TOX/2010/14

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

DRAFT DISCUSSION PAPER ON IDIOPATHIC ENVIRONMENTAL INTOLERANCE (IEI) AND BEHAVIOURAL CONDITIONING

INTRODUCTION

1. In October 2009, the Committee on Toxicity considered a discussion paper which presented an overview of the evidence relating to toxicological mechanisms of idiopathic environmental intolerance (IEI). In discussion about the paper, COT considered that they needed information on psychological aspects of IEI to assist them in their provision of advice.

2. Individuals with IEI report a range of subjective symptoms after exposure to low levels of chemicals.[1] The symptoms are poorly defined, affect multiple organs and can include headache, fatigue, nausea, chest pain and breathlessness. IEI appears to be a complex condition involving heterogeneous etiologic and symptom-maintaining processes, and behavioural conditioning has been suggested as one possible contributor to its development.[2] This discussion paper presents the principles of behavioural conditioning, sensitisation and generalisation and their potential application to the development of IEI.

PRINCIPLES OF BEHAVIOURAL CONDITIONING

Pavlovian Conditioning

3. Pavlovian, or 'classical', conditioning occurs when a neutral stimulus, called the conditional stimulus (CS), is paired with a stimulus that reflexively elicits a particular response (unconditional stimulus (UCS) and response (UCR) respectively).[2] A learned association is formed between the paired stimuli such that subsequent presentation of the CS alone produces a response, known as the conditional response (CR), which is similar to the one elicited reflexively. In Pavlov's experiment in the dog, the sight of food (UCS), which reflexively increased salivation (UCR), was paired repeatedly with the sound of a bell (CS). After several pairings, the sound of the bell alone induced an increase in salivation in the dog (CR).[2]

4. Sensory inputs that coincide with the UCS presentation, known as contextual cues, may subsequently act as CSs. Also, an early response to an agent such as mild respiratory distress or dizziness may, under more benign conditions, subsequently act as a CS for other more serious general symptoms, for example a panic attack, experienced in the previous illness.[2] It has been suggested that this type of Pavlovian conditioning, known as interoceptive conditioning, is involved in the etiology of IEI and some psychological disorders such as panic disorder. With interoceptive conditioning, the CS and/or the UCS are delivered to the mucosa of

specific viscera such that the viscera become signallers or receivers of the conditional information.[2]

Sensitisation

5. Sensitisation refers to the process of increased sensitivity to the effects of a stimulus following an initial exposure(s).[2] Exposures typically tend to be to noxious rather than neutral or pleasant stimuli. Sensitisation typically occurs in the period following an initial exposure, but can occur weeks later.[2] As with Pavlovian conditioning, a stimulus need only precede or coincide with the noxious event for a learned association to form. Sensitisation may result in larger evoked responses to stimuli of equal or lesser intensity than the original stimulus, and even when the original stimulus was not caused by the noxious exposure.[2]

Generalisation

6. Generalisation refers to the ability of novel, non-CS stimuli to regularly elicit a CR, even though they have never been paired with the UCS.[2] New stimuli may elicit a CR as long as they are perceived to be similar to the CS, and often the more similar the stimulus to the original CS, the greater the ability to produce a CR.[2] In time, stimuli that are increasingly less similar to the original CS may develop CR-generating properties.[2] For example, the odour of a chemical proceeding the onset of illness symptoms may act as a CS. Similar odours may cause individuals to respond negatively and, through generalisation, to elicit similar symptoms.[2]

THE PAVLOVIAN CONDITIONING HYPOTHESIS OF IEI

7. With IEI, it is unusual to find specific untolerated compounds that do not possess sensory properties, such as odour.[2] There is potential for such compounds to act as UCSs and, subsequently, for a particular sensory property of the compound to serve as a CS leading to symptoms similar to those experienced from a past exposure.[2] Also, patients with IEI exhibit avoidance and increased sensitivity to agents similarly to other psychological avoidance paradigms.[2]

‘Learned’ Subjective Health Symptoms

8. Several characteristics of IEI appear to be consistent with the development of this condition being in part through a conditioning process.[3] In many patients, IEI was triggered by a ‘toxic’ episode, which can be considered as a UCS, and it has been hypothesised that odours and other environmental cues present during this episode may function as CSs such that subsequent exposures to these cues alone would be sufficient to elicit symptoms.[3] This hypothesis relies on similarity of procedure with Pavlovian conditioning but does not specify the mechanisms through which these cues would cause the symptoms. To investigate the hypothesis for Pavlovian conditioning, laboratory inhalation models have been developed that incorporate the induction of symptoms in an associative learning paradigm.[3]

9. A differential paradigm induces a form of discrimination learning between two odours of which only one co-occurs with the experience of symptoms. A study

involving a differential paradigm incorporated two distinct innocuous odours and two types of breathing trials, one containing the odour mixed with CO_2-enriched air and the other mixed with room air. The concentration levels of the odours were below their threshold limit values for irritancy. Symptoms were induced in participants using inhalations of air enriched with 7.5% CO_2 for 2 minutes.[3] This gas has no odour or taste and only its somatic effects become apparent, such as fast breathing, smothering sensations, chest tightness, feelings of choking, pounding heart, sweating, headache, tension and anxious feelings. An odour serving as predictive cue was mixed with the CO_2-enriched air. In control trials, another odour was mixed with room air. Participants received three breathing trials of each type in the acquisition phase. During the test phase, the same set of trials were administered without the CO_2 and physiological measurements were taken. Participants easily learnt to feel symptoms and perceivance of the odour that had been associated with CO_2-enriched air during the acquisition phase induced respiratory changes and somatic complaints. Conditioning effects only occurred in subjects exposed to CO_2-enriched air paired with a foul smelling odour e.g. ammonia or butyric acid and not a neutral/pleasant-smelling odour e.g. niaouli. The learned symptoms closely resembled the symptoms induced by CO_2 inhalation, were most pronounced for the respiratory symptoms and did not occur for a set of symptoms unrelated to CO_2 inhalation.[3]

10. A conditioning paradigm pairs a single odour with an adverse event, such as CO_2 inhalation, during the acquisition phase. In a study, this conditioning effect was tested between non-IEI subjects using 5 different combinations of exposure conditions during the acquisition phase e.g. pairing of odour and CO_2 or room air, odour or CO_2 or room air only.[4] Ammonia was used as the conditioned odour at a concentration below the threshold limit value for irritancy. In the test trial, the odour was presented alone and symptoms were measured after each trial. During the acquisition phase, complaints during the air trials did not differ and symptom scores were significantly elevated during CO_2 trials. However, no differences were observed between the 5 different combinations of conditions during the test trial, and the study authors concluded that no conditioning effects had been established.[4] The study authors suggested that the experience of symptoms in a differential paradigm may cue the participants more sharply into the critical aspects of the odour as a predictive feature and that this may be absent in a conditioning paradigm.[4]

11. A common feature of the mentioned studies is that maximally 10% CO_2 was used. One study used 20% CO_2 to evoke a more adverse state and more intense symptoms.[5] Two odorous chemicals were used as the conditioning stimuli. In the learning phase, half the participants received breathing trials with one odour and CO_2 and the other mixed with air, and the half with the reversed combination. In the test phase, the trials were repeated without CO_2. Participants rated their anxiety and expectancy to experience symptoms during the trial at the onset of the odour, and respiratory behaviour was measured throughout the trial. Only participants who learned to anticipate symptoms correctly reported elevated symptoms in response to the odorous chemicals. Across the trials, anticipatory anxiety diminished, but learned symptoms did not. Participants failing to learn the prearranged contingencies reported overall more symptoms and anxiety. The study authors concluded that strong respiratory challenges impede extinction of learned symptoms. Also, that conscious expectancy, which may be modulated by odour quality

determines whether learned symptoms develop in response to a specific odour or to the general context. The study authors considered the results supported a symptom learning account of IEI.[5]

12. In addition, a series of experiments using inhalations of CO_2-enriched air and external (odours) or internal (mental images) stimuli as cues have shown that subjective health complaints may occur upon re-exposure to the unpleasant cue alone.[3,6,7]

13. Lightheadedness is one of the frequent neuropsychological complaints associated with IEI. It could be construed that hyperventilation (CS) and its associated symptoms might be conditioned to an odour present at the onset of IEI in terms of Pavlovian learning. A differential paradigm study using 2 odours investigated whether lightheadedness acquired in response to odours could be acquired through previous associations with hyperventilation-induced hypocapnia (an abnormally low concentration of CO_2 in the blood).[8] Hyperventialtion-induced hypocapnia served as the UCS and was used to induce lightheadedness. In the acquisition phase, one odour (ammonia/acetic acid) was paired consistently with the hypocapnic overbreathing, and the control odour was paired with normocapnic overbreathing. Lightheadedness was assessed and hyperventilation symptoms were measured. In the test phase, lightheadedness was found to be acquired easily and was experienced more quickly by participants in response to the odour that had been paired with hypocapnic overbreathing compared with the control odour.[8]

14. As further support for a Pavlovian conditioning hypothesis, a study has demonstrated that after repeated presentation of the odorous CS alone in an extinction procedure, there was a decline in the conditioned somatic symptoms originally acquired when the odorous CS was associated with CO_2-enriched air.[9] No significant extinction effects were found for the acquired altered respiratory responses. In addition, the participants' ratings of odour pleasantness were extinguished and the study authors considered this suggested both subjective symptoms and ratings of pleasantness behave as an example of typical signal learning.

15. It has been suggested that conditioning might not be specific to the chemical itself but might be related to an individual's expectations and prior beliefs. It has been shown that individuals' responses to chemical challenges occur when they can discern differences between active and sham chemicals.[1] However, double-blind, placebo-controlled studies in chemically sensitive participants incorporating an olfactory mask have failed to show any significant association between provocation with chemicals and response.[1]

Effects of Distraction during the Acquisition Phase

16. A study was conducted where patients were distracted during exposure to the conditioning stimulus in order to affect the level of detail of the memory representation.[10] The distraction, simultaneous counting of low tones in a presentation of high and low tones during the acquisition phase, was applied whilst taking care not to interfere with the CS-UCS contingency learning. During the test phase, the breathing trials were repeated but participants had to press the space bar

of a computer as quickly as possible in response to the high tones. If a memory representation of the somatic or subjective responses during exposure to CO_2-enriched air was activated during the test phase as a basis of conditioned complaints, it was expected that distraction during the acquisition phase would have an effect on the reported complaints during the test phase.[10] Distraction prevented the formation of detailed memory representations during the acquisition phase and strongly diminished the conditioning effect on the total complaints. No physiological conditioning effects were found. The effect of distraction was considered by the study authors to support the interpretation that somatic complaints can be learned and that reported complaints during the test phase were based on activated memory information about previous experiences and not on actual physiological responses.[10]

'Learned' Health Symptoms in Individuals with High Negative Affectivity

17. Learned symptoms tended to be more pronounced in individuals scoring high on negative affectivity.[10,11] This is a general tendency to experience and report a variety of negative mood states such as anxiety, anger, disgust, guilt and depression.[12-14] Also, psychosomatic patients showed stronger learning effects compared with normal subjects.[15] These results were considered to provide evidence that the symptoms initially elicited by a specific psychological process may subsequently be elicited by an associated mental or environmental cue.[3] This is more likely when the cue itself is unpleasant or has a negative value and when the subject scores high on negative affectivity.[3]

18. The accuracy of respiratory symptom perception was investigated in different affective contexts in individuals scoring high or low for negative affectivity.[16] Within-subject ratings were calculated for respiratory volume and breathing frequency. The trials utilised 3 air mixtures: room air, air enriched with 7.5% CO_2, and with 10% CO_2. The participants were all female. Half the participants received a pleasant odour and information about pleasant feelings as a result of breathing the air mixtures. The other half received a foul smelling odour and information about unpleasant feelings. Participants with high negative affectivity were significantly less accurate in the perception of respiratory volume and breathing frequency, the latter more so in the distressing information frame and their symptoms were found to be more influenced by the affective context than their physiological responses. With more breathing trials, the number of reported breathing sensations increased in the distressing situation and decreased in the pleasant condition without comparable effects in the physiological measures, the study authors considered that this alluded to a learning effect.[16] Information conveyed by repeated trials with symptom episodes may schematically be represented in memory and may gradually bias new somatic experience.[16] For participants with low negative affectivity the information frame did not matter.[16] The results showed that the accuracy of symptom reports was reduced in individuals with high negative affectivity.[16]

Generalisation of 'Learned' Health Symptoms

19. Symptoms learned in response to a foul smelling odour, regardless of their potential irritancy, have been shown to be generalised to odours that had not been involved in the acquisition phase.[11] The generalisation effect only occurred in

participants who had been conditioned and mainly in those who scored high on negative affectivity, and was confined to new odours. Also, the generalisation affect was not modulated by a delay between acquisition and test.[11,17]

Effects of Environmental Warnings

20. Studies have been undertaken to investigate the relationship between warnings about environmental pollution and the acquisition and learning of symptoms in response to chemicals.[17,18] In one study, a group of individuals received information on chemical pollution prior to exposure to conditioning odour stimuli and a UCS of CO_2-enriched air. Another group received no prior information. The breathing trials were conducted with and without CO_2. Breathing behaviour was measured during each trial and the subjective symptoms were assessed after each trial. Only participants forewarned of environmental pollution reported more symptoms to both the foul- and pleasant smelling odours that had been previously been associated with CO_2, compared to the control odour. The elevation in symptom level could not be accounted for by altered respiratory behaviour or experimental demand effects.[18] Symptom learning did not occur in the group that did not receive warnings. The study authors concluded that raising environmental awareness through warnings about chemical pollution facilitated learning of subjective health symptoms in response to chemicals.[18]

21. In another study, one of 2 foul-smelling odours was mixed with CO_2-enriched air while the other odour was presented in the room during the breathing trials.[17] Information on the health damaging effects of chemical pollution was then given to half the participants. Both odour cues were presented in air to all participants and subjective symptoms were assessed after each trial. The participants reported more symptoms in response to the odour previously presented with air than to the odour previously presented with CO_2-enriched air. The analysis of the results suggested a crucial role for perceived rather than actual contingencies between odour and symptom episodes. The health warnings had no effect. The study authors concluded that believing a specific odour cue was associated with a symptom episode was more important than the actual association in order to provoke symptoms in response to harmless odour cues.[17]

Odour Hypersensitivity and Attention Bias

22. A feature of IEI is self-reported odour hypersensitivity that is usually unaccompanied by enhanced olfactory functioning.[19] The impact of inter-individual differences in olfactory functioning on chemosensory perceptions has been assessed in an age-stratified sample of 44 males and females. The participants were exposed to 9 concentrations of 6 chemicals by flow-olfactometry and rated 4 olfactory and 9 trigeminal perceptions. Subjects with higher sensitivity reported stronger perceptions. The individual odour threshold (n-butanol) exerted no influence on the subjects' ratings of olfactory and trigeminal perceptions. In fact, above-average odour discrimination ability was associated with lower ratings of odour intensity and nausea.[19]

23. Another study assessed the attention bias and enhanced sensitisation to chemical exposure in individuals with self-reported chemical sensitivity.[20]

Chemosomatosensory, olfactory and auditory event-related potentials were recorded from 21 subjects and 17 controls in attend and ignore conditions. In the attend task, participants were instructed to respond to a stimulus as quickly as possible by pressing a mouse button. In the ignore task, participants were told to ignore stimuli and to silently count backwards from 1000 in steps of seven (i.e. 1000, 993, 986 etc.). When a number closest to a nearest round 100 was reached, the participants gave this number to the examiner and were corrected if incorrect. All participants were told to breathe through their mouth, keep their eyes open and fixate on a small area on a computer screen. Reaction times and magnitude estimations of perceived intensity were collected in the attend condition, and event-related potentials were averaged over attention conditions and during the first/second part of testing. The self-reported subjects did not habituate to the same extent as the controls and had difficulties ignoring the chemical exposure. They had faster overall reaction times, and their perceived intensities for the chemosomatosensory stimuli did not decrease with time, which was the case in the control group. The study authors considered that the indication for attention bias and enhanced sensitisation in subjects with self-reported chemical sensitivity suggested alterations in central, cognitive responses to chemical exposure.[20]

Comparison of Individuals with IEI and Somatoform Disorders

24. Analogies have been made between IEI and somatoform disorders. Such disorders are typified by manifold, organically unexplained symptoms, illness cognitions and behaviours, and early stressors.[21] IEI patients score high on measures for somatisation, somatosensory amplification and negative affectivity.[22,23] Furthermore, they display a personality profile that scores highly on hysteria, hypochondriasis and, to a lesser extent, depression.[24] However, in contrast to other somatoform syndromes, symptom attribution in IEI is dominated by the preoccupation with external threat beliefs.[21]

25. A recent study investigated whether IEI was related to the personality trait of absorption. Absorption refers to the predisposition to become immersed deeply in sensory experiences or experience altered states of consciousness and is related to mental constructs with hypnotic suggestibility, imagination and dissociation.[25] Subjects with self-reported IEI were compared to subjects with a somatoform disorder (SFD) but without IEI, and control subjects with neither SFD nor IEI. Participants with SFD and IEI reported similar highly elevated levels of unexplained symptoms compared to the controls.[25] In contrast to SFD, IEI was specifically related to elevated absorption scores, in particular a tendency to experience self-altering states of consciousness.[25] The authors concluded that absorption might contribute to IEI by enhancing the susceptibility for IEI-specific convictions and fostering classical conditioning processes of unexplained symptoms via enhanced cognitive-imaginative representations of assumed IEI triggers.[25]

26. In another study, 2 clinical groups, IEI and SFD and a control group were followed through 32 months to assess both the outcome and the extent which trait anxiety and somatic symptom attribution predict the outcome presented at 12 and 32 months later.[26] Outcome measures were the number of self-reported IEI symptoms and triggers, IEI-associated functional impairments, and the number of somatoform symptoms. Syndrome stability was high over the 32 month study period and it was

found that both trait anxiety and somatic attribution i.e. the tendency to attribute common somatic complaints to an illness, predicted outcome and that somatic attribution was found to partially mediate the effect of trait anxiety on outcome in the IEI group. The study authors concluded the results suggested that trait anxiety contributes to the maintenance of the disorder via somatic attributions.[26]

PEER REVIEW COMMENTS

27. Anonymised comments on this draft discussion paper are provided in Annex 1.

PRESENTATION

In order to aid Members, a presentation on IEI will be given by Professor Omer Van den Bergh, Research Group on Health Psychology, University of Leuven, Belgium.

DISCUSSION

28. IEI is a potentially severe debilitating chronic condition. The Committee discussed a number of proposed toxicological mechanisms as shown below:

Mechanism	**Toxicological (receptor-mediated)**	**Toxicological Idiosyncratic**	**Chemical-Psychological**	**Comments**
Altered Odorant threshold	No differences in odour thresholds identified	No evidence identified or reviewed.	Some evidence for altered cognitive expectations and processing in IEI	Many studies reviewed were undertaken with clinically diagnosed IEI patients.
Primary/ Trigeminal irritancy	Heightened symptoms of sensory irritation reported in IEI. Evidence for increased capsaicin provocation in a small study	No evidence identified or reviewed.	Some evidence for effects on latency of chemosensory evoked potential suggested to reflect top-down processing.	Many studies reviewed were undertaken with clinically diagnosed IEI patients
Immune system effects	No convincing evidence	No evidence identified or reviewed.	No evidence identified or reviewed.	Studies limited by differing case-definitions of IEI.
Neurotoxic effects	Very limited evidence of changes in regional CNS blood flows	Claim that IEI is similar to effects seen in Flinders Cholinergic sensitive rats	No evidence identified or reviewed.	No specific investigations in individuals with clinically diagnosed IEI.
Time-Dependent Sensitisation.	Evidence reported in animals for Neurotoxic drugs	No evidence identified or reviewed.	No evidence identified or reviewed.	Studies were undertaken in subjects with cacosmia or using a chemical intolerance scale in

	and chemicals at overtly toxic dose levels. Evidence for limbic symptoms, increased beta-endorphin levels, increased systolic blood pressure in a series of studies using self reported (or questionnaire assessed) chemical intolerance			young college students or older retired individuals. No subjects with clinically diagnosed IEI used. Studies from one research group from around 1993-1999 with no independent verification of the results
Other mechanisms	No evidence identified or reviewed.	No evidence identified or reviewed.	No evidence identified or reviewed.	A range of hypotheses with little or no supporting evidence in patients with IEI. These include elevated nitric oxide/peroxynitrite sensitivity, Integrated Defense system overlap, Toxicant Induced Loss of Tolerance, porphyria, hypocapnia/hypoxia and the response of the Vomeronasal organ.
Genotype studies	No evidence identified or reviewed	Evidence from one study for association between CYP2D6 homologous active and NAT2 rapid and IEI	No evidence identified or reviewed	No appropriate studies of metabolism in patients with IEI to support hypothesis that increased metabolism is a risk factor.

29. Members are asked to consider how the information on psychological aspects influences the COT assessment of IEI. A copy of the minutes of the COT discussion of toxicological mechanisms of IEI is appended in Annex 2.

QUESTIONS FOR THE COMMITTEE

i. Based on the information presented to COT, can Members conclude that a toxicological mechanism (i.e. receptor-mediated or idiosyncratic) for IEI can be discounted?

ii. Do Members accept the evidence provided for a psychological mechanism appears valid and thus IEI should be considered further by the appropriate specialism within the Department of Health?

iii. Should COT publish a statement on IEI relating to toxicological mechanisms to include a comment on psychological mechanisms?

iv. On balance, is IEI more likely to be explained as a psychological illness rather than a toxicologically mediated condition?

HPA COT Secretariat
May 2010

ANNEXES

Annex 1 Anonymised peer review comments on COT draft discussion paper (TOX/2010/14).

Annex 2 Extract from COT Minutes TOX/MIN/2009/06. IEI: Evidence for a toxicological mechanism. Overview of studies of polymorphisms relevant to toxicological mechanisms. http://cot.food.gov.uk/pdfs/cotmins27oct2009.pdf

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ANONYMISED PEER REVIEW COMMENTS ON COT DRAFT DISCUSSION PAPER (TOX/2010/14)

The draft discussion paper lays out the evidence for IEI being the result of behavioural conditioning. This evidence is compelling. If we have any criticism to make of it, it is that by focusing on experimental work, the author has slightly understated his case. Evidence from outside the laboratory also suggests that the principles outlined in the discussion paper are relevant and important.

The extensive experimental work discussed by the author has demonstrated, repeatedly, that humans can learn to develop adverse physical symptoms of the type reported by IEI sufferers when odours or mental images are paired with a stimulus capable of producing those symptoms. They also demonstrate that once this learning has taken place, toxicological mechanisms are not required to explain why these symptoms might re-occur in the future. Of course, this finding is not unique to IEI. Similar phenomena would be recognised by clinicians in many other disciplines. The anticipatory nausea that cancer patients experience before their second chemotherapy session would be one example of Pavlovian conditioning of symptoms occurring in a real world setting.[1]

More than merely demonstrating that this can happen, the experiments described in the discussion paper also illustrate that several factors make this conditioning more likely to happen. Attention, for example, is very important, as demonstrated by studies which deliberately force participants to focus their attention elsewhere when symptom learning should be taking place, and by studies which use information or media coverage in order to prime participants to expect adverse symptoms as a result of exposure to an odour. The discussion paper does not mention prior beliefs in this context, but these too are relevant. In one prospective cohort study, a New Zealand team assessed levels of general worries about the health effects of modern life among residents of West Auckland. After this assessment was made, a programme of aerial insecticide spraying occurred in the local area. Residents who had greater modern health worries prior to the spraying were significantly more likely to attribute symptoms to the exposure than those with lower modern health worries.[2] *Taken together these factors go some way towards explaining the known geographic variations in rates of self-reported intolerance to different environmental agents. Where a country's scientists, media and government are focused on a particular type of risk, it increases the likelihood of an individual learning to associate symptoms with that risk. Thus in Germany, where there is a high level of concern over 'electrosmog,' around 10% of citizens attribute adverse symptoms to the presence of*

a nearby mobile phone basestation,[3] in Iran, where media reporting about the health effects of mobile phone technology is scarce, few if any people report this affliction.[4] Similar findings have been reported elsewhere with regard to chemical attributions for symptoms.[5]

Negative affect is also flagged by the discussion paper as a key factor increasing the likelihood that someone will learn to experience symptoms when exposed to a chemical odour. Again, this tallys with observational studies demonstrating that negative affect or psychiatric disorder are more likely to be present in people with IEI than in those without it.[6] Clearly, negative affect can be a consequence of suffering from a poorly understood and difficult to treat condition. However, while the experimental work outlined in the discussion paper demonstrate a mechanism for how negative can also be a cause of IEI, recent prospective cohort studies have demonstrated that it is indeed a risk factor for the attribution of symptoms to an environmental trigger and for the development of IEI.[7;8]

A large volume of evidence supports the psychological mechanisms for IEI that the authors have laid out. Two problems remain, however. First, IEI is clearly a heterogenous condition. There is no guarantee that any one mechanism can explain all of the symptoms and phenomena that are included under the term. Second, a key piece of the jigsaw is still missing. While conditioning has been convincingly demonstrated as a possible mechanism for IEI, and while many patients with IEI have psychological components to their illness, it is remarkable that good quality studies of psychological treatments for IEI have yet to be conducted[9] (though see[10] for a review of psychological treatment studies for IEI attributed to electromagnetic fields). Such research would appear to be the logical next step.

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

DRAFT DISCUSSION PAPER ON IDIOPATHIC ENVIRONMENTAL INTOLERANCE (IEI) AND BEHAVIOURAL CONDITIONING

Extract from COT Minutes TOX/MIN/2009/06. IEI: Evidence for a toxicological mechanism. Overview of studies of polymorphisms relevant to toxicological mechanisms.

http://cot.food.gov.uk/pdfs/cotmins27oct2009.pdf

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

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EXTRACT FROM COT MINUTES TOX/MIN/2009/06. IEI: Evidence for a toxicological mechanism. Overview of studies of polymorphisms relevant to toxicological mechanisms.

14. In their conclusions on the Royal Commission on Environmental Pollution (RCEP) report on crop spraying and health of residents and bystanders, the Committee had recommended that a further review of Idiopathic Environmental Intolerance (IEI, also described as Multiple Chemical Sensitivity) be undertaken. Paper TOX/2009/33 provided a review of proposed toxicological mechanisms for IEI. Members had also received confidential comments from a clinical psychiatrist on the review paper, and in particular the strategy used to conduct the review.

15. The evidence presented showed that IEI could be severely disabling in patients suffering from it. However, it was a heterogeneous phenomenon with different manifestations. Members commented on the subjective nature of the diagnosis of IEI based on symptoms and exclusion of other conditions (such as asthma and depression). Members also noted that the terminology used in some accounts was misleading. Thus hypersensitivity was reported in some papers, which implied an immunological pathogenesis, although there was no evidence to support this. Without a reliable case definition, it would be challenging to determine any underlying toxicological mechanisms. It was noted that the review focussed on possible toxicological mechanisms, and largely ignored psychological factors that might contribute to or underlie the disorder. However, the Committee felt that it would not be appropriate to conclude a purely psychological origin for IEI, based simply on the fact that no toxicological mechanism could be established. It was possible that an un-identified toxicological mechanism was involved. It was also noted that physiological mechanisms could be involved in the expression of illness that was psychological in origin. Members noted a recent review of published provocation studies, which reported that acute adverse responses of IEI patients to test exposures were largely dependent on the subjects' perception of a hazardous exposure rather than its chemical characteristics. This would make it very difficult to establish a chemical structure database that would aid the evaluation of possible toxicological mechanisms.

16. The available evidence summarised in TOX/2009/33 was considered to vary in quality. The lack of true blinding of exposure in provocation studies limited the conclusions that could be drawn. With respect to the WHO/IPCS description (quoted in para 6) it was considered that point (ii) should be expanded to reflect that IEI was 'associated with diverse environmental factors tolerated by the majority of people,

with no known toxicological reason to expect an effect at the levels to which subjects were exposed'.

17. There was interest in determining the reason for differences in reporting rates between countries as these could be associated with differences in prevalence, diagnostic practices, or the extent to which people were aware of IEI. In this respect members noted the differences in reporting of IEI between the former West Germany and German Democratic Republic. Epidemiological studies in industrialised societies with low reporting rates might provide insight into the involvement of chemical exposures. In particular, if they confirmed a low prevalence of the disorder despite relatively high chemical exposures, that would make a toxic cause less likely. Another important consideration in epidemiological studies would be the extent to which patients had knowledge of their exposure.

18. The toxicological mechanisms proposed were discussed in turn.

<u>Altered odorant threshold</u>

19. The potential importance of knowledge of exposure was highlighted and it was asked whether IEI manifested as an altered odour threshold or altered sensitivity to odour. The available provocation studies consistently showed no differences in odour thresholds between individuals with and without a diagnosis of IEI. Moreover, it was considered likely that when an unpleasant exposure was administered, changes in objective measures of brain function would result. It was considered that chemosensory event-related potential (CSERP) measurements and PET scans were unlikely to be informative regarding potential toxicological mechanisms. One member noted that the positron emission tomography (PET) scans might reveal changes following exposure to triggering chemicals. However, while a finding of significant objective changes in CERP and PET parameters in association with odorant exposure would be useful insofar as it established that the subjective emotional response to IEI is real, it would be of limited value in the assessment of underlying pathogenesis. This was because such changes could reasonably be expected, whether illness was toxic or psychological in origin.

<u>Primary or trigeminal irritancy of the upper airway</u>

20. Members agreed it was conceivable that sensory irritation mediated by vanilloid receptor binding could trigger the development of IEI in some individuals. However the exaggerated capsaicin response reported in a small study of IEI patients might reflect the co-occurrence of IEI and asthma in some patients. The Committee was not convinced that exposure studies using a range of consumer products, such as fabric softener, represented a good model for the investigation of IEI. Members were aware that patients with asthma had underlying damage to the respiratory tract, which predisposed to hyper-reactivity to irritants but not odours. It was considered unlikely that IEI patients would exhibit morphological changes in the respiratory tract. The Committee considered that a psychological response to sensory irritant triggering could explain the symptoms reported by IEI patients, whereas there was no obvious toxicological mechanism that would account for the diverse range of symptoms that occurred in IEI. Nor was there any known toxicological mechanism that would explain why symptoms of IEI occurred at levels

of exposure orders of magnitude lower than those required to cause adverse effects in most people.

Immune system effects

21. Members observed that a number of patients with allergies also developed IEI. Whilst there was potential for misdiagnosis of these two conditions, it was considered possible also that people with allergy could develop a response, for example to unpleasant smells, through a psychological mechanism. The evidence for the proposed mechanism of dysregulation of T-cells was considered poor. One Member volunteered to review the published papers on this topic.

Neurotoxic effects

22. The Committee considered that none of the hypotheses outlined in TOX/2009/33 was convincing, and that there was a lack of supporting evidence. It might be plausible that a CNS receptor was involved in IEI symptoms in some individuals, but the evidence provided for a role of the GABAa receptor was unconvincing. Members concluded that data on exaggerated cholinergic responses in Flinders Sensitive Line (FSL) rats dosed with a range of pharmacologically active compounds did not point to a plausible mechanism for IEI.

Time-dependent sensitisation (TDS)/Limbic kindling

23. Studies on limbic kindling required doses which approached or were at a toxic level, and were therefore not considered useful. It was not considered possible to distinguish TDS from learning, and therefore TDS did not appear to be a useful concept. Animal models (such as those involving exposure of rats to formaldehyde) that were described in the review, were deemed to reflect learnt responses, and the view of the Committee was that IEI should be better defined, and perhaps classified into subsets, before relevant animal experiments could be designed. Studies in individuals with chemical odour intolerance (cacosmics) suggested that their response to successive low level chemical exposures changed over time, but this did not provide evidence for IEI.

24. There was some discussion of whether IEI could usefully be viewed as the opposite of drug addiction (i.e. abdiction), and if similar neural pathways might be involved. However, the Committee agreed that the proposal was not supported by any evidence and did not appear plausible.

The Vomeronasal Organ

25. This was considered to be a speculative hypothesis with no supporting data.

Other mechanisms

26. There was little convincing evidence for any of the other proposed mechanisms that were reviewed (elevated nitric acid/peroxynitrite sensitivity of N-methyl-D-aspartate receptors, integrated defence system overlap, toxicant induced

loss of tolerance, porphyria and hypoxia/hypercapnia). The genotyping work was considered interesting but in need of much more evidence, as currently there was inadequate justification for the selection of genes that had been studied. In addition, the differences in responses observed between fast and slow metabolisers (e.g CYP2D6 homozygous active and NAT2 rapid) appeared to be in the opposite direction to that which would be expected. The possibility of target organ metabolism e.g. in the brain was suggested. It was agreed that a genetic component to IEI could not be precluded on the basis of the studies described. However, future work would need a biological rationale for selection of genes, and would need to be independently replicated.

27. In summary, a number of the hypothesised toxic mechanisms might plausibly, explain symptoms in some patients with IEI, but there was little convincing evidence to support them, or that would favour one mechanism over another. It is possible that further investigation might lead to more convincing findings as regards causation, and perhaps to diagnostic indicators of clinical value. The Chair noted the one overarching theory, embracing all the forms of the illness, was that IEI occurred as a psychologically-mediated response to perceived exposure (e.g. based on smell or irritancy), conditioned by prior experience and expectations. The exact manifestation of symptoms and signs would depend on expectations and beliefs. Other mechanisms could account for some symptoms in some people e.g. an enhanced response to irritants, and there was an interesting overlap with allergy. However, these would not explain the whole phenomenon.

28. Suggestions for further work included epidemiological studies specifically to gain more information on any association between odour perception and sensitivity, the breadth of the response and any patterns in chemicals triggering, or not triggering, a response in IEI patients, including assessment of route of exposure. Part of this consideration should involve evaluation of any differences in IEI patients where there was evidence of acute exposures as opposed to chronic low level exposures. Further provocation tests could investigate responses in blinded IEI patients using chemicals implicated and those not implicated in the patients' illness. As the current review focussed on toxicological mechanisms, it was felt that further consideration of psychological data should be carried out to give a more complete assessment.

29. It was noted that there should be caution in defining IEI too broadly as this might lead to patients with real but unrecognised toxicological responses (e.g. people exposed to low levels of carbon monoxide) being misdiagnosed.

30. The secretariat would take forward the proposal for additional consideration of psychological aspects of IEI in consultation with experts in psychology and to bring a first draft statement to a future COT meeting.

HPA COT Secretariat
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