulation was not supported by the evidence which they had reviewed.[72]

41. Abnormal $CD4^+$ and $CD8^+$ lymphocyte counts have been reported in some IEI patients,[73-77] and this has been investigated in three case-control studies. Simon and colleagues found a higher percentage of $CD4^+$ cells in the blood of IEI patients (although absolute T-lymphocyte counts were similar to those in controls).[78] The case definition applied in this study was not reported. Mitchell reported evidence for a higher $CD4^+$ count and lower $CD8^+$ count in a group of 23 IEI patients (diagnostic criteria not reported) compared to 21 control subjects.[76] And Baines and colleagues found lower total lymphocyte counts in a group of 223 IEI cases as compared with 194 controls, although the authors did not consider the magnitude of the reduction to be clinically significant.[79] It is unclear whether the diagnostic approach used in this study (based on the University of Toronto Health Survey self-administered questionnaire) would have excluded disorders other than IEI that might have affected immune function.

COT conclusions on immunological mechanisms

42. We find the evidence linking IEI with alterations in immune cell populations unconvincing. A particular concern is that associations may have been confounded by the co-occurrence of allergic diseases such as hay fever in a substantial number of IEI patients. Also, it is possible that some of the IEI cases who were studied were misdiagnosed, and in fact had unrecognised allergic disease.

Neurotoxic mechanisms

43. Persistent abnormalities of regional blood flow in the central nervous system (CNS) have been reported in a number of individuals with self-reported chemical sensitivity.[80] Similarly, changes in single photon emission computed tomography consistent with reduced regional cerebral blood flow have been described in people with past exposure to neurotoxic chemicals.[81] However, we did not find any specific

evidence of chemically induced neurotoxicity in individuals with clinically diagnosed IEI. One study explored autonomic nerve function (breathing rate) in patients with self-reported IEI who had been exposed to solvents.[82] The magnitudes of the abnormalities documented were small and without clinical relevance.

44. Corrigan and colleagues proposed that fatigue syndromes such as IEI may involve altered sensitivity of the GABAa receptor.[83] This would be manifested by impaired concentration, lethargy and increased sensitivity to alcohol. It was proposed that the effects of organochlorine compounds in the CNS could be responsible for IEI. Part of the hypothesis involved mobilisation of organochlorines from adipose tissue following viral infections. It was also postulated that organophosphate effects on the cholinergic system might interact with GABAergic systems of the hippocampus and produce the fatigue symptoms associated with IEI. The hypothesis was developed from observations on a limited number of cases. We found no investigations of GABA system function in people with clinically diagnosed IEI.

45. Overstreet and Djuric observed that many characteristics of Flinders Sensitive Line (FSL) rats – for example, sleep disturbances, loss of drive, reduced activity, cognitive disturbances, and an excess of female animals exhibiting these signs relative to males – were similar to features of IEI and depression.[84,85] Moreover, FSL rats developed greater bronchoconstriction in response to cholinergic and allergen challenge than Flinders Resistant Line (FRL) rats; had elevated levels of muscarinic receptors compared to FRL rats; and were more responsive than FRL rats or open bred strains to a wide range of pharmacological agents. They suggested that the mechanisms underlying the sensitivity/intolerance of FSL rats to multiple chemicals, and in particular cholinergic hypersensitivity, might provide useful insight into the pathogenesis of IEI.[84-86] No studies were found of exposure to environmental chemicals in FSL rats.

COT conclusions on neurotoxic mechanisms

46. Evidence in support of the various neurotoxic mechanisms for IEI that have been hypothesised is limited. It is plausible that abnormalities of a CNS receptor could contribute to IEI symptoms in some individuals, but evidence for a role of the GABAa receptor is currently absent. Data on exaggerated cholinergic responses in Flinders Sensitive Line (FSL) rats dosed with pharmacologically active compounds do not allow inferences about mechanisms for IEI, in which many of the triggering chemicals are pharmacologically inactive.

Time-dependent sensitisation/limbic kindling

47. Time-dependent sensitisation (TDS) is a phenomenon in which responses to a novel stimulus are amplified over time as exposures to the stimulus are repeated. Kindling is a special form of time-dependent sensitisation involving the olfactory-limbic system.[87] Evidence of TDS/limbic kindling has been reported from animal experiments, with indications of neurobehavioural sensitisation in rodents exposed to sub-convulsive doses of pentylenetetrazole (PTZ),[88,89] nicotine,[90] and 3,4-methylene-dioxymethamphetamine.[91] In addition, studies have provided evidence of TDS and/or kindling following administration of acutely toxic doses of chlorinated

pesticides (endosulfan[92], dieldrin[93], lindane[94-98]), chlordimeform[99], cismethrin[100], deltamethrin[100], and toluene.[101]

48. A TDS mechanism for IEI was first proposed in 1992.[87] Activation of the limbic system has been postulated to result in dysregulation of behavioural, autonomic, endocrine and immune functions and hence might be relevant to the pathogenesis of IEI.[102,103] A series of investigations were undertaken in rats using different regimes of inhalation exposure to low levels of formaldehyde. Various adverse effects were reported, including an elevated response to cocaine-induced locomotor activity,[104,105] enhanced conditioned fear response,[106,107] altered sleep architecture[108] and increased serum cortisol.[109] The authors suggested that conditioning to odours was relevant to the mechanism of IEI and that airways irritancy induced by formaldehyde may cause stimulation of neural pathways (predominantly involving the hypothalamic-pituitary axis), leading to avoidance.

49. The processes leading to development of IEI, involving progressive host amplification of a response over time through repeated intermittent exposure to stimuli, including drugs, chemicals, endogenous mediators and exogenous stressors have also been termed 'neural sensitisation'.[110,111] Bell and colleagues have hypothesised that there could be cross-sensitisation between classes of stimuli.[110] The combination of exposure to non-toxic doses of chemicals with heightened amplification of responses via the olfactory pathway was proposed as a possible mechanism for neural sensitisation,[103] one outcome of which would be odour intolerance.[111] Bell and colleagues have also speculated that there is an interaction of chemically induced TDS and kindling with affective spectrum disorders (such as depression), generating behavioural symptomatology in the subset of IEI patients who are already depressed or anxious at the time of exposure.[112]

50. Epidemiological studies of TDS were undertaken by a research team based at the University of Arizona using two groups of subjects: a young adult group of college students enrolling on a psychology course[113,114] and an elderly group obtained from mailed requests to individuals living in a retirement area and others already participating in a study of osteoporosis.[115-117] The Chemical Intolerance Index (CII) was used to rate odour intolerance. Individuals with cacosmia (i.e. a tendency to experience odours as unusually unpleasant) exhibit odour intolerance but not the full range of symptoms associated with IEI. Comparisons were made between cacosmics (in these studies the upper 13%-17% of responses on the CII) and non-cacosmics (with the lowest 25% of responses on the CII). The hypothesis under test was that TDS affects measures of behaviour, autonomic function and/or the hypothalamic-pituitary-adrenal stress response (e.g. leading to an increase plasma β-endorphin). Evidence for hyper-activity of the limbic system and some subtle differences in EEG patterns was reported in the undergraduates with cacosmia.[112,113] Evidence for limbic system dysregulation (increased plasma β-endorphin, systolic blood pressure and slower reaction times in a divided attention task) was found in the elderly subjects who rated more highly on the CI index when compared to those with lower scores on the CI index.[102,114-116] In a further double-blind study, the same group of investigators reported that individuals with intolerance to low levels of environmental chemicals could sensitise their EEG response to brief laboratory exposures to odours.[117]

COT conclusions on time-dependent sensitisation/limbic kindling

51. The studies on limbic kindling in experimental animals have used doses that approached or were at a toxic level, and provide no useful insight into the mechanisms of IEI, which is associated with exposure to chemicals at levels well below those that normally would cause toxicity. The effects observed following exposure of rats to low levels of formaldehyde, may have reflected learnt responses. The studies of odour-intolerant subjects (cacosmics) suggest objectively demonstrable effects on brain function, with a response to successive low level chemical exposures that changed over time. However, the findings would require independent replication before they could be regarded as established. Furthermore, even if they were confirmed and could be extrapolated to IEI (cacosmia is not identical to IEI), they would not necessarily indicate a toxic process. Another possibility is that the abnormalities in brain function reflect a psychologically mediated response to exposure. We consider that it is not possible to distinguish TDS from learning, and therefore that TDS is not a useful concept in relation to possible toxicological mechanisms of IEI, which are the focus of this review.

Other Proposed Toxicological Mechanisms

52. The Committee considered a number of other proposed toxicological mechanisms for which very few supporting data were available. These are described briefly below.

Chemical sensitivity and the vomeronasal organ

53. Greene and Kipen have hypothesised that the vomeronasal organ (VNO), a bilateral tubular organ located in the nose, may respond to environmental chemicals and induce endocrine and neuronal responses.[118] However, a study using phenyl ethyl alcohol and androstenone found no differences in odour detection or identification when the VNO was covered.[119] No investigations of VNO response in chemically sensitive individuals were found.

Elevated nitric Oxide/peroxynitrite and increased sensitivity of N-methyl-D-aspartate receptors

54. Pall has proposed that previous chemical exposure increases nitric oxide and peroxynitrite in the nervous system, resulting in enhanced N-methyl-D-aspartate (NMDA) receptor activity.[120] This theory was developed from an earlier hypothesis that inflammatory cytokines, produced in response to bacterial or viral infection, cause induction of nitric oxide synthase and elevated nitric oxide levels, leading to CFS.[121] The author proposed that prolonged stimulation of NDMA receptors, particularly in the hippocampus, would fit with the time-dependent sensitisation hypothesis (see paragraphs 47-51 above). The multiple feedback loops in the proposed mechanism would ensure that peroxynitrite levels once increased would remain elevated, thus explaining the chronicity of IEI. The hypothesis was also suggested to explain the overlap between IEI and CFS. In support of the theory, Pall noted that organophosphate compounds can induce acetylcholine stimulation of muscarinic receptors, which can then result in elevated nitric oxide levels. In addition, it was proposed that absorbed organic solvents could elevate systemic

nitric oxide levels, although no supporting evidence for this was provided.[120] Pall has also reported that NDMA antagonists can reduce responses of IEI patients to chemical exposures.[122]

Integrated defence system overlap as a disease model

55. Rowat has proposed a scheme of "integrated defence system overlap" whereby the CNS, and immune and endocrine systems communicate through common messengers in producing effects such as the stress response, acute-phase response, innate immune response, immune response to antigen, kindling, time-dependent sensitisation, neurogenic switching and traumatic dissociation.[113] Several models were advanced by which chemical exposures might act in combination with psychological factors, but we have not found direct evidence to support any of these models.

Toxicant-induced loss of tolerance

56. Miller has proposed that a phenomenon of toxicant-induced loss of tolerance, whereby some individuals experience exaggerated symptoms on withdrawal from chemical exposures, might explain both drug addiction and the chemical avoidance (abdiction) that occurs in chemically intolerant individuals.[124] According to this hypothesis, whereas drug addicts seek further exposures to alleviate unpleasant withdrawal symptoms, IEI patients react by trying to avoid the exposures. There are no published studies involving IEI patients to support this hypothesis.

Porphyria

57. One study found evidence of enzymatic or biochemical abnormalities in porphyrin metabolism in 9 out of 14 patients being investigated for IEI.[125] It was noted that there were sometimes multiple enzyme deficiencies in these patients, which were not characteristic of any specific type of porphyria and differed from those that occur in congenital porphyria. How chemical exposures might be involved in the pathogenesis of these abnormalities was unclear. It has since been suggested that a biochemical assay, which may have been used for one of the enzymes studied, could be flawed.[126]

Hypoxia/Hypercapnia

58. Ross proposed that IEI and other chronic syndromes causing fatigue, headache and other protean CNS symptoms could result from hypoxia/hypercapnia due to disturbed breathing, noting that several of the common symptoms of IEI (headache, fatigue and spaciness) overlap with those of sleep apnoea and might result from hypoxia/hypercapnia due to airway obstruction.[127] There is, however, no direct evidence to support this proposal and no indication of how disturbed breathing could give rise to all of the other symptoms that are experienced in IEI.

COT conclusion on other proposed mechanisms

59. There is only very limited direct evidence in patients with IEI to support any of the proposed mechanisms reviewed in this section

DISCUSSION AND CONCLUSIONS

60. Having reviewed the relevant scientific literature, we have been unable to identify any toxic mechanism that could satisfactorily account for all of the clinical features and descriptive epidemiology of IEI. In particular, we have found no convincing evidence for any biological mechanism that would explain why such diverse symptoms are induced in some individuals by such a wide range of chemicals, at levels of exposure well below those that are tolerated by the majority of people. Nor is there any convincing evidence of genetic differences in IEI patients that point to a toxic pathogenesis. It is conceivable that trigeminal irritancy could lead to the development of IEI in some individuals. However, not all of the odours that trigger symptoms in IEI patients are irritant.

61. Whilst an unknown toxicological pathogenesis cannot be totally discounted, on current evidence, a much more plausible explanation for IEI is that it represents a psychologically mediated response to perceived noxious exposures. In support of this theory, IEI is associated with psychiatric morbidity, and overlaps clinically with other illnesses such as CFS that appear also to have a significant psychological component.

62. If psychological mechanisms do have a critical role in the pathogenesis of IEI, this does not preclude the possibility that differences in thresholds for airways irritation might render some individuals more susceptible to the disorder, although the evidence for such predisposition at present is weak.

63. Given the plausibility of an important psychological component in IEI, we recommend that this should be considered further by the appropriate specialism within the Department of Health (and devolved administrations), as there may be implications for the development of treatments.

COT Statement 2011/03
May 2011

References

1. International Programme on Chemical Safety. Report of Multiple Chemical Sensitivities (MCS) Workshop. 1996.IPCS/96.29, pp1-46.

2. Graveling R.A., Pilkington A., George J.P., Butler M.P., and Tannahill S.N. (1999) A review of multiple chemical sensitivity. *Occup Environ Med* 56, 73-85.

3. Eaton. K.K, Anthony. H.M, Birtwhistle. S., Downing. D., Freed. L.J., McLaren Howard. J., Maberly. D.J., Mansfield. J.R., Myhill. S., and Radcliffe. M.J. Multiple Chemical Sensitivity; Recognition and Management. A document on the health effects of everyday chemical exposures and their implications. *Journal of Nutritional & Environmental medicine* 10 , 39-84.

4. Committee on Toxicity of Chemicals in Food Consumer Products and the Environment and Committee on Carcinogenicity of Chemicals in Food Consumer Products and the Environment. Statement on Royal Commission on Environmental Pollution: Crop Spraying and the Health of Residents and Bystanders.

5. Das-Munshi J., Rubin G.J., and Wessely S. (2007) Multiple chemical sensitivities: review. *Curr Opin Otolaryngol Head Neck Surg* 15, 274-80.

6. Das-Munshi J., Rubin G.J., and Wessely S. (2006) Multiple chemical sensitivities: A systematic review of provocation studies. *J Allergy Clin Immunol* 118, 1257-64.

7. Lacour M., Zunder T., Schmidtke K., Vaith P., and Scheidt C. (2005) Multiple chemical sensitivity syndrome (MCS)--suggestions for an extension of the U.S. MCS-case definition. *Int J Hyg Environ Health* 208, 141-51.

8. Hojo S., Ishikawa S., Kumano H., Miyata M., and Sakabe K. (2008) Clinical characteristics of physician-diagnosed patients with multiple chemical sensitivity in Japan. *Int J Hyg Environ Health* 211, 682-9.

9. Eis D., Helm D., Muhlinghaus T., Birkner N., Dietel A., Eikmann T., Gieler U., Herr C., Lacour M., Nowak D., Pedrosa Gil F., Podoll K., Renner B., Andreas Wiesmuller G., and Worm M. (2008) The German Multicentre Study on Multiple Chemical Sensitivity (MCS). *Int J Hyg Environ Health* 211, 658-81.

10. Buchwald D. and Garrity D. (1994) Comparison of patients with chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities. *Arch Intern Med* 154, 2049-53.

11 Bailer J., Witthoft M., Paul c., Bayert C., and Rist F.(2005) Evidence for overlap between idiopathic environmental intolerance and somatoform disorders. *Psychosom Med* 67, 921-9.

12 Hausteiner C., Mergeay A., Bornschein S., Zilker T., and Forstl H. (2006) new aspects of psychiatric morbidity in idiopathic environmental intolerances. *J Occup Environ Med* 48, 76-82.

13. Reid S., Hotopf M., Hull L., Ismail K., Unwin C., and Wessely S. (2001) Multiple chemical sensitivity and chronic fatigue syndrome in British Gulf War veterans. *Am J Epidemiol* 153, 604-9.

14. Baldwin C.M. and Bell I.R. (1998) Increased cardiopulmonary disease risk in a community-based sample with chemical odor intolerance: implications for women's health and health-care utilization. *Arch Environ Health* 53, 347-53.

15. American Academy of Allergy Asthma and Immunology Board of Directors (1999) Position Statement: Idiopathic Environmental Intolerances . *J Allergy Clin Immunol* 103, 36-40.

16. Caress S.M. and Steinemann A.C. (2003) A review of a two-phase population study of multiple

chemical sensitivities. *Environ Health Perspect* 111, 1490-7.

17. Caress S.M. and Steinemann A.C. (2004) A national population study of the prevalence of multiple chemical sensitivity. *Arch Environ Health* 59, 300-5.

18. Baldwin C.M., Bell I.R., and O'Rourke M.K. (1999) Odor sensitivity and respiratory complaint profiles in a community-based sample with asthma, hay fever, and chemical odor intolerance. *Toxicol Ind Health* 15, 403-9.

19. Zucco G.M., Militello C., and Doty R.L. (2008) Discriminating between organic and psychological determinants of multiple chemical sensitivity: a case study. *Neurocase* 14, 485-93.

20. Bailer J., Witthoft M., and Rist F. (2008) Psychological predictors of short- and medium term outcome in individuals with idiopathic environmental intolerance (IEI) and individuals with somatoform disorders. *J Toxicol Environ Health A* 71, 766-75.

21. McKeown-Eyssen G.E., Baines C.J., Marshall L.M., Jazmaji V., and Sokoloff E.R. (2001) Multiple chemical sensitivity: discriminant validity of case definitions. *Arch Environ Health* 56, 406-12.

22. McKeown-Eyssen G.E., Sokoloff E.R., Jazmaji V., Marshall L.M., and Baines C.J. (2000) Reproducibility of the University of Toronto self-administered questionnaire used to assess environmental sensitivity. *Am J Epidemiol* 151, 1216-22.

23. Bolt H.M. and Kiesswetter E. (2002) Is multiple chemical sensitivity a clinically defined entity? *Toxicol Lett* 128, 99-106.

24. Cullen M.R. (1987) The worker with multiple chemical sensitivities: an overview. *Occup Med* 2, 655-61.

25. Levy F. (1997) Clinical features of multiple chemical sensitivity. *Scand J Work Environ Health* 23 Suppl 3, 69-73.

26. Sparks P.J. (2000) Diagnostic evaluation and treatment of the patient presenting with idiopathic environmental intolerance. *Occup Med* 15, 601-9.

27. Szarek M., Bell I., and Schwartz G. (1997) Validation of a brief screening measure of environmental chemical sensitvity: the chemical odor intolerance index . *J Environ Psychol* 17, 345-351.

28. Kreutzer R., Neutra R.R., and Lashuay N. (1999) Prevalence of people reporting sensitivities to chemicals in a population-based survey. *Am J Epidemiol* 150, 1-12.

29. Sparks P.J., Daniell W., Black D.W., Kipen H.M., Altman L.C., Simon G.E., and Terr A.I. (1994) Multiple chemical sensitivity syndrome: a clinical perspective. I. Case definition, theories of pathogenesis, and research needs. *J Occup Med* 36, 718-30.

30. McKeown-Eyssen G., Baines C., Cole DE., Riley N., Tyndale, R F., Marshall L., and Jazmajic V. (2004) Case-control study of genotypes in multiple chemical sensitivity: CYPD2D6, NAT1, NAT2, PON1, PON2 AND MTHR. *Int J Epidemiol* 33, 971-8.

31. Weismuller GA., Nigemann H., Weissbach W., Riley F., Maarouf Z., Dott W., Kunert HJ., Zerres K., Eggermann T., and Blomeke B. (2008) Sequence variations in subjects with self-reported multiple chemical sensitivity (sMCS) a case-control study. *J Tox Environ Health A* 71, 786-94.

32. De Luca C, Scordo MG, Cesareo E, Pastore S, mariani S, Maiani G, Stancato A, Loreti B, Valacchi G, Lubrano C, Raskovic, D, De Padova L, genovesi G, and Korkina LG. (2010) Biological definition of multiple chemical sensitvity from redox state and cytokine profiling and

not from polymorphisms of xenobiotic-metabolising enzymes. *Tox Appl Pharmacol* 248, 285-292.

33. Schnalenberg, E, Fabig KR, Stanulla M, Strobol, N, Lustig M, Fabig, N, and Schloot W (2007). A cross-sectional study of self-reported chemical-related sensitivity is associated with gene variants of drug metabolising enzymes. *Env health* , 6,6.

34. Berg ND, Rasmussen HB, Linneberg A, Brasch-Andersen C, Fenger M, Dirksen A, Vesterhauge S, Werge T and Elberling J (2010) Genetic Susceptibility for multiple chemical sensitivity revisited. *Int J. Hyg. Environ. Health* 213, 131-139.

35. Giardino N.D. and Lehrer P.M. (2000) Behavioral conditioning and idiopathic environmental intolerance. *Occup Med* 15, 519-28.

36. Winters W., Devriese S., Eelen P., Veulemans H., Nemery B., and Van den Bergh O. (2001) Symptom learning in response to odors in a single odor respiratory learning paradigm. *Ann N Y Acad Sci* 933, 315-8.

37. Van den Bergh O., Winters W., Devriese S., and Van Diest I. (2002) Learning subjective health complaints. *Scand J Psychol* 43, 147-52.

38. Meulders A., Fannes S., Van Diest I., De Peuter S., Vansteenwegen D., and Van den Bergh O. (2010) Resistance to extinction in an odor-20% CO2 inhalation paradigm: further evidence for a symptom learning account of multiple chemical sensitivity. *J Psychosom Res* 68, 47-56.

39. Stegen K., De Bruyne K., Rasschaert W., Van de Woestijne K.P., and Van den Bergh O. (1999) Fear-relevant images as conditioned stimuli for somatic complaints, respiratory behavior, and reduced end-tidal pCO2. *J Abnorm Psychol* 108, 143-52.

40. Van den Bergh O., Stegen K., and Van de Woestijne K.P. (1998) Memory effects on symptom reporting in a respiratory learning paradigm. *Health Psychol* 17, 241-8.

41. Devriese S., Winters W., Van Diest I.,De Peuter S., Van de Waestijnek K., and Van den Bergh O. (2004). Perceived relation between odours and a negative event determines learning symptoms in response to chemicals. *Int Arch Occup Environ Health*, 77, 200-4.

42. Devriese S., Winters W., Stegen, K., Van Diest I., Veulemans H., Nemery B., Eelen P., Van de Woestijnek K., and Van den Bergh O. (2000) Generalisation of aquired somatic symptoms in response to odors: a pavlovian perspective on multiple chemical sensitivity. *Psyhosom Med* 62, 751-9.

43. Van den Bergh O., Devriese S., Winters W., Veulemans H., Nemery B., Eelen P., and Van de Woestijne K.P. (2001) Acquiring symptoms in response to odors: a learning perspective on multiple chemical sensitivity. *Ann N Y Acad Sci* 933, 278-90.

44. Ladgrebe M, Barta W, Rosengarth K, Frick U, Hauser S, Langguth B, Rutschmann R, Greenlee MW, Hajak G and Eichhammer P. (2008) Neuronal correlates of symptom formation in functional somatic syndromes: An fMRI study. *NeuroImage* 41, 1336-1344.

45. Eek F, karlson B, Osterberg K, Ostergren PO. (2010) Factors associated with prospective development of environmental annoyance. *J Psychosomatic Res* 69, 9-15.

46. Winder C. (2002) Mechanisms of multiple chemical sensitivity. *Toxicol Lett* 128, 85-97.

47. Ross P.M., Whysner J., Covello V.T., Kuschner M., Rifkind A.B., Sedler M.J., Trichopoulos D., and Williams G.M. (1999) Olfaction and symptoms in the multiple chemical sensitivities syndrome. *Prev Med* 28, 467-80.

48. Caccappolo E., Kipen H., Kelly-McNeil K., Knasko S., Hamer R.M., Natelson B., and Fiedler N.

(2000) Odor perception: multiple chemical sensitivities, chronic fatigue, and asthma. *J Occup Environ Med* 42, 629-38.

49. Hillert L., Musabasic V., Berglund H., Ciumas C., and Savic I. (2007) Odor processing in multiple chemical sensitivity. *Hum Brain Mapp* 28, 172-82.

50. Ojima M., Tonori H., Sato T., Sakabe K., Miyata M., Ishikawa S., and Aizawa Y. (2002) Odor perception in patients with multiple chemical sensitivity. *Tohoku J Exp Med* 198, 163-73.

51. Papo D., Eberlein-Konig B., Berresheim H.W., Huss-Marp J., Grimm V., Ring J., Behrendt H., and Winneke G. (2006) Chemosensory function and psychological profile in patients with multiple chemical sensitivity: comparison with odor-sensitive and asymptomatic controls. *J Psychosom Res* 60, 199-209.

52. van Thriel C., Kiesswetter E., Blaszkewicz M., Golka K., and Seeber A. (2003) Neurobehavioral effects during experimental exposure to 1-octanol and isopropanol. *Scand J Work Environ Health* 29, 143-51.

53. van Thriel C., Kiesswetter E., Schaper M., Juran S.A., Blaszkewicz M., and Kleinbeck S. (2008) Odor annoyance of environmental chemicals: sensory and cognitive influences. *J Toxicol Environ Health A* 71, 776-85.

54. Doty R.L., Deems D.A., Frye R.E., Pelberg R., and Shapiro A. (1988) Olfactory sensitivity, nasal resistance, and autonomic function in patients with multiple chemical sensitivities. *Arch Otolaryngol Head Neck Surg* 114, 1422-7.

55. Hummel T., Roscher S., Jaumann M.P., and Kobal G. (1996) Intranasal chemoreception in patients with multiple chemical sensitivities: a double-blind investigation. *Regul Toxicol Pharmacol* 24, S79-86.

56. van Thriel C., Kiesswetter E., Schaper M., Blaskewicz M., Golka K., and Seeber A. (2005) An integrative approach considering acute symptoms and intensity ratings of chemosensory sensations during experimental exposures. *Environ Toxicol Pharmacol* 19, 589-598.

57. Dalton P., Wysocki C.J., Brody M.J., and Lawley H.J. (1997) The influence of cognitive bias on the perceived odor, irritation and health symptoms from chemical exposure. *Int Arch Occup Environ Health* 69, 407-17.

58. Andersson L, Bende M, Millqvist E and Nordin S. (2009) Attention bias and sensitization in chemical sensitivity. *J Psychosomatic Res* 66, 407-416.

59. Orriols, R, Costa R, Cuberas, G, Jacas, C, Castell J, and Sunyer J. (2009) Brain dysfunction in multiple chemical sensitivity, *J Neurol* Sci 287, 72-78.

60. Bessac BF., and Jordt SE. (2008) Breathtaking TROchannels: TRPA1 and TRPV1 in airway chemosensation and reflex control. *Physiology (Bethesda)* 23, 360-70.

61. Shusterman D. (2007) Trigeminally-mediated health effects of air pollution: sources of inter-individual variability. *Hum Exp Toxicol* 26, 149-57.

62. Osterberg K., Orbaek P., Karlson B., Akesson B., and Bergendorf U. (2003) Annoyance and performance during the experimental chemical challenge of subjects with multiple chemical sensitivity. *Scand J Work Environ Health* 29, 40-50.

63. Meggs W.J. (1993) Neurogenic inflammation and sensitivity to environmental chemicals. *Environ Health Perspect* 101, 234-8.

64. Meggs W.J. (1995) Neurogenic switching: a hypothesis for a mechanism for shifting the site of inflammation in allergy and chemical sensitivity. *Environ Health Perspect* 103, 54-6.

65. Bascom R., Meggs W.J., Frampton M., Hudnell K., Killburn K., Kobal G., Medinsky M., and Rea W. (1997) Neurogenic inflammation: with additional discussion of central and perceptual integration of nonneurogenic inflammation. *Environ Health Perspect* 105 Suppl 2, 531-7.

66. Pall M.L. and Anderson J.H. (2004) The vanilloid receptor as a putative target of diverse chemicals in multiple chemical sensitivity. *Arch Environ Health* 59, 363-75.

67. van Thriel C., Haumann K., Kiesswetter E., Blaszkewicz M., and Seeber A. (2002) Time courses of sensory irritations due to 2-butanone and ethyl benzene exposure: influences of self-reported multiple chemical sensitivity (sMCS). *Int J Hyg Environ Health* 204, 367-9.

68. Ternesten-Hasseus E., Bende M., and Millqvist E. (2002) Increased capsaicin cough sensitivity in patients with multiple chemical sensitivity. *J Occup Environ Med* 44, 1012-7.

69. Holst H, Arendt-Nielsen L, Mosbech H, Vesterhauge S, and Elberling, J. (2010) The capsaicin cough reflex in patients with symptoms elicited by odorous chemicals. *Int J. Hyg. Environ. Health* 213, 66-71.

70. Kimata H. (2004) Effect of exposure to volatile organic compounds on plasma levels of neuropeptides, nerve growth factor and histamine in patients with self-reported multiple chemical sensitivity. *Int J Hyg Environ Health* 207, 159-63.

71. Sibbison J. (1991) USA: Multiple chemical sensitivty. *Lancet* 337, 1469-1470.

72. Mitchell C.S., Donnay A., Hoover D.R., and Margolick J.B. (2000) Immunologic parameters of multiple chemical sensitivity. *Occup Med* 15, 647-65.

73. Bernstein D.I. (1996) Multiple chemical sensitivity: state of the art symposium. The role of chemical allergens. *Regul Toxicol Pharmacol* 24, S28-31.

74. Kipen H., Fiedler N., Maccia C., Yukow E., Todaro J., and Laskin D. (1992) Immunologic evaluation of chemically sensitive patients. *Toxicol Ind Health* 8, 125-33.

75. Levin AS.,and Byers VS. (1992) Multiple chemical sensitivities: a practicing clinician's point of view. Clinical and Immunological research findings. *Toxicol Ind Health* 8, 95-109

76. Albright J.F. and Goldstein R.A. (1992) Is there evidence of an immunologic basis for multiple chemical sensitivity? *Toxicol Ind Health* 8, 215-9.

77. Thomas J.G. (1998) A critical analysis of multiple chemical sensitivities. *Med Hypotheses* 50, 303-11.

78. Simon G.E., Daniell W., Stockbridge H., Claypoole K., and Rosenstock L. (1993) Immunologic, psychological, and neuropsychological factors in multiple chemical sensitivity. A controlled study. *Ann Intern Med* 119, 97-103.

79. Baines C.J., McKeown-Eyssen G.E., Riley N., Cole D.E., Marshall L., Loescher B., and Jazmaji V. (2004) Case-control study of multiple chemical sensitivity, comparing haematology, biochemistry, vitamins and serum volatile organic compound measures. *Occup Med (Lond)* 54, 408-18.

80. Simon T.R., Hickey D.C., Fincher C.E., Johnson A.R., Ross G.H., and Rea W.J. (1994) Single photon emission computed tomography of the brain in patients with chemical sensitivities. *Toxicol Ind Health* 10, 573-7.

81. Heuser G., Mena I., and Alamos F. (1994) NeuroSPECT findings in patients exposed to neurotoxic chemicals. *Toxicol Ind Health* 10, 561-71.

82. Haumann K., Kiesswetter E., van Thriel C., Blaszkewicz M., Golka K., and Seeber A. (2003)

Breathing and heart rate during experimental solvent exposure of young adults with self-reported multiple chemical sensitivity (sMCS). *Neurotoxicology* 24, 179-86.

83. Corrigan F.M., MacDonald S., Brown A., Armstrong K., and Armstrong E.M. (1994) Neurasthenic fatigue, chemical sensitivity and GABAa receptor toxins. *Med Hypotheses* 43, 195-200.

84. Overstreet D.H. and Djuric V. (1999) Links between multiple chemical sensitivity and asthma in a rat model of cholinergic hypersensitivity: a brief review. *Toxicol Ind Health* 15, 517-21.

85. Overstreet D.H. and Djuric V. (2001) A genetic rat model of cholinergic hypersensitivity: implications for chemical intolerance, chronic fatigue, and asthma. *Ann N Y Acad Sci* 933, 92-102.

86. Overstreet D.H., Miller C.S., Janowsky D.S., and Russell R.W. (1996) Potential animal model of multiple chemical sensitivity with cholinergic supersensitivity. *Toxicology* 111, 119-34.

87. Bell I.R., Miller C.S., and Schwartz G.E. (1992) An olfactory-limbic model of multiple chemical sensitivity syndrome: possible relationships to kindling and affective spectrum disorders. *Biol Psychiatry* 32, 218-42.

88. De Sarro G., Palma E., Costa N., Marra R., Gratteri S., De Sarro A., and Rotiroti D. (2000) Effects of compounds acting on GABA(B) receptors in the pentylenetetrazole kindling model of epilepsy in mice. *Neuropharmacology* 39, 2147-61.

89. Mortazavi F., Ericson M., Story D., Hulce V.D., and Dunbar G.L. (2005) Spatial learning deficits and emotional impairments in pentylenetetrazole-kindled rats. *Epilepsy Behav* 7, 629-38.

90. Kirshenbaum A.P., Brown S.J., Hughes D.M., and Doughty A.H. (2008) Differential-reinforcement-of-low-rate-schedule performance and nicotine administration: a systematic investigation of dose, dose-regimen, and schedule requirement. *Behav Pharmacol* 19, 683-97.

91. Colussi-Mas J. and Schenk S. (2008) Acute and sensitized response to 3,4-methylenedioxymethamphetamine in rats: different behavioral profiles reflected in different patterns of Fos expression. *Eur J Neurosci* 28, 1895-910.

92. Gilbert M.E. (1992) Proconvulsant activity of endosulfan in amygdala kindling. *Neurotoxicol Teratol* 14, 143-9.

93. Joy R.M., Stark L.G., Peterson S.L., Bowyer J.F., and Albertson T.E. (1980) The kindled seizure: production of and modification by dieldrin in rats. *Neurobehav Toxicol* 2, 117-24.

94. Joy R.M., Stark L.G., and Albertson T.E. (1983) Proconvulsant action of lindane compared at two different kindling sites in the rat--amygdala and hippocampus. *Neurobehav Toxicol Teratol* 5, 465-8.

95. Gilbert M.E. (1995) Repeated exposure to lindane leads to behavioral sensitization and facilitates electrical kindling. *Neurotoxicol Teratol* 17, 131-41.

96. Cloutier S., Forquer M.R., and Sorg B.A. (2006) Low level lindane exposure alters extinction of conditioned fear in rats. *Toxicology* 217, 147-54.

97. Llorens J., Tusell J.M., Sunol C., and Rodriguez-Farre E. (1992) Repeated lindane exposure in the rat results in changes in spontaneous motor activity at 2 weeks post-exposure. *Toxicol Lett* 61, 265-74.

98. Llorens J., Tusell J.M., Sunol C., and Rodriguez-Farre E. (1990) On the effects of lindane on the plus-maze model of anxiety. *Neurotoxicol Teratol* 12, 643-7.

99. Gilbert M.E. and Mack C.M. (1989) Enhanced susceptibility to kindling by chlordimeform may be mediated by a local anesthetic action. *Psychopharmacology (Berl)* 99, 163-7.

100. Gilbert M.E., Acheson S.K., Mack C.M., and Crofton K.M. (1990) An examination of the proconvulsant actions of pyrethroid insecticides using pentylenetetrazol and amygdala kindling seizure models. *Neurotoxicology* 11, 73-86.

101. Gralewicz S. (1999) Organic solvents and time-dependent sensitization. *Int J Occup Med Environ Health* 12, 371-81.

102. Bell I.R., Schwartz G.E., Peterson J.M., Amend D., and Stini W.A. (1993) Possible time-dependent sensitization to xenobiotics: self-reported illness from chemical odors, foods, and opiate drugs in an older adult population. *Arch Environ Health* 48, 315-27.

103. Bell I.R., Baldwin C.M., and Schwartz G.E. (1998) Illness from low levels of environmental chemicals: relevance to chronic fatigue syndrome and fibromyalgia. *Am J Med* 105, 74S-82S.

104. Sorg B.A., Willis J.R., Nowatka T.C., Ulibarri C., See R.E., and Westberg H.H. (1996) Proposed animal neurosensitization model for multiple chemical sensitivity in studies with formalin. *Toxicology* 111, 135-45.

105. Sorg B.A., Willis J.R., See R.E., Hopkins B., and Westberg H.H. (1998) Repeated low-level formaldehyde exposure produces cross-sensitization to cocaine: possible relevance to chemical sensitivity in humans. *Neuropsychopharmacology* 18, 385-94.

106. Sorg B.A. and Hochstatter T. (1999) Behavioral sensitization after repeated formaldehyde exposure in rats. *Toxicol Ind Health* 15, 346-55.

107. Sorg B.A., Swindell S., and Tschirgi M.L. (2004) Repeated low level formaldehyde exposure produces enhanced fear conditioning to odor in male, but not female, rats. *Brain Res* 1008, 11-9.

108. Sorg B.A., Tschirgi M.L., Swindell S., Chen L., and Fang J. (2001) Repeated formaldehyde effects in an animal model for multiple chemical sensitivity. *Ann N Y Acad Sci* 933, 57-67.

109. Sorg B.A., Bailie T.M., Tschirgi M.L., Li N., and Wu W.R. (2001) Exposure to repeated low-level formaldehyde in rats increases basal corticosterone levels and enhances the corticosterone response to subsequent formaldehyde. *Brain Res* 898, 314-20.

110. Bell I.R., Baldwin C.M., Fernandez M., and Schwartz G.E. (1999) Neural sensitization model for multiple chemical sensitivity: overview of theory and empirical evidence. *Toxicol Ind Health* 15, 295-304.

111. Sorg B.A. (1999) Multiple chemical sensitivity: potential role for neural sensitization. *Crit Rev Neurobiol* 13, 283-316.

112. Bell I.R., Kline J.P., Schwartz G.E., and Peterson J.M. (1998) Quantitative EEG patterns during nose versus mouth inhalation of filtered room air in young adults with and without self-reported chemical odor intolerances. *Int J Psychophysiol* 28, 23-35.

113. Bell I.R., Schwartz G.E., Peterson J.M., and Amend D. (1993) Self-reported illness from chemical odors in young adults without clinical syndromes or occupational exposures. *Arch Environ Health* 48, 6-13.

114. Bell I.R., Schwartz G.E., Bootzin R.R., and Wyatt J.K. (1997) Time-dependent sensitization of heart rate and blood pressure over multiple laboratory sessions in elderly individuals with chemical odor intolerance. *Arch Environ Health* 52, 6-17.

115. Bell I.R., Bootzin R.R., Davis T.P., Hau V., Ritenbaugh C., Johnson K.A., and Schwartz G.E.

(1996) Time-dependent sensitization of plasma beta-endorphin in community elderly with self-reported environmental chemical odor intolerance. *Biol Psychiatry* 40, 134-43.

116. Bell I.R., Wyatt J.K., Bootzin R.R., and Schwartz G.E. (1996) Slowed reaction time performance on a divided attention task in elderly with environmental chemical odor intolerance. *Int J Neurosci* 84, 127-34.

117. Bell I.R., Szarek M.J., Dicenso D.R., Baldwin C.M., Schwartz G.E., and Bootzin R.R. (1999) Patterns of waking EEG spectral power in chemically intolerant individuals during repeated chemical exposures. *Int J Neurosci* 97, 41-59.

118. Greene G.J. and Kipen H.M. (2002) The vomeronasal organ and chemical sensitivity: a hypothesis. *Environ Health Perspect* 110 Suppl 4, 655-61.

119. Knecht M., Lundstrom J.N., Witt M., Huttenbrink K.B., Heilmann S., and Hummel T. (2003) Assessment of olfactory function and androstenone odor thresholds in humans with or without functional occlusion of the vomeronasal duct. *Behav Neurosci* 117, 1135-41.

120. Pall ML. (2003) Elevated nitric oxide/peroxynitrite theory of multiple chemical sensitivity: central trole of N-methyl-D-aspartate receptors in sensitivity mechanism. *Environ Health Perspect* 11, 1461-4.

121. Pall M.L. (2000) Elevated, sustained peroxynitrite levels as the cause of chronic fatigue syndrome. *Med Hypotheses* 54, 115-25.

122. Pall ML. (2010) Multiple chemical sensitivity is a response to chemicals acting as toxicants via excessive NDMA activity. *J Psychosomatic Res* 69, 327-328.

123. Rowat S.C. (1998) Integrated defense system overlaps as a disease model: with examples for multiple chemical sensitivity. *Environ Health Perspect* 106 Suppl 1, 85-109.

124. Miller C.S. (2001) Toxicant-induced loss of tolerance. *Addiction* 96, 115-37.

125. Ziem G. and McTamney J. (1997) Profile of patients with chemical injury and sensitivity. *Environ Health Perspect* 105 Suppl 2, 417-36.

126. Hahn M, Bonkovsky HL. (1997) Multiple Chemical Sensitivity Syndrome and Porphyria, A note of caution and concern. *Arch Intern Med* 157, 281-5.

127. Ross P.M. (2000) Chemical sensitivity and fatigue syndromes from hypoxia/hypercapnia. *Med Hypotheses* 54, 734-8.

128. Staudenmayer H., Binkley K.E., Leznoff A., and Phillips S. (2003) Idiopathic environmental intolerance: Part 1: A causation analysis applying Bradford Hill's criteria to the toxicogenic theory. *Toxicol Rev* 22, 235-46.

129. Staudenmayer H., Binkley K.E., Leznoff A., and Phillips S. (2003) Idiopathic environmental intolerance: Part 2: A causation analysis applying Bradford Hill's criteria to the psychogenic theory. *Toxicol Rev* 22, 247-61.

130. Miller C.S. (2001) The compelling anomaly of chemical intolerance. *Ann N Y Acad Sci* 933, 1-23.

Annex 1

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

STATEMENT ON IDIOPATHIC ENVIRONMENTAL INTOLERANCE (IEI)

APPROACH TO COT REVIEW

1. The COT considered draft discussion papers at the October 2009 meeting (Review of proposed toxicological mechanisms http://cot.food.gov.uk/cotmtgs/cotmeets/cot2009/cotmeet27oct2009/cotagendapapers27oct09 TOX-2009-33) and the June 2010 meeting (review of IEI and behavioural conditioning http://cot.food.gov.uk/cotmtgs/cotmeets/cotmeet2010/cotmeet22jun2010/cotagendapapers22jun10 TOX-2010-14). In order to aid Members, a presentation on the psychological aspects of IEI was be given by Professor Omer Van den Bergh, Research Group on Health Psychology, University of Leuven, Belgium at the June 2010 meeting.

2. The literature search strategy was published as an addendum to TOX/2009/33. The search strategy on the epidemiology of IEI and proposed toxicological mechanisms yielded a database of 231 references which covered investigations published both prior to and after the previous COT consideration of IEI in 2000, of which 155 references were cited in the draft COT discussion paper TOX 2009/33. An additional 26 published references were cited in TOX/2010/14 on behavioural conditioning. Peer review comments on TOX/2010/14 were provided by the Institute of Psychiatry which cited an additional 10 published references.

3. The available reviews on IEI reported a large number of potential mechanisms for IEI which essentially divided into two groups, namely; toxicological or psychological with some degree of overlap for a number of proposed mechanisms.[128,129] There were relatively few reviews which provided information on proposed toxicological mechanisms for IEI.[2,46,128,130] A number of collations of published material which included information on potential toxicological mechanisms. (e.g. A conference on The Role of Neural Plasticity in Chemical Intolerance (held at New York Academy of Sciences June 16-19, 2000) published in Annals of New York Academy of Sciences, volume 933, 1-331, 2001, and Occupational Medicine State of Art Review; volume 15, July-September 2000) were also used to overview proposed toxicological mechanisms and to supplement literature searches to identify published studies for review.

An updated literature search was conducted in January 2011, and seven additional references were considered relevant for this statement.

Glossary of terms not explained in the text of statement
(sourced from cited publications or US National Library of Medicine online dictionary MedlinePlus)

Chemosensory event related potential (CSERP): Measurement of olfactory, trigeminal and cortical nerve activity using Electroencephalograph (EEG) techniques. (Stuck BA et al Neuroscience Letters, 406, 222-226, 2006. Nordin S et al Int J Psychophysiol, 55, 243-55, 2005. Dalton P and Hummel T Occup Med, 15, 539-556, 2000)

Flinders Sensitive and Resistant Lines (FSL and FRL): Two animal strains derived from a breeding programme at Flinders University, Adelaide, Australia. FSL animals were originally bred to be sensitive to the toxicity induced by organophosphorous compounds. Control animals from which FSL animals were bred are considered to be Flinders Resistant Line animals (FRL) FSL animals are very sensitive to muscarinic agonists. Colonies of FSL and FRL rats have also been maintained at the University of North Carolina, Chapel Hill, USA where they have been proposed as an animal model for depression. Overstreet D et al Toxicology, 111, 119-134, 1996. Overstreet DH et al Neurosci Biobehav Rev, 29, 739-59, 2005)

Positron Emission Tomography (PET): A method used to investigate regional brain activity. : tomography in which an *in vivo*, noninvasive, cross-sectional image of regional metabolism is obtained by a usually color-coded representation of the distribution of gamma radiation given off in the collision of electrons in cells with positrons emitted by radionuclides incorporated into metabolic substances—abbreviation *PET*

Somatoform disorder: any of a group of psychological disorders (as body dysmorphic disorder or hypochondriasis) marked by physical complaints for which no organic or physiological explanation is found and for which there is a strong likelihood that psychological factors are involved

Somatisatio: conversion of a mental state (as depression or anxiety) into physical symptoms ; *also* **:** the existence of physical bodily complaints in the absence of a known medical condition