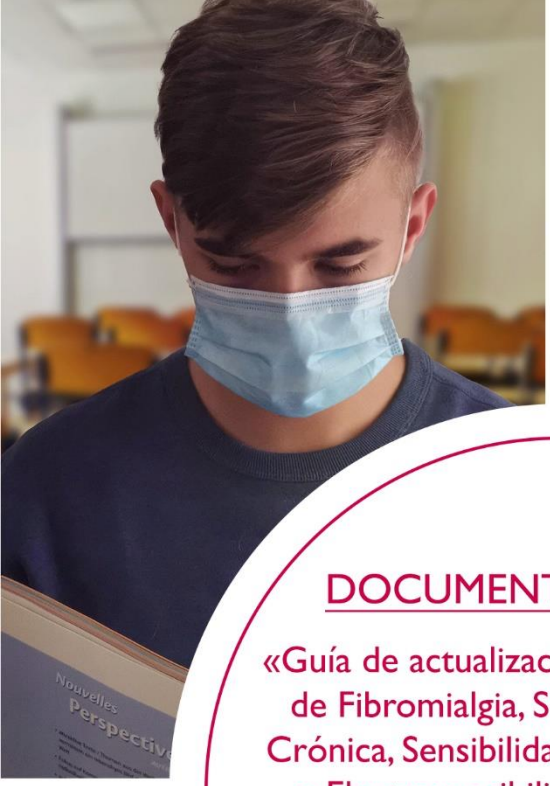

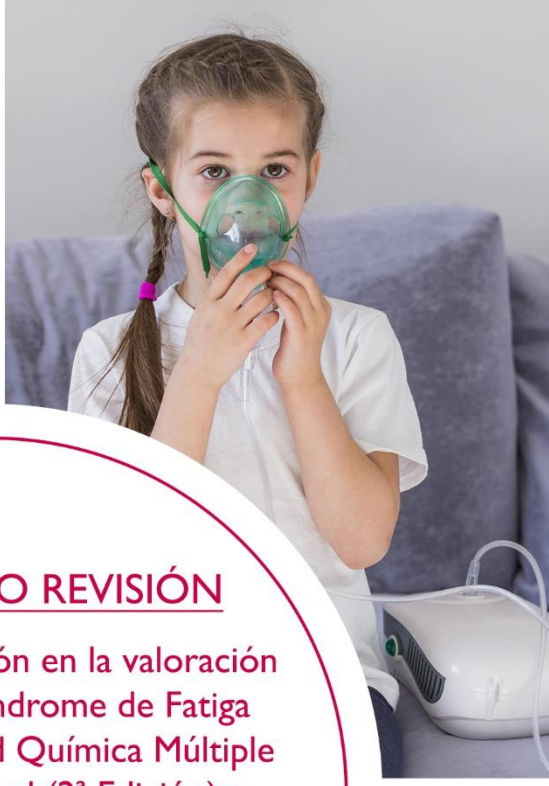

DOCUMENTO REVISIÓN

«Guía de actualización en la valoración de Fibromialgia, Síndrome de Fatiga Crónica, Sensibilidad Química Múltiple y Electrosensibilidad (2ª Edición)».

SENSIBILIDAD QUÍMICA MÚLTIPLE

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Subvencionado por:

Ministerio de Sanidad, Consumo y Bienestar Social

(1ª Edición)

ÍNDICE

INTRODUCCIÓN

El presente documento tiene por objetivo recoger los aspectos básicos en relación a la Sensibilidad Química Múltiple, (SQM), que se pretenden poner de manifiesto a objeto de hacer una crítica fundamentada sobre el contenido y conclusiones que se han expuesto en el documento llamado: «Guía de Actualización en la Valoración de Fibromialgia, Síndrome de Fatiga Crónica, Sensibilidad Química Múltiple, Electrosensibilidad y Trastornos Somatomorfos, 2ª Edición», elaborada por el Instituto Nacional de la Seguridad Social. Ministerio de Trabajo, Migraciones y Seguridad Social, publicado en enero de 2019. (De ahora en adelante se citará como: Guía del INSS, 2ª Edición.).

Este documento consta de dos secciones, la sección A) Sensibilidad Química Múltiple, y la sección B) Revisión Guía del INSS, 2ª Edición, bibliografía y cuatro anexos.

En la sección A) se hace una revisión de algunos de los aspectos relevantes de esta enfermedad, concretamente bajo el título A4) Bases biológicas/fisiológicas de la enfermedad, se recogen algunos de los principales mecanismos que más aparecen en la literatura científica. El objeto de esta sección no es hacer una revisión de todas las bases fisiológicas propuestas en la literatura, sino el de revisar algunos de los mecanismos propuestos para posteriormente en la sección B) fundamentar las objeciones al contenido de la Guía del INSS en su capítulo 5. Intolerancia Ambiental Idiopática y concretamente en 5 A. Sensibilidad Química Múltiple.

Para la elaboración del documento se han tenido en cuenta las principales publicaciones científicas sobre esta enfermedad, así como los documentos publicados en nuestro país por el Ministerio de Sanidad, en 2011 y 2015, y en 2018 por el Instituto Nacional de Seguridad y Salud en el Trabajo, del propio Ministerio de Trabajo, así como otros documentos publicados por instituciones de europeas y de otros países.

Queremos dedicar este documento a la memoria del Dr. Julián Márquez Sánchez, brillante neurólogo y exjefe de la Sección de Neurofisiología Clínica del Hospital U. de Bellvitge, fallecido el pasado 10 de Julio de 2020. Durante años impulsó los avances en el tratamiento y diagnóstico de la SQM, y la defensa de los derechos de los pacientes, siendo uno de los expertos encargados de confeccionar el primer «Documento de consenso en SQM», aprobado en 2011 por el Ministerio de Sanidad de nuestro país. Los pacientes mantendremos una deuda perpetua con la obra de este extraordinario médico.

A. ¿QUÉ ES LA SENSIBILIDAD QUÍMICA MÚLTIPLE?

A1. DISTINTOS NOMBRES DE LA MISMA ENFERMEDAD

La Sensibilidad Química Múltiple, conocida en español por sus siglas SQM, y en ingles por MCS, es una enfermedad descrita desde comienzo de los años 50 en EEUU por Theron Randoplh que observó como algunas personas desarrollaban una sintomatología concreta cuando se exponían a niveles muy bajos de sustancias presentes en el medio ambiente, en el trabajo o en el hogar. Se le conoce también por otros nombres como: «Sensibilidad Química», «Enfermedad del siglo XX», «Alergia Universal», «Síndrome de respuesta a las sustancias químicas», «Pérdida de Tolerancia Inducida por Tóxicos», «Síndrome de Sensibilidad Múltiple Sensorial», «Enfermedad Ambiental Idiopática»…

También se le han dado otros nombres que se aproximan a sus localizaciones particulares, como por ejemplo: El «*Síndrome de la Guerra del Golfo*» (Golf War Syndrome) de la primera guerra del Golfo (1990-91), el «*Síndrome del Edificio Nuevo*» que se desarrolla en edificios mal ventilados con mobiliario nuevo, en los que existe una alta presencia de Compuestos Orgánicos Volátiles (COVs) que por sí mismos, como se verá más adelante en el informe, son capaces de desencadenar la enfermedad de Sensibilidad Química en algunas personas.

Hay otras enfermedades cuyas características guardan estrecha relación con la SQM, como en el «*Síndrome del Edificio Enfermo*» más caracterizado por mala ventilación, contenido en amianto u otros materiales tóxicos, presencia de hongos y alta carga de radiación electromagnética, etc, o incluso el: «*Síndrome del restaurante chino*» el alto contenido en glutamato monosódico hace que se desarrolle sintomatología similar a la SQM.

Tal cantidad de nombres y orígenes refleja el desafío médico y científico del estudio de una enfermedad tan compleja. Su comprensión es fundamental para su diagnóstico temprano y Por tanto evitar el desarrollo de sintomatología más severa e incapacitante.

En este documento se utilizará para referirse a la enfermedad el término de Sensibilidad Química Múltiple (SQM) o Sensibilidad Química (SQ).

Los términos utilizados con más frecuencia reconocen que las personas afectadas detectan que los productos químicos y el medio ambiente se asocian con su enfermedad. El término «*Enfermedad Ambiental Idiopática*» que es utilizado en algunas publicaciones científicas y del que se hace eco la Guía del INSS, 2ª Edición, es el único en el que no se establece la relación causal entre el origen de la enfermedad y la toxicidad química. El origen de este término se discute más adelante en la sección *B1) Origen del término Enfermedad Ambiental Idiopática y posición de la OMS al respecto.*

A2. DEFINICIÓN

La Comisión Canadiense de Derechos Humanos en el año 2007 define así la enfermedad:

«La Sensibilidad Química Múltiple (SQM) es la denominación más utilizada para describir un síndrome complejo que se presenta como un conjunto de síntomas vinculados con una amplia variedad de agentes y componentes que se encuentran en el medio ambiente, presentándose dichas reacciones con una exposición a niveles comúnmente tolerados por la mayoría de las personas».

Esta definición se recoge en nuestro país en el Documento de Consenso del Ministerio de Sanidad, 2011.

Es una enfermedad que se caracteriza porque está solapada con otras enfermedades comórbidas con las que convive como Fibromialgia (FM), Síndrome de Fatiga Crónica (SFC), y Electrosensibilidad (EHS). Es multisistémica y de curso crónico, está caracterizada porque se producen procesos inflamatorios y degenerativos.

Definición de caso

Cullen define en el año 1987 lo que actualmente se conoce como «Sensibilidad Química Múltiple», e indica una serie de características de la enfermedad. No obstante, esta definición carecía de consenso, pues en ella no se recogen todos los matices de la enfermedad. Finalmente, en el año 1999 en un **Consenso Internacional** se establecieron los criterios de definición de caso en base a los **patrones consistentes con la enfermedad internacionalmente observados[1].** Estos criterios recibieron la aprobación y el consenso de 34 investigadores y

[1] Bartha et al., 1999.

médicos clínicos norteamericanos, todos ellos tenían amplia experiencia pues trataban a cientos de pacientes con SQM. Estos criterios de definición de caso introducen, con respecto a la definición de *Cullen* el matiz de la evitación como elemento terapéutico.

Queda por tanto la definición de caso establecida por Consenso Internacional, de la siguiente forma:

- ✓ Los síntomas son reproducibles con la exposición química repetida.
- ✓ La condición es crónica.
- ✓ Niveles bajos de exposición ocasionan manifestaciones del síndrome (dichos niveles son más bajos que los usuales o previamente tolerados).
- ✓ Los síntomas mejoran o se resuelven cuando los incitantes son eliminados.
- ✓ Las respuestas se presentan a múltiples sustancias sin relación química.
- ✓ Los síntomas implican múltiples sistemas orgánicos.

Hay otras muchas características típicas de esta enfermedad que no están recogidas en la definición de caso del Consenso como se indica en *McKeown-Eyssen et al, 2001*, que además de los criterios anteriores, sugirieron el de tener un fuerte sentido del olor (hiperomia) en la mayoría de las personas, sentirse aturdido y embotado y tener dificultad para concentrase. No obstante, estas aportaciones no han sido recogidas pues a pesar de ser características, no todas las personas con SQM las presentan.

A3. SINTOMATOLOGÍA

En *Pall 2009* se dice que la enfermedad de SQM es una enfermedad compleja cuyos casos se inician a menudo después de una exposición aguda a algún compuesto químico, aunque en la mayoría de los casos no existe un evento particular de exposición y es la **exposición crónica a diversos compuestos a bajas dosis** lo que puede iniciar la mayoría de los casos.

Una vez que se ha desencadenado la enfermedad, los afectados refieren sensibilidad o intolerancia a bajos niveles de un amplio espectro de químicos. Los síntomas informados por la exposición química son diversos y variables

de un paciente a otro, pero incluyen dolor, especialmente cefalea, dolor muscular y articular, confusión, alteración cognitiva, síntomas de tipo asmático, rinitis, alteración del sueño, fatiga e incluso síntomas de esfera emotiva en algunas personas tales como ansiedad, depresión, y menos frecuentemente rabia e ira. En la revisión de *Sorg, 1999* se enumeraron un total de 41 síntomas diferentes, muchos de los cuales ocurrían solo en una minoría de personas. *Sorg* afirma que entre los síntomas más comunes después de una exposición química en pacientes con SQM están la fatiga extrema, cefalea, problemas gastrointestinales, náuseas, ansiedad, depresión, irritación de las vías respiratorias superiores, dolor muscular y articular y dificultad en la concentración mental. En *Miller 2001*, se relacionan 74 síntomas que dividieron en neuromusculares, relacionados con el sistema nervioso, musculoesqueléticos, gastrointestinales cardíacos, de las vías aéreas, cognitivos y otros.

Relación entre la exposición y la SQM

En *Hooper 2011*, se resalta que hay muchos estudios que han documentado que la contaminación química está extendiéndose a lo largo de todo el mundo. Es muy llamativo el hecho de que la sangre del cordón umbilical contiene cientos de compuestos tóxicos, lo cual implica que ya en el útero, cuando la replicación celular es mayor y no hay protección frente a los compuestos tóxicos. En el estudio de *Eis et al., 2008*, se identificaron 287 diferentes productos químicos en la sangre del cordón umbilical de recién nacidos. De estos químicos, 17 eran tóxicos para el cerebro y el sistema nervioso, 208 podían causar problemas de desarrollo, y 108 causar cáncer en humanos y animales. La contaminación química y electromagnética avanza a un ritmo que no tiene precedentes en la historia de la humanidad. Lo que antes eran enfermedades típicamente asociadas a profesiones, (pintores, pastoreo, fabricantes de alfombras, etc.) ahora se está extendiendo a ámbitos no ocupacionales.

Son numerosas las publicaciones científicas que han evidenciado un patrón de exposición química precediendo al desarrollo de la SQM, o bien una exposición de alto nivel o una exposición constante a tóxicos a bajo nivel. En *Ashford y Miller 1998* y *Sorg 1999* se recoge evidencia de la aparición de la

enfermedad después de la exposición a bajos niveles de toxicidad. En *Pall 2007a capítulo 13* se informa de 24 estudios distintos que muestran que existe una exposición química previa a la aparición de la enfermedad y en *Miller 2000* se citan otros doce estudios adicionales en los que también hay exposición química previa a la aparición de la enfermedad. En *Pall 2009* se detallan también otros estudios adicionales a los anteriores que confirman la aparición de la enfermedad de SQM después de la exposición química.

Pall 2009 describe que los productos químicos que están implicados más frecuentemente en la aparición de la enfermedad son los Compuestos Orgánicos Volátiles (COVs), pesticidas, especialmente pesticidas organofosforados y carbamatos[2].

Pall 2009 describe que la exposición a solventes orgánicos que está presente en el «Síndrome del Edificio Enfermo», parece iniciar casos de SQM. Dos de los casos más llamativos de «Edificio enfermo» fueron el edificio de la Agencia de Protección Ambiental en Washington, DC, en el que aproximadamente 200 personas enfermaron con casos de SQM[3] y en el *Brigham and Women´s Hospital* en Boston, parte del complejo de la Escuela de Medicina de Harvard. En *Kawamoto et al., 1997* se describe este hecho. Posteriormente se disminuyó el uso de químicos y aumentó el flujo de aire lo que condujo a un descenso sustancial de nuevos casos de SQM y enfermedades relacionadas, sugiriendo por ello una relación causal entre la exposición química y la aparición de SQM.

En *Pall 2009* se describen estudios epidemiológicos que han estimado la prevalencia de SQM en diversas profesiones, incluidas las que se espera que tengan una exposición química importante a algunas clases de químicos implicados en el SQM como consecuencia del trabajo. Asimismo, se detectó una mayor prevalencia de SQM en varias profesiones que involucran tal exposición química, otra vez sugiriendo un papel causal de la exposición química en el desarrollo de SQM. Dos ejemplos de desarrollo de SQM ocupacional por exposición a COVs se muestran en *Zibrowski y Robertson, 2006*, que describen una mayor prevalencia de síntomas de SQM entre técnicos de laboratorio expuestos a disolventes orgánicos, en comparación con

[2] Ver: Ashford y Miller, 1998; Sorg, 1999; Rea 1992; Ziem y McTamney 1997.

[3] Ver: Miller 2001.

otros técnicos similares sin exposición aparente. Asimismo, en *Yu et al, 2004* se encontraron altas prevalencias de síntomas de SQM entre pintores expuestos a solventes en comparación con los controles no expuestos químicamente.

Pall 2009 plantea que además de los COVs y compuestos relacionados, pesticidas organofosforados y carbamatos, son numerosos los estudios científicos que indican que hay otras clases adicionales de químicos que inician casos de SQM como los pesticidas organoclorados: clordano, aldrín, dieldrín, y lindano, (se ha visto como el lindano inicia casos de SQM en modelos animales como otro antagonista del GABAa, ácido gamma-aminobutírico) y también con una amplia variedad de pesticidas piretroides, muy utilizados actualmente en los hogares, así como la exposición a sulfuro de hidrógeno (H2S)[4], y al monóxido de carbono[5]. También se ha descrito que el mercurio y los compuestos mercuriales parecen iniciar algunos casos de SQM[6]. Otro elemento importante que desencadena casos de SQM es el moho presente en edificios «enfermos» infectados, pues se ha descrito que en algunos de sus ocupantes se produce un aumento del óxido nítrico, (NO) y de las citoquinas inflamatorias en las fosas nasales; también se han visto respuestas similares en los pulmones de las personas expuestas al moho.

El óxido nítrico y las citoquinas inflamatorias son aspectos importantes de la SQM como se describe a continuación.

[4] Ver: Kilburn, 1997 y 2003.

[5] Donnay 2000.

[6] Ver: Latini et al., 2005; Brent, 2001; De Luca et al. 2011.

Figura 1: Principales clases de químicos asociados con SQM[7]

Table 50.5 Major classes of chemicals associated with multiple chemical sensitivity (MCS)

Chemical class	Known biological activities	Common sources/uses
Highly substituted, poly- or per-halogenated organic compounds with chlorine, bromine or fluorine atoms*, e.g. DDT, DDE, lindane, hexachlorobenzene, hexachlorocyclohexanes, PCBs, aldrin, dieldrin, PBDEs, perfluorooctanoic acid polymers and derivatives	Carcinogenic, mutagenic, kidney and liver damage, endocrine disruption	Household and agricultural pesticides as sprays and dusts, electrical insulation, flame-retardants, non-stick kitchen utensils, stain-resistant fabrics
Organophosphates, nerve agents	Nerve toxins, immune dysregulation, inhibition of key enzymes	Various pesticides in agriculture, fisheries, herbicides, engine oils
Phthalates, nonylphenol, bisphenol A and B*	Endocrine disruption	Polymers, plasticizers, toys, babies' pacifiers, dialysis tubing
VOCs, aliphatic and aromatic compounds*, formaldehyde, aldehydes, esters, ketones, acids, alcohols, toluene	Disruption of brain function, nerve damage, carcinogenic	Ubiquitous in fragrances, perfumes, household goods, solvents, fuels, paints, polymers
PAHs	Carcinogenic, mutagenic	Burning fuels, exhaust fumes, power stations
Heavy metals: mercury*, lead, cadmium, arsenic, organometallics, tributyltin*	Neurotoxicity, tissue damage, endocrine disruption	Anti-fouling paints, fuels, preservatives, pesticides, electrical goods, crematoria

*Bioaccumulative and biomagnified through the food chain.

DDT, dichlorodiphenyltrichloroethane; DDE, dichlorodichlorophenylethene (major metabolite of DDT); PAHs, polyaromatic hydrocarbons; PBDEs, polybromodiphenylethers; PCBs, polychlorobiphenyls; VOCs, volatile organic compounds.

Para poder comprender como el cuerpo es capaz de gestionar la exposición química, es necesario tener en cuenta factores individuales, incluyendo la absorción, distribución, metabolismo, excreción, genética, edad, sexo, medio ambiente y estado nutricional.

A4. BASES BIOLÓGICAS/FISIOLÓGICAS DE LA ENFERMEDAD

En este epígrafe se describen algunas de las principales bases fisiológicas de la enfermedad. No es objeto del mismo recoger todos los posibles mecanismos de acción implicados y descritos en la literatura científica.

A4.1 SENSIBILIZACIÓN NEURAL, incluido el sistema límbico

Hay que destacar el hecho de que una gran cantidad de la sintomatología asociada a esta enfermedad se atribuye al Sistema Nervioso Central.

Se han mostrado cambios en la función cerebral de las personas afectadas de SQM en Tomografía de Emisión de Positrón Cerebrales y PET[8]. Estos

[7] Fuente: Psychiatry an Evidence Based Text. Chapter 50: Multiple Chemical Sensitivity.
[8] Ver: Heuser and Wu, 2000.

pacientes presentan un hipermetabolismo en la subcorteza profunda, incluyendo la límbica. También se han visto cambios en la actividad EGG[9] y en escáneres SPECT cerebral en la SQM[10].

Algunos autores han propuesto un modelo de sensibilización neural e inflamación neurogénica, donde los químicos actuarían también aumentando la sensibilización en el cerebro, vía neuroinflamación, particularmente en el sistema límbico[11].

Figura 2: **Ganglios basales situados alrededor del tálamo, en la zona profunda del cerebro[12]**

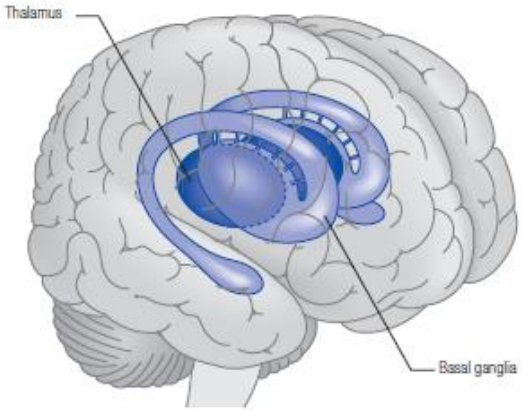

Figure 50.9 Basal ganglia wrapped round the thalamus, deep in the brain

En SQM, los cambios observados en las estructuras profundas del cerebro son consistentes con la penetración de químicos tóxicos a través de la barrera hematoencefálica. *Ashfor y Miller* 1*998* sugieren que la entrada de los tóxicos se produce o bien a través del torrente sanguíneo o bien a través del transporte intraneuronal, a lo largo del conducto olfativo.

[9] Ver: Lorig et al., 1999, Bell et al., 1999b; Muttray et al., 1995; Ross et al., 1999; Schwartz et al., 1994; Fernandez et al. 1999.

[10] Ver: Simon et al., 1994; Heuser et al, 1994; Fincher et al. ,1997.

[11] Ver: Bell et al., 1992; Bell et al., 1999, Anntelman 1994; Rossi 1996; Friedman 1994; Sorg et al. 1997, Meggs 93 y 95, Miller 97; Halley et al., 2000.

[12] Fuente: Psychiatry an Evidence Based Text. Chapter 50: Multiple Chemical Sensitivity.

Figura 3: **Interacciones potenciales entre la Sensibilidad Química y los dominios de la inflamación neurogénica, integración perceptual y frontal, inflamación no neurogénica**[13]

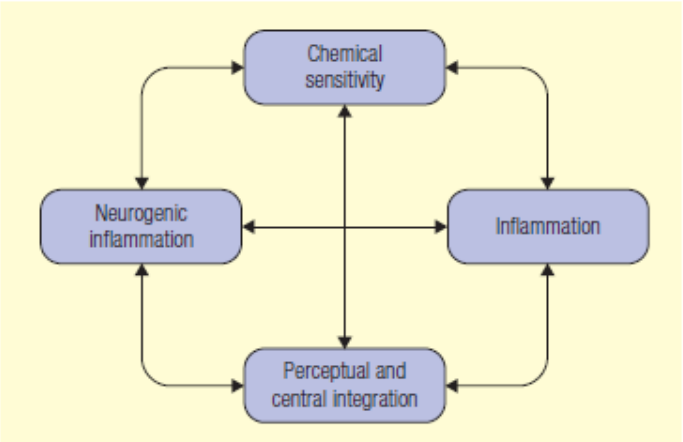

Figure 50.8 Potential interactions between chemical sensitivity and the domains of neurogenic inflammation, perceptual and central integration, and non-neurogenic inflammation

A4.2 CICLO VICIOSO METABÓLICO: ciclo NO/ONOO-

Los sistemas metabólicos humanos son similares en todas las células y son los responsables de la conversión de materia en energía en forma de moléculas de Adenosín Trifosfato (ATP), para realizar todas las funciones necesarias para la vida.

En las personas afectadas de SQM, se pone en funcionamiento un ciclo metabólico vicioso bioquímico, el llamado ciclo NO/$ONOO^-$ o ciclo del óxido nítrico-peroxinitrito.

En el capítulo 92: **MCS. Toxicological Questions and Mechanisms**, de la enciclopedia de Toxicología: General and Applied Toxicology, *Pall* explica los fundamentos y la base del ciclo NO/$ONOO^-$, de forma bien documentada y muy ampliamente relacionada con los otros autores que antes investigaron sobre ello, y basándose en los modelos de experimentación animal desarrollados.

[13] Fuente: Psychiatry an Evidence Based Text. Chapter 50: Multiple Chemical Sensitivity.

Una de las claves importantes en el desarrollo de la SQM es la excesiva actividad del receptor NMDA (N -methyl-D-aspartate), pues los químicos actúan aquí, en muchos casos de forma indirecta aumentando la actividad de dichos receptores. El camino o ruta por el que se va a producir este aumento de la actividad en el NMDA no va a ser el mismo en todos los casos, sino que dependiendo de cuál sea el grupo de tóxicos al que se esté expuesto, la vía será diferente. *Pall* documenta cada una de las rutas ampliamente en su trabajo.

En el caso de tóxicos organofosforados y carbamatos (como son algunos pesticidas), el efecto se produce porque actúan inhibiendo la enzima acetilcolinesterasa (encargada del catabolismo de la acetilcolina) y produciendo por tanto un aumento de acetilcolina. Como consecuencia, se estimulan los receptores muscarínicos, lo cual produce por tanto un aumento de la liberación de glutamato que conduce a una estimulación del receptor NMDA. También se estimularían otros receptores del glutamato. Muchos estudios muestran que el efecto de los organofosforados puede disminuirse ampliamente usando antagonistas del NMDA, siendo esto un indicador de que la activación del receptor NMDA tiene un papel importante en el efecto de estos tóxicos en el organismo.

Pero ¿cómo actúan los otros pesticidas y los otros grupos de químicos implicados?: los organoclorados y pesticidas organoclorados actúan disminuyendo la actividad del receptor GABAa, (*ácido gamma-aminobutírico*) y se sabe que esto produce elevada actividad del receptor NMDA. Los pesticidas piretroides actúan produciendo apertura a largo plazo de los canales de sodio[14] y esto produce un aumento en la estimulación NMDA.

Pall refiere que, de los siete grupos de químicos vistos en la literatura científica que iniciaban casos de SQM, (cada grupo engloba muchos compuestos diferentes: solventes orgánicos volátiles (COVs), organofosforados, carbamatos, organoclorados, monóxido de carbono, mercurio y compuestos mercuriados, sulfuro de hidrógeno, además del moho)

[14] Ver: Narahashi et al., 1995; Valentine, 1990; Wu and Liu, 2003; Bradberry et al., 2005; Proudfoot, 2005.

actúan como tóxicos en la SQM **porque producen de forma indirecta una excesiva actividad del receptor NMDA**.

Figura 4: Ruta de acción de pesticidas y solventes orgánicos[15]

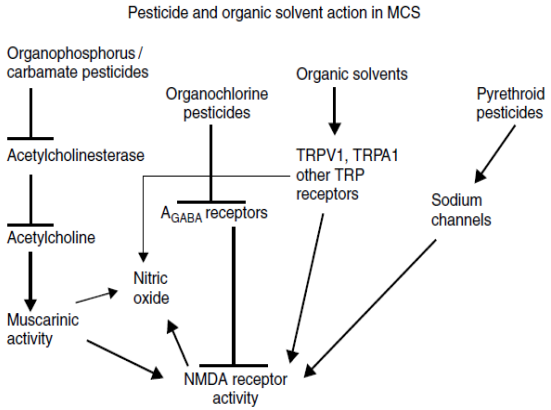

Figure 1. Pathways for action of pesticides and organic solvents. Each chemical class implicated in the initiation of cases of MCS can act along a distinct pathway to generate increases in NMDA activity, as shown in the figure. Each arrow represents a mechanism by which one parameter stimulates another. Some inhibitory (negative) interactions are also indicated. Both the organophosphorus/carbamate toxicants and the organochlorine pesticides have doubl- negative interactions. Such negative interactions, together with the arrows in the figure, indicate that the each of the four classes of compounds acts along one of these pathways, leading to an increase in NMDA activity

Cada clase de químico implicado en la iniciación de los casos de SQM puede actuar en distintas rutas para generar un aumento de la actividad NMDA, como se ve en la figura. Cada flecha representa un mecanismo por el que un parámetro estimula a otro. Algunas interacciones inhibitorias (negativo) también se han indicado. Tanto los tóxicos organofosforados/carbamatos como los pesticidas organoclorados tienen interacciones negativas dobles. Estas interacciones negativas, juntas con las flechas en la figura, indican que cada una de las cuatro clases de compuestos, actúan a lo largo de una de estas rutas, conduciendo a un aumento en la actividad NMDA[16].

[15] Capítulo 92. MCS. Toxicological questions and mechanisms. General and Applied Toxicology.

[16] Capítulo 92. MCS. Toxicological questions and mechanisms. General and Applied Toxicology.

Como consecuencia de la activación de los receptores NMDA, aumenta el nivel del Óxido nítrico (NO), lo cual conduce a que se ponga en funcionamiento el ciclo NO/ONOO. En donde el **NO** reacciona con el **ión Superóxido** que se genera principalmente en la mitocondria en pequeñas cantidades, como parte de la síntesis normal del Adenosín Trifosfato (ATP), la principal molécula de energía en el cuerpo. El NO y el Superóxido se unen para formar el **Peroxinitrito ($ONOO^-$)**, una molécula fuertemente oxidante. Esto, por tanto, genera estrés oxidativo, que es una de las características principales de la SQM y de todos los síndromes que se solapan con ella.

El estrés oxidativo activa el **factor de transcripción genética NFkB**, aumentando la actividad de la enzima **Óxido Nítrico Sintasa (i NO**S) y los niveles de citoquinas inflamatorias (como, por ejemplo: **interleukina 6, IL-6**) que también estimula la **i NOS**. Al mismo tiempo, el **ión calcio (Ca^{2+})** se libera desde los almacenamientos intracelulares, pasando al interior de la célula, produciendo apoptosis celular y estimulando la actividad de la enzima **Óxido Nítrico Sintasa Neuronal (n NOS)** y la **Óxido Nítrico Sintasa Endotelial (e NOS**). El estrés oxidativo y el superóxido además estimulan los **receptores vaniloides, VR1**, que son quimiorreceptores que se encuentran en las fibras del nervio C. El receptor vaniloide y el NO evocan la estimulación de la excitación de los receptores NMDA del glutamato, completando así el ciclo. Estos ciclos interactivos de retroalimentación positiva son ciclos bioquímicos viciosos y destructivos. Su comprensión permite tener una visión más completa de la enfermedad y explica los signos y síntomas de todas las enfermedades que se superponen a la SQM en el contexto sindrómico de la Sensibilización Central.

Figura 5: Ciclo NO/ONOO$^-$ [17]

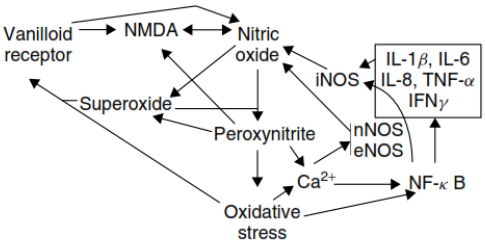

Figure 2. Vicious (NO/ONOO$^-$) cycle diagram. Each arrow represents one or more mechanisms by which the variable at the foot of the arrow can stimulate the level of the variable at the head of the arrow. It can be seen that these arrows form a series of loops that can potentially continue to stimulate each other. An example of this would be that nitric oxide can increase peroxynitrite, which can stimulate oxidative stress, which can stimulate NF-κB, which can increase the production of iNOS, which can, in turn increase nitric oxide. This loop alone constitutes a potential vicious cycle and there are a number of other loops, shown diagramatically in the figure that can collectively make up a much larger vicious cycle. The challengein these illnesses, according to this view, is to lower this whole pattern of elevations to get back into a normal range. You will note that the cycle not only includes the compounds nitric oxide, superoxide and peroxynitrite, but a series of other elements, including the transcription factor NF-κB, oxidative stress, inflammatory cytokines (in box, upper right), the three different forms of the enzymes that make nitric oxide (the nitric oxide synthases iNOS, nNOS and eNOS), and two neurological receptors, the vanilloid (TRPV1) receptor and the NMDA receptor. (The figure and legend are taken from the author's web site with permission.)

La experimentación en modelos animales confirma la relación entre la SQM y la supraregulación NMDA. Se ha observado que el antagonista de este receptor, el dextrometorfano, disminuye la reacción a sustancias químicas en pacientes con SQM.

[17] MCS: Toxicological questions and mechanisms.

En estudios de polimorfismos genéticos se ha visto que en el gen CCK-B, el alelo del gen que actúan indirectamente para producir un aumento de la actividad NMDA está asociado con un aumento de la prevalencia de SQM[18].

Bell y otros científicos han propuesto que el modelo de sensibilización neural, clave en personas con SQM, sugieren que el probable mecanismo para tal sensibilización es la llamada **Potenciación a largo plazo (LTP**), este mecanismo, LTP, c**onlleva un aumento de la actividad NMDA**. También se ha visto en muchos modelos animales de SQM que la excesiva actividad NMDA juega un papel importante en esta enfermedad.

Conclusiones:

En la SQM, las alteraciones del ciclo NO/ONOO- se basan en cinco principios[19]:

- ✓ Los factores que inician los casos con repercusión multisistémica actúan aumentando la síntesis de NO y los niveles consiguientes de ONOO- y/o otros elementos del ciclo.
- ✓ Tras la iniciación, se convierte en una **enfermedad crónica** debido a que las reacciones que se producen en el ciclo se mantienen, por lo que de forma crónica los distintos elementos del ciclo como son NO, ONOO- y otros estarán elevados.
- ✓ Los síntomas y signos de esta enfermedad se generan por los elevados niveles de NO y/otras importantes consecuencias del mecanismo propuesto como son los elevados niveles de ONOO, NO, citoquinas inflamatorias, estrés oxidativo y elevados receptores NMDA, TRPV1, entre otros. Ello pone de manifiesto la activación inmune y caracteriza los **procesos inflamatorios, oxidativos y degenerativos** que se dan en esta enfermedad.
- ✓ Debido a los componentes implicados, el NO, el superóxido y ONOO- tienen distancias de difusión bastante limitadas en los tejidos biológicos y debido a que el mecanismo involucrado en el ciclo actúa a nivel de células individuales, **los mecanismos fundamentales son**

[18] Binkley et al., 2001.

[19] Pall and Bedient, 2007.

locales. Esta naturaleza local implica que podemos tener variación en el tejido afectado y éste ser diferente de un afectado a otro. Esto explica la variación de síntomas de un individuo a otro. **Esto no quiere decir que no haya efectos sistémicos, sino que además hay efectos locales.**

- ✓ La terapia tiene que tener por objetivo regular a la baja la bioquímica del ciclo NO/ONOO. Es decir, ha de enfocarse en disminuir la causa de la enfermedad, no solo en tratar los síntomas.

Pall 2009, refiere que cuando el mecanismo de la elevada actividad receptor NMDA e iniciación del ciclo NO/ONOO se fusiona con el modelo de sensibilización neural y de inflamación neurogénica, es capaz de explicar los principales aspectos más desafiantes de esta enfermedad, como su cronicidad, la diversidad de efectos que produce y la implicación de muchos sistemas corporales dado que los tejidos afectados pueden ser diversos.

El propio autor señala la necesidad de seguir profundizando e indagando en este sentido.

Otros autores[20] que han investigado las enfermedades sistémicas autoinflamatorias relacionan la iniciación de este ciclo con un mayor número de sustancias químicas.

[20] Von Baehr V, 2012.

Figura 6: Patogénesis de la inflamación, mitocondriopatía y estrés nitrosativo como resultado de la exposición a desencadenantes[21]

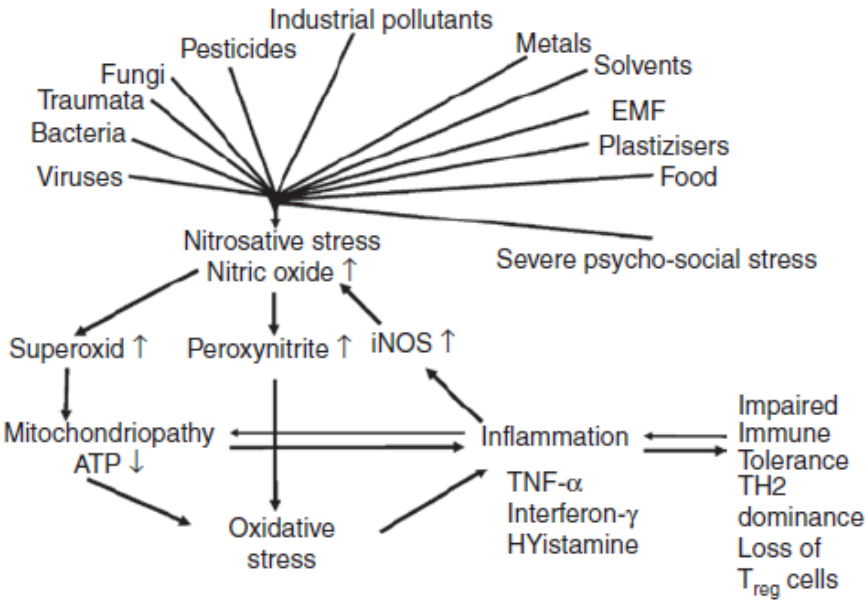

Figure 1: Pathogenesis of inflammation, mitochondriopathy, and nitrosative stress as a result of the exposure to trigger factors (248).

A4.3 METABOLISMO DE TÓXICOS

El hígado es el principal, pero no el único órgano del metabolismo y es crucial para la eliminación de compuestos tanto exógenos como endógenos y, por tanto, de los xenobióticos del cuerpo. Los procesos metabólicos han sido ampliamente estudiados y conllevan una serie de reacciones químicas bien definidas. La comprensión y el estudio de la fase I y II del metabolismo de moléculas endógenas y exógenas es de particular importancia, muy

[21] Von Baehr V. Rational Laboratory Diagnostics in Chronic Enfermedades sistémicas inflamatorias. Sociedad de medicina ambiental 2012; 25 (4): 244-7.

especialmente para comprender la importancia de la desintoxicación en los afectados de SQM.

La fase 1 está formada por una gran familia de encimas, como mono-oxigenasas y enzimas del citocromo P-450 que introducen átomos de oxígeno en compuestos orgánicos que son ampliamente solubles en lípidos, creando intermedios altamente reactivos. En la fase II, estos compuestos intermedios se conjugan con una variedad de moléculas para generar productos solubles en agua que pueden ser excretados por la orina. En una fase III posterior, se produce la excreción de compuestos lipídicos en las heces. Las enzimas CYP humanas ocupan un papel clave en la excreción de muchos compuestos endógenos fundamentales, y han sido estudiados ampliamente por su relación con el metabolismo de los fármacos y compuestos carcinogénicos.

Hay fundamentalmente seis rutas de conjugación en la fase II:

- Conjugación Glutation
- Conjugación Aminoácido
- Metilación
- Sulfatación
- Acetilación
- Glucuronidación

El CYP humano tiene un papel importante en la transformación de muchos compuestos endógenos, pero ha sido más estudiado por su relación con el metabolismo de ciertos fármacos y compuestos carcinogénicos (por ejemplo, los Hidrocarburos Aromáticos Policíclicos, PAHs).

El metabolismo y la eliminación de xenobióticos se han convertido en un área de estudio importante dentro de la toxicología. Los CYP450s están implicados en el metabolismo de alrededor del 75 por ciento de los medicamentos y xenobióticos y están presentes en muchas áreas importantes del cuerpo, incluyendo las membranas mitocondriales, la barrera hematoencefálica, tracto gastrointestinal e hígado.

Muchos de los xenobitóticos que se encuentran ampliamente distribuidos en el medio ambiente son PAHs. El metabolismo de la fase I transforma los PAHs en compuestos muy reactivos como son los epóxidos, que a su vez se conjugan en la fase II en compuestos polares, que pueden ser excretados por la orina. Si

el proceso de fase I no se realiza adecuadamente y no se conjuga con la fase II, entonces se forman **especies de oxígeno reactivas (ROS),** que son muy destructivas y llevan a producir daño oxidativo, lo cual puede causar daño en los distintos tejidos, que es una característica de todas las enfermedades multisistémicas como la SQM, FM, SFC y la EHS.

Por tanto, hay que resaltar la importancia de que el ratio al que la fase I produce los intermediarios activados tiene que estar equilibrado o ser menor que el ratio al cual la fase II conjugue y excrete las toxinas en la orina vía los riñones, o por la bilis y heces vía intestino, y por el sudor. Como se ha dicho, si la fase I es más rápida que la fase II, se producen metabolitos intermedios activos más tóxicos que los originales y muy destructivos.

Muchos fármacos son inhibidores de la enzima P-450, lo cual puede resultar en una acumulación de medicación y químicos externos (xenobióticos) que aumenta los efectos secundarios y la toxicidad de los mismos. Ejemplos de fármacos inhibidores: cimetidina, ciprofloxacina, diltiazem, erytromicina, ketoconazol, verapamil, y un número selectivo de inhibidores de recaptación de la serotonina (SSRIs).

Para una comprensión más profunda de estos aspectos se recomienda la lectura de las siguientes citas:

- ✓ **Jakoby WB**, Enzimatic Basis of Detoxification. Vol 1, Academic Press. 1980. Este libro explica en detalle el mecanismo catalítico y la expresión fisiológica de las enzimas que están implicadas en la detoxificación, fase 1 y fase 2 incluyendo la acción de las enzimas alcohol desidrogenasa, aldehído oxidasa, superóxido dismutasa, glutation peroxidasa y monoamín oxidasa así como la acción del citocromo P-450. El libro explora el metabolismo de los xenobioticos y qué hacen las enzimas específicas.
- ✓ ***Jakoby* WB**, Enzimatic Basis of Detoxification. *Vol. 2,* Academic Press, New York (1980). Este volumen detalla la bioquímica de todas las rutas de la conjugación.

Desnutrición y alta carga tóxica corporal

Hay que tener en cuenta que para que se produzcan todas estas reacciones bioquímicas que se han indicado someramente, el organismo necesita

disponer de las enzimas adecuadas que catalizan cada una de las reacciones, así como de los nutrientes que actúan como coenzimas, asistiendo en cada uno de estos procesos. Hay autores que han objetivado el bajo estado nutricional que tienen los afectados de SQM y patologías relacionadas[22]. Por tanto, al no disponer de una reserva nutricional adecuada, los cofactores no están disponibles para asistir en estas reacciones. Como consecuencia, se produce una incapacidad de desintoxicar correctamente produciendo una acumulación de tóxicos, y aumentando lo que se conoce como **carga tóxica corporal**, acumulando más toxicidad en el organismo y haciéndolos más vulnerables al impacto de los químicos tóxicos en el cuerpo, pues queda alterada la capacidad de regulación homeostática.

Otros estudios[23] han relacionado la alta carga tóxica corporal con la enfermedad de Sensibilidad Química Múltiple (SQM), y enfermedades relacionadas, y confirman la existencia de una alta concentración de compuestos orgánicos hidrocarburos que es mayor en personas con SQM, o en donde se encuentra una alta concentración de hidrocarburos solventes alifáticos entre los afectados[24]. También se muestra la existencia de una alta concentración de Pesticidas Organoclorados y Solventes clorados en la sangre de personas con SQM[25].

En *Ziem 1999*, la autora señala que la lesión tóxica por la exposición reiterada a disolventes, pesticidas, fragancias, etc, puede causar deterioro de los sistemas inmunológico, endocrino y nervioso, alteraciones del metabolismo de desintoxicación, energía y neurotransmisores, deficiencias en proteínas, minerales y nutrientes y cambios gastrointestinales como candidiosis parasitosis, reducción de la función de la enzima pancreática, intolerancia al gluten, reducción de IgA secretora o insuficiencia suprarrenal.

En *Carrasco NJ 2009*, el autor muestra como la desnutrición y la toxicidad ambiental están influyendo en la enfermedad de las últimas generaciones,

[22] Ver: Jacoby, 1980, Ross et al., 1989, Rea 1986, Cox et al.,1991, Romano et al., 1994, Rogers 1990.

[23] Rea 1987.

[24] Pan et al., 1987/88.

[25] Rea 1986.

llegando incluso a afirmar que esta generación venidera puede ser la primera en la que los niños estén más enfermos que sus padres, ya que a la edad de 7 años se están presentando actualmente procesos de enfermedad avanzada anteriormente sólo vista en adultos.

Además, hay que tener en cuenta que los afectados de SQM portan polimorfismos genéticos que hacen que la desintoxicación no se produzca de forma tan eficiente como en el resto de la población. Esto puede explicar por qué las personas no reaccionan igual ante la misma exposición química.

Para una mejor comprensión de todos estos factores se recomienda la lectura de las siguientes reerencias:

- ✓ **Rea, William J.:** Chemical Sensitivity, Volume I, Lewis Publishers, Boca Raton, Florida, 1992.
- ✓ **Rea, William J.:** Chemical Sensitivity, Volume 3, Lewis Publishers, Boca Raton, Florida, 1996.
- ✓ **Rea, William J:** Chemical Sensitivity, Volume 4, Lewis Publishers, Boca Raton, Florida, 1997.

A4.4 GENÉTICA

Marshal et al., 2011 afirma que se han encontrado polimorfismos genéticos en personas con SQM en comparación con grupos control que parecen indicar que estas personas tienen mayor dificultad que la mayoría de la población en la metabolización y excreción de los químicos comunes en el medio ambiente y de los fármacos. La Epigenética y la influencia de los estímulos ambientales activando o inhibiendo la expresión de enzimas metabólicas, a pesar de ser relativamente reciente, está evolucionando muy rápidamente.

En *Genuis, 2008* se afirma: «Just as a loaded gun needs to be triggered to unload destruction, epigenetic research confirms that disease is often the result of vulnerable genes being triggered by specific determinants. Mounting evidence suggest that without activation, some disease processes will not develop, and removal of the initiating trigger may allow developing illness to abate or subside».

Traducción: «Al igual que un arma cargada debe activarse para causar la destrucción, la investigación epigenética confirma que la enfermedad es a menudo el resultado de genes vulnerables activados por determinantes

específicos. La evidencia acumulada sugiere que, sin la activación, algunos procesos de la enfermedad no se desarrollarán, y la eliminación del desencadenante iniciador puede permitir que la enfermedad en desarrollo disminuya o subsista».

En un estudio italiano[26] se comparaba los pacientes diagnosticados de SQM o los que sospechaban que tenían SQM con controles sanos. Aunque no se observó que algunos genes analizados fueran diferentes en la población combinada «caso», si se encontró que varias enzimas metabolizantes sí lo eran. Los autores de este estudio concluyeron que: **«Los patrones redox y de citoquinas alterados sugieren una inhibición de la expresión/ actividad de las enzimas metabolizantes y antioxidantes en la SQM. Debe de considerarse en la definición biológica y diagnóstico de SQM Los parámetros metabólicos que indican la aceleración de la oxidación de los lípidos, el aumento de la producción de óxido nítrico y el agotamiento del glutatión en combinación con el aumento de citoquinas inflamatorias en plasma**».

Pall 2009, describe que hay estudios genéticos sobe la mayor susceptibilidad o propensión a padecer SQM. Hay tres estudios que se nombran en los que en cada uno de ellos los químicos juegan un papel causal en la iniciación de los casos de SQM.

El primer estudio es el de *Haley et al. 1999,* los veteranos de la guerra del Golfo incluyendo aquellos que sufrieron SQM, también sufrieron de enfermedades relacionadas como FM o SFC. Fueron sometidos a más una docena de estresores que pudieron tener un papel significativo en el inicio de la enfermedad, como la exposición a tóxicos organofosforados, (sarín, ciclosarín). Lo que *Haley et al. 1999* informaron es que aquellos veteranos portadores de una forma del gen para el PON1, que los hacía menos capaces de metabolizar estos neurotóxicos, eran más susceptibles a desarrollar síntomas neurológicos. Esto proporciona evidencia sustancial de que los gases sarín/ciclosarin jugaron un papel crucial en el desarrollo de la enfermedad en aquellos sujetos cuya enzima codificada por el gen PON1 tenía menor actividad, lo que los hacía menos capaces de desintoxicar los tóxicos y más propensos a padecer la enfermedad. Respecto del gen PON1, *Mackness et al.,*

[26] De Luca et al., 2010.

2003, también informaron que entre los granjeros que usaban organofosforados para el lavado de las ovejas, padecían enfermedades crónicas aquellos cuyo alelo para el PON1 producía un menor metabolismo del pesticida, comparado con los granjeros que reportaban mejor salud.

El segundo y el tercer estudio están realizados sobre población civil con SQM, comparándolos con grupos control. Uno fue el estudio de Canadá por *McKeown-Eyssen et al., 2004,* y el segundo fue el estudio alemán de *Schnakenberg et al., 2007.*

Ambos estudios mostraban que los tres polimorfismos genéticos distintos estaban implicados en el metabolismo de químicos que a la vez estaban implicados en la iniciación de casos de SQM, tenían una influencia estadísticamente significativa sobre la susceptibilidad. En el estudio *Schnakenberg et al., 2007,* hubo un muy alto nivel de significación estadística para cada uno de estos tres genes, por lo que la probabilidad de obtener estos resultados por casualidad si no hay verdadera correlación es menor de 1 en $10^{11.}$ En *McKeown-Eyssen et al., 2004,* se mostró un aumento de 18 veces de riesgo de padecer SQM cuando se dieron interacciones entre las enzimas metabolizadoras de CYP2D6 y NAT2.

De los tres grandes estudios realizados sobre este tema: *Haley et al. 1999, McKeown-Eyssen et al., 2004, Schnakenberg et al., 2007,* se puede obtener un patrón de evidencia que muestra que los genes que metabolizan los químicos implicados en la iniciación de la SQM, tienen influencia en la susceptibilidad para desarrollar MCS. Estos resultados apoyan la inferencia de que los químicos actúan como tóxicos causantes de muchos casos de SQM, y que estos químicos deben de estar en su forma tóxica para actuar. Por tanto, alelos de genes polimórficos que o bien aumentan o bien disminuyen el metabolismo de los químicos, influenciarán la susceptibilidad a padecer SQM.

Figura 7: Polimorfismos genéticos que influyen en la susceptibilidad de SQM[27]

Table 1. Genetic polymorphisms influencing MCS susceptibility

Gene	Study	Function—chemical metabolism	Comments
PON1	H, M	Detoxification of organophosphorus toxicants	—
CYP2D6	M	Hydroxylation of hydrophobic compounds	Hydroxylation of compounds without hydrogen binding group may be expected to lead to greater activity as a TRPV1 agonist
NAT2	M, S	Acetylation	May produce more or less activity depending on the specific compound involved
GSTM1	S	Provide reduced glutathione for conjugation	Should increase detoxification and excretion
GSTT1	S	Glutathione conjugation	Should increase detoxification and excretion
GSTP1	S	Glutathione conjugation	Should increase detoxification and excretion; only statistically significant role was in conjunction with specific alleles of other genes

H, Haley *et al*. (1999); M, McKeown-Eyssen *et al*. (2004); S, Schnakenberg *et al*. (2007).

En *Hooper 2011*, se indica que el estudio de los genes que portan las personas con SQM es muy importante. En la literatura científica la importancia de las variaciones genéticas en la metabolización de fármacos y xenobióticos ya fueron reconocidas a principios del siglo XXI[28].

«La predisposición genética subyacente de cada paciente, reflejará combinaciones de fenotipos de metabolizadores lentos o pobres o fenotipo de metabolizador rápido o extenso. Si estas enzimas participan en la misma vía metabólica para cualquier fármaco o agente ambiental dado, tal variabilidad genética podría ser sinérgica y conducir hasta diferencias de 30 o 40 veces de diferencias en la activación o degradación de moléculas. El resultado final puede ser de grandes diferencias interindividuales en el riesgo de toxicidad ambiental[29]».

En Wiesmuller *et al., 2008*, no se encontró ningún vínculo con algunas frecuencias alélicas, pero se consideró solo NAT1, NAT2, PON1 y PON2,

[27] Fuente: MCS: Toxicological questions and mechanisms.

[28] Ver: Nebert DW 2000, Ma MK, et al., 2000.

[29] Cory-Slechta et al., 2008.

Hooper 2011 dice al respecto que no se consideraron los genes CYP2D6 o GST, por tanto, debido a la gran cantidad de variantes genéticas de las muchas enzimas involucradas en el metabolismo xenobiótico, el área de estudio es compleja pero urgente ya que será muy fructífera para comprender las variaciones generalizadas en la SQM.

En *Cui et al. 2013,* se concluye que personas con sensibilidad química alta presentaron mayor asociación con polimorfismos SOD2.

Caccamo et al. 2013, estudió los polimorfismos genéticos asociados a las enzimas metabolizadoras de la fase I y II. Comparando las frecuencias de los polimorfismos genéticos para las enzimas metabolizadoras en el P450 (CYP) y por primera vez la frecuencia del receptor de xenobióticos Aryl hydrocarbon (AHR), en las tres cohortes utilizadas para el estudio. Se encontró una frecuencia significativamente mayor de polimorfismos CYP2C9 ∗ 2, CYP2C9 ∗ 3, CYP2C19 ∗ 2, CYP2D6 ∗ 4 y CYP2D6 ∗ 41 en pacientes en comparación con los controles. Esto confirma que estas variantes genéticas representan un factor de riesgo genético para las enfermedades relacionadas con las Sensibilidades Ambientales.

Por tanto, es importante considerar el factor de la presencia de polimorfismos genéticos en aquellos genes implicados en la bioquímica o transformación de moléculas que interviene en procesos fundamentales para la detoxificación y desintoxicación.

CONCLUSIÓN:

Como se puede ver, todos los principios fisiológicos/bioquímicos expuestos en este apartado, junto con otras propuestas en la literatura científica no entran en contradicción, sino que son distintas piezas de un mismo puzzle que han de juntarse para una completa comprensión de la SQM.

A5. DIAGNÓSTICO

El diagnóstico en la SQM, se encuentra bien recogido en nuestro país en el Documento de Consenso del Ministerio de Sanidad del año 2011 y el documento de Actualización de la Evidencia Científica sobre SQM de 2015.

Un buen resumen de este aspecto se recoge en la parte III[30], en el que se indica de forma clara y sintética cuál es la definición de caso, criterios diagnósticos, etiopatogenia, diagnóstico, anamnesis y exploración física, pruebas complementarias. Además, cita cuestionarios que sirven de apoyo para el diagnóstico de la SQM. En esta sección, también se hace especial hincapié en la evitación de las sustancias desencadenantes para evitar los síntomas como única herramienta conocida, al mismo tiempo que propone un algoritmo de atención sanitaria que también está recogido en la GUÍA del INSS, 2ª Edición.

Recomendamos a los clínicos la aplicación de todos los puntos expuestos en la parte III del Documento de Consenso del Ministerio de Sanidad, 2011.

El diagnóstico de la SQM es un diagnóstico clínico, basado en la presencia de síntomas y signos. Para ello, la realización de una buena anamnesis con una historia clínica detallada, así como con una historia de exposición ambiental, no solo en el ámbito laboral, sino también exposición ambiental en el ámbito doméstico, personal, ocio, hobbies, etc. El cuestionario QEESI es la herramienta más usada de diagnóstico en la literatura científica y validada clínicamente. Esta herramienta permite hacer una graduación de la intensidad de los síntomas. Respecto a las pruebas complementarias que pueden realizarse para valorar el estado del general del paciente, el documento de consenso propone algunas de ellas. En esta sección expondremos algunas de las que la literatura científica se hace eco:

Es importante incidir en que la SQM, no tiene ningún biomarcador patognómico. Es decir, no existe ninguna prueba específica que confirme o excluya la enfermedad.

A continuación, se exponen algunas **pruebas complementarias orientativas**, sugeridas en distintos artículos que pueden realizarse para ayudar en la valoración del estado general del paciente en relación a la enfermedad que padece.

«Realizar una buena exploración física, en relación con los síntomas que padece, con atención a la observación de signos, si los hubiera: eritema,

[30] Conclusiones y Recomendaciones Consensuadas por el Grupo Redactor, (página 57 del primer documento).

ronquera, trastornos del habla, atención, distensión o aumento del perímetro abdominal, taquicardia, arritmia, taquipnea, hiperactividad motora, descoordinación motora, bradispsiquia, vulvo-vaginitis, asterixis[31]».

«La petición de otras pruebas complementarias debe ser individualizada, en función del cuadro clínico, la exploración física y la sospecha de una enfermedad asociada (Por ejemplo: analítica de la Función Tiroidea o Cortisol basal o FR o ANA o 25 OH-D o PTHi o Prolactina o Ferritina, Vitamina B12 o Ácido fólico)[32]».

Otros autores[33] proponen las siguientes pruebas:

- ✓ Histamina, como marcador inflamatorio.
- ✓ 6-OHMS, como marcador del insomnio crónico.
- ✓ HSP27 y HSP70, como marcadores de estrés celular.
- ✓ Anticuerpos anti-Po de la mielina, como marcador autoinmune.
- ✓ Eco-Doppler Cerebral Pulsado, para medir el flujo sanguíneo cerebral.
- ✓ Nitrotirosina, como marcador de estrés oxidativo ($ONOO^-$).

Algunos clínicos han recomendado:

- ✓ Test de perfil de ATP: medición de ubiquinona, citocromos, etc… para valorar la afectación mitocondrial.
- ✓ Pruebas de esfuerzo, para medir la limitación funcional, pueden ser orientativas.
- ✓ NIRS: Near infrared spectroscopy. Mujeres expuestas a organofosforados presentan una liberación de oxígeno alterada después del ejercicio[34].
- ✓ Pruebas de autoinmunidad, como, por ejemplo: anticuerpos para descartas tiroiditis Hashimoto, etc.
- ✓ SPECT u otras pruebas como PET, EEG. cerebral para valorar disfunción cerebral.

[31] Documento de Consenso, Ministerio de Sanidad 2011.

[32] Documento de Consenso, Ministerio de Sanidad 2011.

[33] Belpome et al., 2015.

[34] Verdaguer-Codina, Valls- Llobet, Pujol Amat 2004.

Con respecto a las pruebas de imagen, se deben proponen a partir de los hallazgos de la presencia de disfunción cerebral, lo que puede reflejarse en las mismas. Pero hay que considerar que, en los pacientes con grado moderado o intenso de SQM, estas pruebas pueden afectar marcadamente a su salud. También hay que considerar el hecho de que no son marcadores definitivos ni patognomónicos.

- ✓ Valoración de procesos inflamatorios crónicos subyacentes, evaluándolo mediante el factor de riesgo inflamatorio con exámen de polimorfismos genéticos en relación a IL1-alfa, IL1-beta, TNFα, y receptor de IL1RA. Se evalúa el factor de riesgo de 0 a 5.
- ✓ Valoración de todas aquellas enzimas que están vinculadas con la capacidad de eliminación de sustancias tóxicas y cancerígenas: la SOD, dependiente del Mg, la SOD dependiente del cobre y del zinc, la glutation peroxidasa, transferasa, catalasa…
- ✓ Valorar la presencia de fenómenos alérgicos: pruebas LTT (pruebas de transformación de linfocitos, test melisa y test de hipersensibilidad).
- ✓ Valorar la presencia de mercurio y de otros metales pesados, en sangre (plasmático, intraeritrocitario), pelo y orina. Esta valoración es muy importante si ha habido exposición laboral, se tienen o han tenido amalgamas de mercurio o alta ingesta de pescado.
- ✓ Muchos fenómenos inflamatorios y tóxicos son debidos a sustancias medibles en los propios fluídos y tejidos biológicos, mediante análisis de sangre, orina y cabello, así como en biopsia grasa, pudiendo identificarse presencia de disolventes, pesticidas, metales pesados, PAHs o compuestos orgánicos persistentes. No siempre es fácil detectar la presencia de estas sustancias, por eso es importante, porque estas sustancias pueden determinar las enfermedades inflamatorias[35].
- ✓ Valorar si los afectados son portadores de implantes dentales, u otros tipos de prótesis, y si existen fenómenos reactivos de tipo inflamatorio, no en un sentido alérgico, sino con una base tóxica directa. Ejemplo: el test de provocación con titanio nos permite

[35] Rea, W. J. 1997 Chemical Sensitivity: Tools of Diagnosis and Methods of Treatment, Vol. 4, Lewis Publishers, Boca Raton.

comprobar si existe reactividad, se ponen en contacto los linfocitos del paciente con micropartículas de titanio y se miden la producción de citoquinas inflamatorias producidas por los linfocitos. Para otros tipos de metales se pueden realizar Test Melisa con distintos perfiles, en función de los metales de prótesis e implantes[36].

- ✓ Otro elemento causal importante pueden ser los hongos, que producen millones de toxinas que pueden causar inflamación y otros síntomas. Es importante la valoración de hongos en la vivienda o trabajo.

A6. TRATAMIENTO

La primera y esencial herramienta de tratamiento es **la evitación** de las sustancias desencadenantes. El objetivo es conseguir una vivienda libre de químicos y radiaciones electromagnéticas, pues es la opción que consigue mejorar los síntomas en la mayor parte de los casos. No obstante, cuando hay un grado moderado a intenso de la enfermedad, se presentan multitud de síntomas aun cuando la persona no se está exponiendo a agentes desencadenantes. Dichos síntomas empeoran aún más ante la exposición.

Ante el hecho de que algunos afectados tienen una gran constelación de síntomas que aumentan cuando se evitan las sustancias desencadenantes, algunos autores[37] afirman que *la reducción de la carga tóxica total para mejorar y reforzar los procesos internos de eliminación de tóxicos, es el objetivo deseable de tratamiento, así como la reducción a la baja de la actividad del ciclo NO/ONOO-*.

La Doctora *Miller* afirma que*: los suplementos específicos tolerados pueden tener un costo prohibitivo, pero si los pacientes no mantienen una nutrición adecuada, se puede acumular en el cuerpo cada vez más una carga de sustancias dañinas y encontrarse tan sobrecargados que incluso cantidades mínimas de los factores químicos desencadenantes que deben evitar, iniciarán graves síntomas que pueden ser invalidantes y prolongarse por días o periodos de tiempo mucho más largos…*

[36] Rea, W. J. 1997 Chemical Sensitivity: Tools of Diagnosis and Methods of Treatment, Vol. 4, Lewis Publishers, Boca Raton.

[37] Marshal 2011. Pall 2007a: Explicando las «enfermedades inexplicadas», Capítulo 15: Tratamiento. Rea WJ 1997: Chemical Sensitivity: Tools of Diagnosis and Methods of Treatment, Vol. 4, Lewis Publishers, Boca Raton.

Rea WJ 1997 refiere que la inmunoterapia a bajas dosis ha ayudado a muchos afectados en procesos de mejora de sus síntomas. En *Genuis 2013* se describe también del uso de la Inmunoterapia de desensibilización destinada a disminuir la respuesta inmune de hipersensibilidad asociada a la exposición en individuos susceptibles y se afirma:

(…) l*as intervenciones psicoterapéuticas no han logrado hasta ahora éxito. En general, los tratamientos fisiológicos parecen de forma consistente tener resultados superiores y sostenidos en comparación con las terapias psicológicas.*

(…) e*l manejo médico preferido, diseñado para restaurar la salud y liberase, conlleva la eliminación de la carga corporal inicial de toxinas primarias. La disminución de la carga tóxica mediante los mecanismos innatos de eliminación de tóxicos o mediante las intervenciones clínicas de detoxificación para contaminantes persistentes, parecen disminuir consistentemente la desregulación inmune, asociada con la SQ y aminorar gradualmente las manifestaciones clínicas de SQ.*

Hay que tener en cuenta que estos tratamientos propuestos son de larga duración y si bien no consiguen curar la enfermedad, sí logran aumentar el margen de tolerancia y disminuir la sintomatología en la mayoría de los casos su efectividad está sujeta a la realización de cambios en la vida diaria para evitar las sustancias desencadenantes. Hay que considerar que para estas personas que padecen tal cantidad de síntomas, que les lleva a un aislamiento voluntario para poder sentirse mejor, cualquier mejoría en sus síntomas, ayudaría mucho a proporcionar mejor calidad de vida. Sin embargo, no existe una evidencia científica suficiente como para recomendar los tratamientos de quelación o de eliminación activa de tóxicos de forma sistemática.

B. REVISIÓN GUÍA DEL INSS, 2ª EDICIÓN

A la luz de algunos de los aspectos de la enfermedad de SQM recogidos en el apartado *A) Sensibilidad Química Múltiple* de este documento, obtenida de la revsión de las publicaciones científicas que cuentan con mayor respaldo por la comunidad científica, se quiere poner de manifiesto los desacuerdos surgidos tras hacer una lectura minuciosa del apartado 5A. Sensibilidad Química Múltiple de la GUÍA del INSS, 2ª Edición.

B1. DEFINICIÓN

En la introducción (Pág. 123) de la GUÍA del INSS, 2ª Edición, se dice lo siguiente:

Los términos sensibilidad química múltiple (SQM), hipersensibilidad electromagnética (HE), alergia ambiental, alergia universal, hipersensibilidad acústica, entre otros, son cada vez más frecuentes en nuestras consultas. Con el fin de abarcarlos todos, la Organización Mundial de la Salud (OMS), en 1996, propuso que se utilizar el término «enfermedad ambiental idiopática (IAI)», *ya que la palabra* «sensibilidad» *puede ser entendida como un fenómeno relacionado con la alergia, lo que carece de fundamento científico (…).*

A este respecto hay que decir que, aunque algunas instituciones y algunos autores afirman esto, y pueden encontrase publicaciones científicas que utilizan la denominación de IAI, en cambio, no se trata de una denominación mayoritaria para la SQM, como se reconoce en la propia Guía del INSS, 2ª Edición y como se desprende de la revisión de las publicaciones científicas sobre esta enfermedad. Esto se debe a que hay autores que dicen que no es cierto que fuera la OMS la entidad que propusiera el nombre de «enfermedad ambiental idiopática» para abarcar todos los términos. Se puede comprobar esta afirmación en la página de inicio del documento en el que tuvo lugar este debate, se aporta como **anexo I.** Esto se argumenta a continuación y se aporta el **anexo I** para su corroboración.

B1.1 Origen del término enfermedad ambiental idiopática y posición de la OMS al respecto

El término de EAI, es el único en el que no se establece la relación causal entre el origen de la enfermedad y la toxicidad química.

Algunos autores[38] se han pronunciado sobre la afirmación de que fue la OMS la que propuso utilizar este nombre:

«No fue la OMS la que propuso o respaldó el término IEI. Fue la industria química: (…) Una de las afirmaciones más escandalosas que hacen la industria química y sus asociados es que la Organización Mundial de la Salud (OMS) apoya el cambio de nombre de SQM a EAI. La OMS fue uno de los patrocinadores de un taller del Programa Internacional de Seguridad Química (IPSC) en SQM celebrado en Alemania en febrero de 1996. Este taller estuvo dominado por participantes asociados a la industria y no contó con representantes de grupos ambientales, laborales o de consumidores. En cambio, los participantes no gubernamentales eran personas empleadas por BASF, Bayer, Monsanto y Coca Cola (…) Fue en esta reunión donde se tomó la decisión de intentar cambiar el nombre de MCS a IEI (...)».

En cualquier caso, la OMS emitió una declaración a los participantes del taller después de la reunión para intentar detener las declaraciones de que la OMS apoyaba el cambio de nombre de SQM a EAI. La OMS declaró textualmente: **«un informe del taller para la OMS, con conclusiones y recomendaciones, presenta las opiniones de los expertos invitados y no representa necesariamente la decisión o la política declarada de la OMS»**. Continúa diciendo que «con respecto a la SQM, **la OMS no ha adoptado ni aprobado una opinión política o científica[39]»**.

A pesar de este descargo de responsabilidad explícito, las afirmaciones de que la Organización Mundial de la Salud respalda el EAI continúan siendo realizadas por oponentes de MCS.

[38] Ann McCampell, MD: MCS Under Siege.

[39] Ver: McCampbell Ann, 2001.

Otros científicos[40] también escribieron sobre el taller de 1996 en Alemania y la propuesta del cambio de denominación[41]. Ambos científicos afirman:

«Los cuatro *representantes de las ONGs* eran empleados a tiempo completo de BASF, Bayer, Monsanto y Coca Cola, los tres primeros de los cuales afirmaron su afiliación a un instituto de ciencia financiado por la industria (el Centro Europeo para el Medio Ambiente y la Toxicología) (…) ».

(…) Después de que ciertos participantes declararan erróneamente que el EAI era ahora el nombre oficial de la OMS para la SQM. El IPCS (Programa Internacional de Seguridad Química) **recibió una carta de protesta de 80 científicos y médicos destacados de los EE. UU.** El IPCS aclaró el estado del nombre de EAI (enfermedad Ambiental Idiopática) con la emisión de un aviso que indicaba que la **OMS «no adoptaba ni aprobaba una opinión política o científica sobre la SQM».**

Puede confirmarse esto último leyendo el documento que se adjunta en el **Anexo I[42].**

«This report contains the views of an international group of experts and does not necessarily represent the decisions of the stated policy of the United Nations Environment Programme, the International Labour Ortanization, or the World Health Organization».

B2. ETIOPATOGÉNIA

En la página 124 del documento encontramos las siguientes declaraciones:

Si bien existe una teoría etiopatogénica que postula un origen orgánico tóxico, la mayoría de los autores defienden una causa psicopatológica de la enfermedad. (…) pero ninguna de las teorías anteriores tiene una evidencia ni un respaldo científico suficiente.

Cuando la Guía del INSS, 2ª Edición hace estas afirmaciones tan rotundas, genéricas y sin referenciar se **entra en contradicción con la Enciclopedia Práctica de Medicina del Trabajo, del Instituto Nacional de Seguridad y**

40 Ashford y Miller: Low Levels, High Stakes, 1998.

41 Ashford y Miller, 1998: 9.

42 Documento del IPCS. *Report of Multiple Chemical Sensitivities.* (MCS) Workshop. Berlin, Germany, 21-23 February *1996*. (Pág. 3, página de inicio del documento después de la portada).

Salud en el trabajo, diciembre de 2018, órgano del Ministerio de Trabajo, Migraciones y Seguridad Social que dice:

*El paciente tipo afectado es una mujer de mediana edad, con historial de exposición previa, por motivos laborales o no, a sustancias reconocidas como quimiosensibilizantes frente al SQM. Si bien no hay hoy en día pruebas definitivas sobre la etiología del proceso, se han detectado altos niveles de pesticidas en la sangre de pacientes afectadas por SQM**, lo que da mayor peso a la hipótesis de la fuente química de la patología frente a hipótesis psicosomáticas o psiquiátricas, aunque sin descartar la influencia de la susceptibilidad por base genética de cada individuo u otras causas no determinadas,*** (Pág. 856).

Llama la atención que en la Guía del INSS se puedan hacer estas afirmaciones con tal rotundidad y no se tenga en cuenta el hecho de que el propio Ministerio de Sanidad Español, en su Documento de Consenso en SQM, 2011 dijera:

A medida que se avanza en el conocimiento de la SQM, cada vez son menores los trabajos que hacen referencia al origen psicopatológico, predominando los trabajos que enfocan la investigación hacia un origen órgano-tóxico. En ambos casos, hay cabida para la exposición ambiental, fundamentalmente química, como desencadenante del proceso, (Pág. 21).

De igual manera, tampoco disponemos de pruebas concluyentes que sitúen su origen en factores psicológicos y/o psiquiátricos, (Pág. 33).

Cuando la Guía del INSS, 2ª Edición dice: *pero ninguna de las teorías anteriores tiene una evidencia ni un respaldo científico suficiente.* Cabe preguntarse si acaso los autores que han hecho esta afirmación son conocedores de la literatura científica publicada sobre esta enfermedad o es únicamente la ignorancia de ésta la que les conduce a tales declaraciones.

En el ámbito de la toxicología el respaldo a las bases fisiológicas de la SQM y patologías relacionadas viene amplia y detalladamente documentada en la enciclopedia de toxicología: **General And Applied Toxicology. 3ª Edición, 2009** que es una de las enciclopedias que cuentan con más prestigio a nivel mundial por el gran rigor de sus contenidos, dedica un capítulo entero, capítulo 92, a la enfermedad de SQM, bajo el nombre: ***MCS: toxicological questions and mechanisms***. Hay que decir que esta enciclopedia cuenta con tanto respaldo en la ciencia de la toxicología porque cada capítulo está revisado por

otros tres toxicólogos, no dando lugar a errores metodológicos o de diseño que sí que se han observado en otras obras. En el capítulo 92 de esta obra, el autor, *M. Pall*, dedica 50 páginas a la explicación detallada de los principales aspectos biológicos y fisiológicos subyacentes en esta enfermedad, y otras enfermedades relacionadas. Estos hallazgos están bien documentados y relacionados en este capítulo que cuenta con más de 400 referencias a publicaciones científicas anteriores, incluida su relación con interesantes estudios genéticos, y estudios en modelos animales que soportan dichos hallazgos.

Otro hecho que no se ha tenido en cuenta al hacer estas afirmaciones es que en una de las principales obras en psiquiatría del Reino Unido que es la enciclopedia: **Psychiatry An Evidence based test**[43], *Malcolm Hooper,* escribe un capítulo entero, el capítulo 50, ***Multiple Chemical Sensitivity,*** en el que se dedican 27 páginas, con 191 referencias bibliográficas, a explicar las principales características de la enfermedad, así como otras consideraciones toxicológicas. En las referencias bibliográficas de este documento, se encuentra el link donde se puede descargar gratuitamente esta obra.

Para entender la relevancia que tiene esta enciclopedia en el ámbito de la psiquiatría, hay que decir que forma parte de los textos estándar para la preparación del *exámen MRCPsych* en el Reino Unido e Irlanda. Hay que considerar también que la revista Británica de Psiquiatría[44] publicó un estudio denominado *Book Reviews* en el que se hizo una revisión de los principales libros en el ámbito de la psiquiatría. Las buenas críticas respecto a esta enciclopedia, y sus comentarios sobre la atención que dedica a la Sensibilidad Química Múltiple, pueden verse en la revista que se aporta como **anexo II** de este documento.

Hooper, el autor del capítulo 50, dice:

It must be noted that ***there is no proof that it is justified to apply the label somatisation*** *to such conditions as chronic fatigue syndrome and several more illnesses that established medicine has so far failed to explain*

[43] Editado por: Basant K. Puri & Ian Treasaden. Hodder Education. 2010.

[44] The British Journal of Psychiatry (2011), 198, 160-164.

*scientifically... **Don't hesitate to ask questions about scientific evidence behind this talk about somatisation.** Be persistent, because a diagnosis of somatisation is definitely not an innocuous label. It will close various doors and lead (to) treatments that usually get nowhere.*

Traducción:

«Se debe tener en cuenta que **no hay pruebas de que esté justificado aplicar la etiqueta somatización** a condiciones como el síndrome de fatiga crónica y varias enfermedades más que la medicina establecida no ha podido explicar científicamente... No dude en hacer preguntas sobre la evidencia científica detrás de este discurso de somatización. Sea persistente, porque un diagnóstico de somatización definitivamente no es una etiqueta inocua. Cerrará varias puertas y llevará a tratamientos que generalmente no llegan a ninguna parte».

Cuando la Guía del INSS afirma: *Ninguna de las teorías anteriores tiene una evidencia ni un respaldo científico suficiente*, tampoco se están considerando los trabajos de N. *Ashford* y C. *Miller*, dos científicos cuyas contribuciones en el campo de la SQM son notorias. La Dra. *Claudia Miller* fue la que desarrolló el cuestionario QEESI, utilizado como herramienta de valoración de SQM más aceptada, como lo refleja el hecho de que una amplia mayoría de las investigaciones científicas publicadas lo utilizan, junto con los criterios de caso del Consenso Internacional de 1999.

Prueba de la importancia que tienen los trabajos de *N. Ashford y C. Miller* en el ámbito de la SQM es que algunas de sus obras son tan relevantes que son citadas en una gran parte de los trabajos de investigación realizados en este ámbito, y se basan en ellas para desarrollar investigación posterior. Un ejemplo es que en la anterior guía del INSS, (Protocolo de Actuación para Médicos del INSS) en la sección de SQM, *Clasificación*, se utilice la clasificación propuesta por estos autores. Sus trabajos también se han recogido en el Documento de Consenso del Ministerio de Sanidad, 2011 y en los Documentos realizados por estamentos oficiales de otros países, como el de Canadá, Australia, Alemania, etc…

- ✓ La afirmación de la Guía del INSS. Pág. 124 (…) *la mayoría de los autores defienden una causa psicopatológica de la enfermedad*, es fácilmente rebatible, no solamente por el hecho de que como se ha expuesto anteriormente, el Ministerio de Sanidad y el propio Ministerio

de Trabajo en la Enciclopedia Práctica de Medicina del Trabajo del INSST, AFIRMAN LO CONTARIO, sino por el hecho de que como puede verse en los anexos III y IV es mayor la documentación científica que defiende una causa orgánica para esta enfermedad.

En el **anexo III** se aporta una relación de documentación recopilada por *Albert H. Donnay* hasta septiembre del año 1999, en el que queda constancia de que hasta entonces había 311 artículos científicos, editoriales, libros, capítulos de libros e informes publicados que respaldan una causa física de MCS, (excluyéndose publicaciones en revistas de ecólogos clínicos o cartas al editor).

Dicho autor, ya en 1999, publicó un artículo llamado: ***On the Recognition of Multiple Chemical Sensitivity in Medical Literature and Government Policy***, en la revista de toxicología: *International Jornal of Toxicology*.

En esta publicación, se revisa la literatura sobre SQM en América desde sus primeras descripciones hasta 1999. Se puede leer en el Abstract: (...) m*ás de la mitad de los más de 500 artículos revisados por expertos en MCS apoyan una base orgánica para MCS, en lugar de una cuarta parte de apoyo psiquiátrico (…) Una interpretación psicógena de la MCS está específicamente rechazada en la declaración de posición sobre el tema más reciente, en un consenso de 1994 de la American Lung Association, American Medical Association (AMA), la Agencia de Protección Ambiental de EEUU, (US EPA), y la Comisión de Seguridad de Productos del Consumidor de EUU (US CPSC) (…).*

En el **anexo IV** se aporta un documento de recopilación, realizado en 2010 por la *Dra. Steneimann*, de las citas y resúmenes de artículos publicados en revistas científicas, que cuentan con revisión por pares, que apoyan una base fisiológica para SQM. Como puede verse, es abrumadora la literatura científica que apoya una base fisiológica de esta enfermedad, revisada por pares, lo cual ya implica un respaldo por parte de la comunidad científica.

Después del año 2010 se han seguido publicando mucho sobre esta enfermedad, pero como puede constatarse, al hacer una búsqueda sencilla en bases de datos de publicaciones científicas, no son mayoritarios los trabajos en la línea de la hipótesis psicológica.

B2.1 Justificación del origen psicopatológico de la enfermedad

En la Guía del INSS, 2ª Edición, Pág. 124, se justifica el origen psicopatológico de la enfermedad apoyándose en los siguientes aspectos:

- ✓ *Etiología desconocida. El listado de los factores ambientales ligados a la IAI es innumerable (Wadell WJ),* (Pag. 124).

Aunque algunos autores sostienen que es de etiología desconocida, son numerosos los autores que relacionan la exposición química como la causa del desarrollo de la enfermedad, fundamentada en los estudios en los que se muestra que la aparición de la enfermedad surge después de exposiciones a tóxicos, este aspecto se recoge en el apartado A3. Sintomatología/Relación entre la exposición y la SQM de este informe.

- ✓ *Etiopatogenia desconocida. Como hemos visto, se han propuesto múltiples teorías orgánicas, pero ninguna de ellas es aceptada en la actualidad.*

No es cierto que ninguna de las teorías orgánicas no sea aceptada, más bien: **Ninguna de las teorías orgánicas propuesta es rechazada en la actualidad.** ¿Puede acaso alguno de los autores que concluyen que la SQM es una enfermedad de somatización negar que se producen algunos de los mecanismos fisiológicos descritos? No existe en la literatura científica ningún artículo que rebata ninguna de las hipótesis fisiológicas, como mucho se puede añadir la de somatización, **pero no se pueden rebatir las anteriores**.

A la luz de todo lo expuesto en el documento, se justifica que existen mecanismos biológicos que pueden explicar los procesos inflamatorios, oxidativos y sensibilizantes que caracterizan esta patología. Todo lo recogido en este informe son algunas de las teorías propuestas que cuentan con más respaldo. Hay otros autores que resaltan otros factores influyentes, como el papel sensibilizante de los estrógenos en esta enfermedad, u otros. Todas ellas son piezas de un puzzle que ha de ensamblarse para llegar a la visión más completa.

- ✓ *Trastorno adquirido. Síntomas ante la exposición a dosis bajas de agentes químicos, que previamente eran bien tolerados,* (Pág. 125).

Efectivamente, todas las enfermedades debutan en un momento dado, excepto las enfermedades congénitas. Esto no es una justificación que apoye que se trata de una enfermedad psicológica.

- ✓ *Susceptibilidad individual. Síntomas ante exposiciones toleradas por la gran mayoría de las personas*, (Pág. 125).

El hecho de que no todas las personas reaccionan de la misma manera ante los productos químicos es algo fácilmente comprensible. La individualidad bioquímica de cada persona es un factor imprescindible a considerar en cualquier enfermedad. En el caso de la exposición a químicos foráneos, incluso a bajas dosis es fundamental considerar la carga tóxica que tiene cada individuo en el momento de dicha exposición, ésta es diferente en función del estado de saturación de las rutas de detoxificación y desintoxicación, que también viene condicionado por el estatus mineral y nutricional de cada individuo, así como de los polimorfismos genéticos que porta la persona en relación a las enzimas que actúan en cada uno de los pasos metabólicos, etc. (la importancia de estos factores ya se han expuesto anteriormente en este documento).

La justificación de que una enfermedad pueda tener un origen psicopatológico por esta afirmación no se sostiene.

- ✓ *Falta de biomarcadores. La detección de la SQM se basa en criterios clínicos, no existe ningún biomarcador que permita confirmar el diagnóstico*, (Pág. 125).

Existen muchísimas enfermedades para las que no existe un marcador inclusivo o excluyente y no por eso se las atribuye la etiqueta de somatizaciones. Como se ha expuesto en la sección *A5: Diagnóstico*, hay pruebas que pueden realizarse para averiguar el estado general del afectado.

- ✓ *Heterogeneidad de síntomas. Con frecuencia se presenta afectación de órganos y síntomas médicamente inexplicables (...) Heterogeneidad de los grados de afectación, que no se relaciona con la intensidad de la exposición*, (Pág. 125).

Puede que estos sean dos de los factores que más confunden a los especialistas. Pero las explicaciones del profesor *Pall*[45] que se han expuesto someramente en este documento, justifican, tal como dice el propio autor, que sean distintos los sistemas orgánicos implicados, los mecanismos del ciclo NO/ONOO- son

[45] Capítulo 92: MCS: Toxicological Questions and Mechanisms.

principalmente locales. Es, por tanto una enfermedad con repercusión sistémica.

Hace falta investigación adicional para que puedan comprenderse con mayor detalle todas las características tan complejas de esta enfermedad.

- ✓ *Ausencia de tratamientos que mejoren la enfermedad, salvo la prevención de la exposición a las sustancias desencadenantes*, (Pág. 125).

La evitación es la principal opción terapéutica. Como dicen los propios autores, hace falta más investigación en cada uno de los campos abiertos. Se trata de una enfermedad compleja que involucra diferentes sistemas orgánicos que todavía sigue estudiándose y sobre la que no se ha dicho la última palabra, ante esta situación es lógico que no se halla desarrollado un tratamiento curativo, pero que todavía se siga estudiando en ella no quiere decir que sea una enfermedad psicosomática. Prueba de ello es que los tratamientos que disminuyen la carga tóxica, regulan a la baja el ciclo NO/ONOO y mejoran la función inmune, se han demostrado eficaces en la disminución de los síntomas, esto establece una relación causal con estos factores. En cambio, *las intervenciones psicoterapéuticas no han logrado hasta ahora éxito*[46].

- ✓ Respecto a los estudios que se citan en la Guía del INSS, 2ª Edición, (Pág. 124)[47] de los cuales se dice: *(…) cuando en enmascaramiento se realiza de forma correcta; los pacientes con SQM no son capaces de diferenciar entre estímulos verdaderos y placebo*, hay que **decir que existe abundante literatura científica muy crítica con estos estudios.**

Concretamente, el trabajo de *Dans-Munshi et all* 2006, ha sido revisado por las autoras *Goudsmit, y Howes*, quienes, en una publicación de septiembre de 2008, hacen una revisión de todos los estudios de provocación incluidos en *Dans-Munshi et all* 2006, bajo el título: *Is multiple chemical sensitivity a learned response*? *A critical evaluation of provocation studies*[48]. Las autoras revelaron un número de debilidades metodológicas que en *Dans-Munshi et all*

[46] Genuis, 2013.

[47] Dans-Munshi et all, Eis D. et all; Bornschein S. et all.

[48] Ver: Goudsmit y Howes, 2008.

2006, no parecen haber tenido debidamente en cuenta al interpretar los resultados.

Algunos de los fallos metodológicos detectados en este estudio son:

a) Las características de la muestra y exactitud del diagnóstico

En algunos estudios se seleccionaron a los pacientes mediante un cuestionario, por tanto muchos investigadores evaluaron a personas que creían ser sensibles o utilizaban criterios vagos o ambiguos para seleccionar a sus sujetos. Varios estudios se centraron en individuos que reportaban reacciones a un grupo de productos químicos relacionados, como los disolventes, y, por lo tanto, no habrían cumplido con los Criterios de consenso para SQM. Otros, están hechos en personas con SFC o hiperventilación que quizá debieron haber sido excluidos de la revisión. Muy pocos de los participantes fueron diagnosticados usando los criterios disponibles para SQM, como los criterios de Consenso 1999, este es un defecto grave que hace que sea aún más difícil sacar conclusiones firmes sobre los mecanismos subyacentes a esta enfermedad.

Las autoras señalan que quizás la mayor debilidad que no se abordó fue el tamaño de la muestra. De los 34 estudios incluidos en la revisión, 19 (56%) incluyeron 20 sujetos o menos.

b) Diseño:

En cuanto al diseño, muchos de los estudios testaban los efectos de los productos químicos que no se habían seleccionado en función de la historia de cada persona (es decir, a pesar de tener SQM podrían no ser sensibles a ese producto en concreto).

Pocos de los informes dieron detalles de la gravedad de los síntomas, ya sea en la vida real o en el laboratorio, aunque un estudio encontró diferencias significativas entre las personas con quejas leves y aquellas con síntomas que dieron como resultado un cambio de estilo de vida.

También se describe que muchos de los estudios están específicamente diseñados para averiguar el papel de los factores psicológicos, pero estos estudios parten de un sesgo de diseño en la medida en que no se consideran las variables que afectan a la sintomatología de la enfermedad. Una de las principales críticas es que se excluyeron biomarcadores periféricos al auto-diagnóstico de SQM, y la medición de otras funciones que podían alterarse.

Dans-Munci et al., señalaron el uso de diferentes concentraciones y tipos de exposiciones, pero no sobre los problemas asociados con algunos de los estímulos considerados «neutrales» y la posibilidad de que las molestias como la fatiga y el mareo hubieran sido inducidas por el incitante, que no necesariamente era un estímulo neutral para el afectado, en lugar de variables como la aprensión y la hiperventilación. Las personas con SQM pueden reaccionar al propio ambiente «neutro» del laboratorio o a la «sustancia relajante» empleada para enmascarar los controles.

Otra variable que puede influenciar los resultados y que no fue debidamente considerada es la intensidad de los síntomas.

Goudsmit y Howes concluyen lo siguiente:

- ✓ «Desde nuestro punto de vista, es difícil extrapolar los resultados de individuos generalmente sanos evaluados en diferentes condiciones en un laboratorio a individuos que experimentan SQM en su vida diaria».
- ✓ «La revisión ofrece un paradigma relativamente simple, basado en el supuesto de que la exposición a los productos químicos da como resultado una *respuesta universal*».
- ✓ «Las debilidades metodológicas y los hallazgos inconsistentes significan que no es posible hacer nada más que especular sobre los posibles factores psicológicos que influyen en la naturaleza, el momento y la gravedad de los síntomas».
- ✓ «A la luz de las deficiencias los autores pueden haber sobreestimado el papel del factor psicológico en la etiología de la SQM».

Respecto a los estudios de provocación realizados al objeto de abordar los rasgos psicopatológicos de las personas con SQM, algunos autores afirman:

«La presencia de ansiedad y depresión en los afectados ha hecho que las causas psicógenas hayan sido estudiadas como potenciales mecanismos causantes de la SQM. Factores de personalidad (mujeres, ansiedad crónica, etc.) que también encontramos en otras enfermedades incluidas las ambientales hacen que se hayan planteado factores psicosomáticos en la patogénesis de la SQM**. No obstante, la gran mayoría de estudios que han**

investigado la importancia de los problemas psicológicos en relación a la SQM presentaban considerables problemas metodológicos[49]».

Los autores[50] expusieron en el resumen de su artículo:

«Cuando se obtienen datos de síntomas psicológicos/ psiquiátricos anormales en pruebas de personalidad o entrevistas psiquiátricas realizadas a pacientes que reportan síntomas de Síndrome de Sensibilidad Química Múltiple, los investigadores suelen atribuirlos a rasgos psiquiátricos o al origen psicogénico de la enfermedad. El objetivo principal de estos estudios fue la evaluación de la plausibilidad de las explicaciones no psiquiátricas de los datos de síntomas psicológicos/ psiquiátricos (…)».

Para ello los autores hicieron tres estudios en los que concluyeron lo siguiente: ***la estrategia de administrar pruebas psicométricas a poblaciones enfermas con el propósito de evaluar enfermedades o rasgos psiquiátricos y/ o los orígenes psicogénicos de la enfermedad se mostró potencialmente engañosa.***

Como se detallará más adelante, en el apartado *Otros estudios que abordan el tema de los factores psicológicos en la SQM,* se puede ver el resumen de algunas publicaciones científicas que abordan el asunto de la enfermedad de SQM y aspectos psicológicos/psiquiátricos de la misma.

- ✓ Guía del INSS, 2ª Edición, (Pág. 124): *la alta prevalencia de trastornos psiquiátricos en pacientes afectados de SQM. Los más frecuentes son la depresión, la ansiedad y el trastorno por somatización.*

«Los efectos neurotóxicos de algunos agentes causantes pueden afectar la salud mental de las personas que sufren SQM y a su entorno psicosocial, pudiendo desencadenar manifestaciones psicológicas o incidir de forma especial en personas con patología psiquiátrica previa[51]».

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[49] Estrada MD, Hipersensibilidad química múltiple: estado de conocimiento de la etiología y el tratamiento**.** Agència d'Avaluació de Tecnologia i Recerca Mèdiques. Servei Català de la Salut. Departament de Salut. Generalitat de Catalunya; 2009.

[50] Davidoff AL, Fogarty L, Keyl PM. Psychiatric inferences from data on psychologic/psychiatric symptoms in multiple chemical sensitivities syndrome. Arch Environ Health. 2000 May-Jun;55 (3):165-75.

[51] Documento de Consenso del **Ministerio de Sanidad**, 2011, Pág. 59.

- ✓ Guía del INSS, 2ª Edición, (Pág. 124): *los pacientes con SQM o con trastorno somatoforme comparten síntomas y características psicológicas*[52].

El hecho de que esto pueda ser así, no es motivo suficiente para afirmar que la SQM es una enfermedad originada por somatización. En la literatura científica encontramos respecto a este asunto las siguientes declaraciones:

«Se define la sensibilidad química múltiple (SQM) como un conjunto de manifestaciones clínicas súbitas ante la exposición a productos químicos a bajas dosis que previamente eran bien toleradas. No existe ninguna prueba analítica, ni exploración complementaria específica de confirmación diagnóstica, y la exploración física es normal[53] *(…)* **Aunque existe frecuentemente comorbilidad asociada depresiva, en la actualidad la mayoría de los estudios no consideran la SQM como una enfermedad psiquiátrica. No cumple ningún criterio DSM-V o CIE-10, y no se puede incluir como trastorno afectivo, somatomorfo, adaptativo o de la personalidad».**

«A las características psicológicas de los enfermos y a sus posibles trastornos psiquiátricos se les ha dado mucha relevancia, como ocurre con otras muchas enfermedades crónicas. Desde los factores psicológicos hasta la autosugestión, la respuesta condicionada, los sistemas de creencias en las enfermedades y el síndrome afectivo estacional. Varias enfermedades psiquiátricas han sido relacionadas con la SMC, entre ellas el ataque de pánico, el trastorno psicosomático y la simulación[54] (...) **La SMC y el trastorno somatoforme tienen muchas manifestaciones comunes, que afectan a varios aparatos y sistemas del organismo; sin embargo, por definición, las manifestaciones de éste *no pueden explicarse por trastornos orgánicos después de un examen minucioso*, lo que significa que, si se diagnostica una SMC, el trastorno somatoforme quedará automáticamente excluido».**

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[52] Baile J. et all. Godás T. et all.

[53] Conrad Surribas Figuls, Cristina Giménez Muniesa, Judit Raventós Olivella. Multiple chemical sensitivity: Antidepressant treatment and clinical response in the absence of personality disorder. A case report. Pág. 89-126.

[54] Ortega Pérez, Arturo. Sensibilidad a múltiples compuestos, una enfermedad comúnmente inadvertida. (Med Clin (Barc). 2005; 125(7):257-62).

B2.2 Otros estudios que abordan el tema de los factores psicológicos en la SQM

En este apartado se exponen las conclusiones de algunos de los estudios que comparan variables físicas y psiquiátricas/psicológicas en la SQM.

Resumen:

«Cuando se obtienen datos de síntomas psicológicos/ psiquiátricos anormales en pruebas de personalidad o entrevistas psiquiátricas realizadas a pacientes que reportan síntomas de Síndrome de Sensibilidad Química Múltiple, los investigadores suelen atribuirlos a rasgos psiquiátricos o al origen psicogénico de la enfermedad. El objetivo principal de este estudio fue la evaluación de la plausibilidad de las explicaciones no psiquiátricas de los datos de síntomas psicológicos/ psiquiátricos[55]…».

Para ello los autores hicieron tres estudios que se recogen en esta publicación y concluyen lo siguiente:

«La estrategia de administrar pruebas psicométricas a poblaciones enfermas con el propósito de evaluar enfermedades o rasgos psiquiátricos y / o los orígenes psicogénicos de la enfermedad, se mostró potencialmente engañosa».

Asimismo, otro de los estudios[56] indica:

«(…) A las características psicológicas de los enfermos y a sus posibles trastornos psiquiátricos se les ha dado mucha relevancia, como ocurre con otras muchas enfermedades crónicas. Desde los factores psicológicos hasta la autosugestión, la respuesta condicionada, los sistemas de creencias en las enfermedades y el síndrome afectivo estacional. Varias enfermedades psiquiátricas han sido relacionadas con la SMC, entre ellas el ataque de pánico, el trastorno psicosomático y la simulación. Bornschein et al llevaron a cabo una entrevista clínica estructurada con ayuda de la cuarta edición de Diagnostic and statistical manual of mental disorders a 120 pacientes con

[55] Davidoff AL, Fogarty L, Keyl PM. Psychiatric inferences from data on psychologic/psychiatric symptoms in multiple chemical sensitivities syndrome. *Arch Environ Health. 2000* May-Jun;55 (3):165-75.

[56] Ortega Pérez, Arturo. Sensibilidad a múltiples compuestos, una enfermedad comúnmente inadvertida. (*Med Clin (Barc).* 2005; 125(7):257-62).

SMC en busca de enfermedades psiquiátricas. El 44% de ellos cumplía los criterios de trastorno somatoforme, el 32% los de trastornos afectivos, actuales o permanentes, el 24% los de trastornos de ansiedad, el 21% los de abuso de dependencia de drogas y el 13% los criterios de trastornos de personalidad. Al 7,5% los diagnosticaron de trastorno psicótico. Esta investigación reafirma la asociación entre una enfermedad crónica grave y muy limitante y una o más enfermedades psiquiátricas, pero no establece ninguna relación causal entre ellas y en absoluto apoya que los trastornos psiquiátricos favorezcan o causen la SMC. **La SMC y el trastorno somatoforme tienen muchas manifestaciones comunes, que afectan a varios aparatos y sistemas del organismo; sin embargo, por definición, las manifestaciones de este *no pueden explicarse por trastornos orgánicos después de un examen minucioso*, lo que significa que, si se diagnostica una SMC, el trastorno somatoforme quedará automáticamente excluido. *Miller* y *Mitzel* insistían en las diferencias entre ambas al destacar que la SMC se había iniciado después de los 30 años de edad en el 83% de los casos, que en ella predominaban las manifestaciones cognitivas y que el problema se atribuía a causas ambientales. Tal vez lo que ocurre es que muchos enfermos diagnosticados de trastorno somatoforme padecen en realidad una SMC.**

En *Saito el al, 2005*[57] «se investigó a 14 pacientes con SQM diagnosticados con el criterio de consenso de 1999, de los cuales el 79% tenía un trastorno psiquiátrico. Ninguno de los 12 controles sanos tenía un diagnóstico psiquiátrico. Se les pidió que anotaran cualquier síntoma en un diario electrónico, tanto cuando se sentían mal como después de un pitido que sonaba a intervalos aleatorios. También llevaban una bomba de muestreo de aire y se les indicó que la encendieran cuando experimentaron una reacción de hiperreactividad. Doce de los pacientes informaron reacciones durante la semana y, en todos excepto uno, se detectaron pruebas de un químico «causativo» en sus bombas. Los diarios electrónicos revelaron puntuaciones elevadas para 11 de los 17 síntomas evaluados y en las cuatro escalas de estado de ánimo en el momento de la exposición, pero no hubo diferencias entre los pacientes y los controles cuando los participantes se evaluaron al azar. **Por lo**

[57] Saito M, Kumano H, Yoshiuchi K, Kokubo N, Ohashi K, Yamamoto Y, Shinohara N, Yanagisawa Y, Sakabe K, Miyata M, Ishikawa S, Kuboki T. Symptom profile of multiple chemical sensitivity in actual life. *Psychosom Med.* 2005 Mar-Apr; 67 (2):318-25.

tanto, las personas con SQM evaluadas en la vida diaria no parecen tener síntomas somáticos o psicológicos cuando no son provocadas».

La similitud entre los grupos cuando los pacientes no estaban experimentando una reacción proporciona un apoyo adicional para la visión de que el SQM está más estrechamente relacionado con la exposición a sustancias químicas que con trastornos como la ansiedad, los trastornos somatomorfos y la depresión.

Además, una de las investigaciones[58], resume:

«Este artículo revisa la literatura clínica y experimental en pacientes con múltiples respuestas adversas a sustancias químicas (síndrome de sensibilidad química múltiple-MCS) y desarrolla un modelo para MCS basado en la disfunción del sistema olfativo-límbico que se superpone en parte con el modelo de encendido de Post para trastornos afectivos. El MCS abarca una amplia gama de afecciones polisintomáticas crónicas y quejas cuyos desencadenantes incluyen niveles bajos de sustancias químicas ambientales comunes en interiores y exteriores, como pesticidas y disolventes. **Otros investigadores han encontrado evidencia de un aumento en la prevalencia de depresión, ansiedad y trastornos de somatización en pacientes con SQM y han concluido que sus afecciones psiquiátricas explican el cuadro clínico. Sin embargo, ninguno de estos estudios ha presentado datos sobre los efectos de los químicos en los síntomas o en las medidas objetivas de la función del sistema nervioso**. La síntesis de la literatura de SQM con grandes investigaciones sobre neurotoxicología, medicina del trabajo y psiquiatría biológica sugiere que la fenomenología de los pacientes con MCS se superpone a la de los trastornos del espectro afectivo y que ambos implican disfunción de las vías límbicas. Los estudios en animales demuestran que la exposición a sustancias químicas ambientales repetitivas intermitentes de bajo nivel, incluidos los pesticidas, causan la neuroinflamación límbica. La activación (total o parcial) es un mecanismo del sistema nervioso central que podría amplificar la reactividad a niveles bajos de químicos inhalados e ingeridos e iniciar una sintomatología afectiva, cognitiva y somática persistente, tanto en entornos ocupacionales como no ocupacionales. Al igual que en estudios con animales, los estresores ineludibles y novedosos podrían

[58] 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. *Biological Psychiatry* 32(3): 218-42.

sensibilizarse con la exposición química en algunos individuos para generar respuestas adversas sobre una base neuroquímica. El modelo olfativo-límbico plantea hipótesis neurobiológicas comprobables que podrían aumentar la comprensión de la etiología multifactorial del SQM y de ciertos trastornos del espectro afectivo superpuestos».

Por otro lado, según el consenso de varios autores[59]:

«Se define la sensibilidad química múltiple (SQM) como un conjunto de manifestaciones clínicas súbitas ante la exposición a productos químicos a bajas dosis que previamente eran bien toleradas. No existe ninguna prueba analítica, ni exploración complementaria específica de confirmación diagnóstica, y la exploración física es normal. (….) **Aunque existe frecuentemente comorbilidad asociada depresiva, en la actualidad la mayoría de los estudios no consideran la SQM como una enfermedad psiquiátrica. No cumple ningún criterio DSM-V o CIE-10, y no se puede incluir como trastorno afectivo, somatomorfo, adaptativo o de la personalidad».**

XLI CONGRESO NACIONAL DE LA SEPAR ÁREA DE ENFERMEDADES RESPIRATORIAS DE ORIGEN MEDIOAMBIENTAL (EROM)[60]

Conclusiones: «los pacientes con SQM no mostraron diferencias en la personalidad respecto a los controles, aunque sí peor calidad de vida. Al presentar síntomas tras la prueba de provocación no se observaron trastornos emocionales ni psicopatológicos. En los pacientes con SQM se constataron fundamentalmente déficits de tipo cognitivo tanto antes como después de la prueba de provocación».

Resumen extraído del informe de Genuis SJ.[61]:

[59] Conrad Surribas Figuls, Cristina Giménez Muniesa, Judit Raventós Olivella. Multiple chemical sensitivity: Antidepressant treatment and clinical response in the absence of personality disorder. A case report. Pág. 89-126.

[60] R. Costa Solà, C. Jacas, R. Hernando, X. Guardino, S. Torrado, J. Castells, G. Cuberas, M. Negre y R. Orriols Martínez. Estudio neuropsicológico en el síndrome de sensibilidad química múltiple.

[61] Genuis SJ. *C*hemical Sensitivity: Pathophysiology or Pathopsychology? *Clin Ther.* 2013 May;35(5):572-7.

«El estado de sensibilización de la SQ parece iniciarse por una exposición tóxica significativa, que ocurre como un evento de una sola vez, o al sobrepasar un umbral de toxicidad después de la acumulación de sustancias tóxicas por exposiciones repetidas de niveles más bajos. Una vez sensibilizados a través de una pérdida de tolerancia inducida por sustancias tóxicas, las personas expuestas a factores desencadenantes, como cantidades mínimas de diversos productos químicos cotidianos, pueden experimentar diversas secuelas clínicas e inmunitarias, que a veces involucran respuestas de linfocitos, anticuerpos o citoquinas. La prevención de la activación de los desencadenantes prevendrá los síntomas, y la inmunoterapia o la supresión inmunológica pueden mejorar los síntomas en algunos casos. La resolución sostenida del estado de SQ se produce después de la eliminación exitosa de la carga corporal acumulada de tóxicos a través de mecanismos naturales de bioeliminación tóxica y / o intervenciones de desintoxicación clínica. A pesar de la extensa evidencia clínica para respaldar la veracidad de este estado clínico, muchos miembros de la comunidad médica se muestran reacios a aceptar esta condición como un trastorno fisiopatológico».

Conclusiones: «el problema emergente de la exposición a sustancias tóxicas adversas ubicuas en la sociedad moderna ha resultado en un aumento en el número de individuos que desarrollan la enfermedad de SQ. Como es habitual en la historia médica, las ideas iconoclastas y la evidencia emergente con respecto a nuevos mecanismos de enfermedades, como la patogénesis de la SQ, se ha encontrado con controversia, resistencia y lentitud en la traducción de conocimientos».

Por último, *Pall M.*[62] dice al respecto de categorizar la enfermedad de SQM como una enfermedad psiquiátrica/psicológica:

- ✓ «Las teorías psicogénicas han fallado en considerar como los químicos implicados en la SQM pueden impactar en el cuerpo humano y específicamente en el cerebro humano.
- ✓ No han considerado los modelos animales de SQM y qué lecciones pueden extraerse sobre los mecanismos de SQM.

[62] Pall M, 2009. General and applied Toxicology. VI Volum, Chapter 92: Multiple Chemical Sensitivity: Toxicological Questions and Mechanisms. Bryan Ballantyne (Editor), Timothy C. Marrs (Editor), Tore Syversen (Editor).

- ✓ Han fallado en la mayoría de los casos en proporcionar cualquier cosa que se parezca a una evaluación objetiva de la literatura científica sobre SQM. Dado que la mayoría de los defensores psicógenos tienen claros conflictos de interés.
- ✓ Su interpretación de la SQM y otras enfermedades multisistémicas están dominadas por la opinión de que estas enfermedades son producidas por las creencias de los pacientes y que son trastornos somatomorfos generados por un proceso llamado somatización. Sin embargo, no han proporcionado ninguna evidencia de que no pueda haber una explicación fisiológica para la SQM.
- ✓ Su argumento de que los factores psicológicos son necesarios y suficientes para explicar la MCS y otras enfermedades multisistémicas queda oscurecido cuando se conocen los estudios sobre los datos genéticos, tanto de genes específicos implicados en la SQM por su conocida función, como del hallazgo general de que los genes tienen un papel en los factores biológicos que implican determinadas susceptibilidades porque los genes actúan en la determinación de la estructura y la bioquímica del organismo.
- ✓ Sus publicaciones están llenas de declaraciones cargadas de emoción.
- ✓ Otro aspecto importante a reseñar es que a lo largo de la historia ha habido falsas atribuciones psicogénicas a enfermedades de las que posteriormente se ha conocido su mecanismo, como es el caso de la esclerosis múltiple, párkinson, lupus, cistitis intersticial, artritis reumatoide, etc. en cada una de estas enfermedades posteriormente se ha mostrado que se trataba de una enfermedad real física estas enfermedades anteriormente se pensaban que eran de tipo psicológico/psiquiátrico pues cursaba a brotes y no se conocía el mecanismo implicado. En el caso de la esclerosis múltiple, los afectados fueron tachados de enfermos que somatizaban algún trauma, cuando en realidad era el desconocimiento de los procesos autoinmunes que caracterizaba estas patologías».

B3. DATOS EPIDEMIOLÓGICOS

Los datos dados en el Documento de Consenso del Ministerio de Sanidad difieren de las cifras dadas en la Guía del INSS, 2ª Edición. Estas cifras también difieren de los dados en el Primer Documento del INSS: Protocolo de Actuación para médicos del INSS que daba una cifra de un 2% a un 15% que, de entre los encuestados en estudios poblacionales, podían reunir criterios que justificaran el diagnóstico.

Ver siguiente apartado:

B3.1 Últimos estudios de incidencia de SQM en EEUU, Australia, Reino Unido y Suecia

Los últimos estudios de prevalencia de la SQM en algunos países:

Un estudio[63] evaluó la prevalencia de la SQM en EEUU, diferenciando entre aquellas personas diagnosticadas por un médico de SQM y las que se autoreportan con Sensibilidad Química. Los datos de junio de 2016 muestran que un **12.8% de la población tenía SQM diagnosticada medicamente** y un **25, 8%** reportaban ellos mismos padecer sensibilidad química en base a notar especial sensibilidad a los químicos diarios y productos químicos perfumados**.**

Los resultados de otro[64] del mismo autor mostraban que, por todo el país, un **6.5% tenían SQM médicamente diagnosticada**, y un **18.9%** reportaban tener Sensibilidad Química en base a notar especial sensibilidad a los químicos diarios y productos químicos perfumados, y un 19,9% reportaba un de las de la situación o las dos.

También se expone que un **6.6%** de la población del Reino Unido está **diagnosticada clínicamente de SQM** y un **16.3%** reportaban tener

[63] Steinemann, A. National Prevalence and Effects of Multiple Chemical Sensitivities. Journal of *Occupational and Environmental Medicine*: March 2018 - Volume 60 - Issue 3 - p e152–e156.

[64] Steinemann, A. Prevalence and effects of multiple chemical sensitivities in Australia. *Preventive Medicine Reports.* Volume 10, June 2018, Pages 191-194.

Sensibilidad Química en base a notar especial sensibilidad a los químicos diarios y productos químicos perfumados[65].

Sin embargo, en la población de Suecia un **3.6% de la población padecen SQM diagnosticada clínicamente** y un **18.5%** reportaban tener Sensibilidad Química en base a notar especial sensibilidad a los químicos diarios y productos químicos perfumados[66].

B4. CRITERIOS DE DIAGNÓSTICO

B4.1 Anamnesis y exploración física

Respecto al apartado 5.A.IV CRITERIOS DE DIAGNÓSTICO, de la Guía del INSS, (página 126), se establecen las pautas para hacer una buena anamnesis y también se describe la clínica más característica.

A este respecto los médicos formados en Medicina Ambiental que conocen la SQM tanto a nivel internacional como nacional afirman que en medicina una de las herramientas más importantes para hacer un diagnóstico certero es la Historia Clínica del paciente, en el caso concreto de la enfermedad de SQM dicha historia y examen físico es particularmente relevante para su diagnóstico.

«La Historia Clínica sirve para un doble propósito, en primer lugar, facilita información sobre la salud del paciente y posibilita las claves para determinar la susceptibilidad ambiental específica del paciente. Se necesita una información extensa acerca de la ocupación, hábitos alimenticios y de bebida, conocer el ambiente en el que vive, sensibilidad a los olores y uso de fármacos, la información obtenida de esta parte de la historia es fundamental porque sugiere por un lado exposiciones que pueden haber tenido lugar causando sensibilidad y por otro lado indica agentes desencadenantes potenciales que pueden mantener o exacerbar las enfermedades. Lamentablemente, hoy día los médicos y sanitarios no tienen los suficientes conocimientos ni los

[65] Steinemann, A. Chemical sensitivity, asthma, and effects from fragranced consumer products: National Population Study in the United Kingdom. *Air Quality, Atmosphere & Health.* 2019, Volume 12, Issue 4, pp 371–377.

[66] Steinemann, A. Chemical sensitivity, asthma, and effects from fragranced consumer products: national population study in Sweden. *Air Quality, Atmosphere & Health*. 2019, Volume 12, Issue 2, pp 129–136.

cuestionarios adecuados para obtener todos estos datos imprescindibles para el diagnóstico[67]».

«(…) precisamente debido a la importancia de la historia en el diagnóstico y tratamiento con éxito de la SQM, la información recibida debe analizarse e interpretarse de manera fundamentalmente distinta a como se haría en una historia médica estándar».

«Por ejemplo, un paciente aquejado de fatiga, la fatiga suele valorarse como un inicio de anemia o proceso infeccioso o muy probablemente se etiquetará como psicosomática (a pesar de ser imposible de probarlo) si los resultados de los análisis son negativos. Sin embargo, un médico con acceso a una Historia Ambiental más completa podría vincular este síntoma a exposiciones ambientales como alimentos, aditivos, fenol, tetraclolroetileno, Compuestos Orgánicos Volátiles, COVs, etc. y determinar que este síntoma es indicador de SQM[68]».

«(…) otra manera por la que se distingue una historia para Sensibilidad Química de una estándar es que registra los antecedentes médicos cronológicamente en vez de en presente y pasado, de esta forma se preserva la secuencia de desarrollo, importante para la identificación de la SQM.

Por ejemplo, un paciente nota que está enfermo en el otoño cuando se pone en macha la calefacción de gas, un año en esta misma época desarrolla colitis de causa desconocida, el médico que desconoce la visión ambiental sugiere un origen psicosomático; otro año, por esa misma época presenta asma transitoria y desconoce su origen más adelante, el paciente desarrolla cefaleas severas, también de etiololgía desconocida. Un médico orientado ambientalmente que afronta una historia así, sospecharía inmediatamente de una sensibilidad al gas natural iniciando las pruebas diagnósticas necesarias para la comprobación de esta sensibilidad[69]».

«Como en muchas otras enfermedades, el examen físico y los signos clínicos encontrados al explorar al paciente son enormemente importantes y representativos. En el caso de la Sensibilidad Química, el análisis detallado de estos signos reflejara las pautas específicas en las que estarán implicados el

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[67] Rea, W.J. (1997). Chemical Sensitivity: Tools of Diagnosis and Methods of Treatment, Vol.4, Lewis Publishers, Boca Raton.

[68] Rea, W.J. (1997). Chemical Sensitivity: Tools of Diagnosis and Methods of Treatment, Vol.4, Lewis Publishers, Boca Raton.

[69] Rea, W.J. (1997). Chemical Sensitivity: Tools of Diagnosis and Methods of Treatment, Vol.4, Lewis Publishers, Boca Raton.

sistema muscular liso, así como las respuestas en piel, mucosa y sistemas neurológicos y del colágeno. La señal más evidente y patognomónica de la Sensibilidad Química es la palidez de la piel que va de blanca a amarilla intensa y que se encuentra siempre en ausencia de ictericia esclerótica. Este color amarillento se confunde muchas veces con carotenemia, pero se produce en ausencia de caroteno en la sangre. Se describe clásicamente en algún envenenamiento por pesticidas, pero aparece en la mayoría de pacientes con SQM.

Rubor crónico, picor (muchos pacientes muestran urticaria, pero otros no), eczema, dermatitis, sudor excesivo o más frecuentemente dificultad para sudar, petequia, púrpura, edema, hematomas y extremidades frías son signos extremadamente comunes usados para el diagnóstico del paciente con sensibilidad química.

Grietas en las uñas de las manos, puños blancos, crestas en las uñas y padrastros aparecen con frecuencia, así como acné y forúnculos. En algunos pacientes con SQ se observan quistes y múltiples telangiectasias. Se ven con frecuencia pólipos cutáneos secos y escamosos y como pérdida de cabello. Es frecuente rubor en la cara, así como sarpullidos eritematosos. Los nevus se inflaman después de exposición química, emitiendo cuando se retira el incitante.

El signo clínico que habla de la implicación del sistema respiratorio en la SQM es la hipersensibilidad al humo del tabaco, lacas de pelo, perfumes y pesticidas que conllevan rinorrea nasal, ronquera, tos y sibilancias provocando rinitis vasomotora con estornudos y cornetes inflamados o nariz congestiva, tinnitus, sinusitis, pérdida de voz, tos, sibilancias, senos doloridos, inestabilidad en los pies, falta de aliento, edema periorbital y círculos negros periorbitales. Puede haber también asma.

Las dificultades gastrointestinales se manifiestan con mal aliento, eructos, ulceras bucales, lengua geográfica, laxitud abdominal, hinchazón, gases, prurito anal, estreñimiento y diarrea. Puede aparecer exofagitis con y sin reflujo. Gastritis, colon espástico, enteritis, y ileitis o colitis. Las hemorroides son frecuentes.

Los signos genitourinarios en Sensibilidad Química incluyen frecuencia y urgencia urinarias, vejiga neurógena o cistitis hemorrágica. En mujeres, los signos incluyen sangrado uterino, laxitud en zona lumbar con leucorrea vaginal, que puede estar asociada a cistitis no específica y vaginitis, debilidad en región posterior, endometriosis y síndrome premenstrual; puede haber también lesiones de endomertiosis. En hombres, la sensibilidad puede

evidenciarse por el fallo al iniciar la erección o imposibilidad de eyaculación. También la patología prostática puede ser señal de SQM».

«Los síntomas vasculares son a menudo difusos, sí están implicadas las pequeñas arteriolas, vénulas y capilares o pueden observarse en órganos concretos como lengua, cara y ojos.

Pueden encontrarse síntomas como fatiga y cefaleas de tipo vascular y de presión asociadas a otros signos: hemorragias nasales, hematomas espontáneos, petequias, edema periférico y periorbital, cianosis, fenómeno de Raynaud, extremidades heladas, arritmias y acné. Todos ellos pueden deberse a vasculitis de los vasos pequeños. La implicación de venas, arterias de mayor calibre o corazón pueden generar flebitis recurrente, problemas de colágeno, artritis, y una variedad de arritmias idiopáticas sin base arterioesclerótica. Más del 50% de los pacientes con SQ tienen síndrome de válvula mitral prolapsada y otros signos de disautonomia. Pueden encontrarse arritmia de nódulos sinoatriales, taquicardia auricular paroxística y fibrilación auricular. También pueden estar presentes contracciones ventriculares prematuras unifocales y multifocales, así como taquicardia ventricular.

Ocasionalmente, se observan hipostesias o hiperestesias, o incluso parálisis en cara y extremidades, estas no deben confundirse con histeria. Son compatibles con disfunción del sistema nervioso autoinmune. Puede haber atrofia e hipertrofia de ciertos músculos, así como espasmos musculares y tétanos. También puede haber debilidad muscular, ósea o inflamación de articulaciones.

Los aspectos unilaterales de la SQ pueden explicarse por la participación del sistema nervioso autónomo o la disfunción de vasos sanguíneos regionales. Torpeza, tropiezos, incapacidad para recordar números, memoria a corto plazo reducida y pobre coordinación pueden ser síntomas neurológicos precoces. En los pacientes con implicación del SNC está presente con frecuencia un test de Rhomberg positivo, así como la incapacidad de andar en línea recta. En un tercio de los pacientes hay miosis. Algunos pacientes tendrán parálisis de la campanilla. En ocasiones, sensación disminuida a los pinchazos, perdida de oído o mayor sensibilidad al sonido[70]».

Por tanto, una buena historia clínica, anamnesis y exploración física, conociendo la interpretación ambiental, son lo más importante para hacer un buen diagnóstico.

[70] Rea, W.J. (1997). Chemical Sensitivity: Tools of Diagnosis and Methods of Treatment, Vol.4, Lewis Publishers, Boca Raton.

«Cualquier paciente con sintomatología que sugiera una enfermedad ambientalmente inducida, debería someterse siempre a una historia y un reconocimiento médico diseñados para aislar su naturaleza y factores causales. Este reconocimiento debe siempre incluir una buena anamnesis que identifique la correspondencia entre posibles exposiciones químicas y la aparición de signos y síntomas. El estilo de vida del paciente y el ambiente de su hogar y de su trabajo, tienen q ser valorados de forma exhaustiva, ya que a partir de ellos pueden identificarse contaminantes ambientales que potencialmente causen o exacerben la SQM[71]».

B4.2 Pruebas complementarias

Para confirmar la naturaleza y grado de implicación que pueden tener los tóxicos en una enfermedad, el médico con formación en Medicina Ambiental puede utilizar medidas objetivas (específicas, pruebas de provocación con desafío y retirada del estímulo).

Todo lo anterior puede acompañarse de pruebas analíticas y valoración de parámetros variados, **tal como ya se ha indicado en el aparatado A.5 Diagnóstico del documento**, en el que se proponen algunas pruebas complementarias con carácter orientativo, además de las indicadas en A.5, otras podrían ser[72]:

Sistema cardiovascular

Pruebas básicas

Presión arterial y frecuencia cardíaca (en todos los casos la frecuencia cardíaca en reposo por la mañana antes de levantarse), incluyendo su supervisión por el propio paciente, posiblemente varias veces al día, por ejemplo, en diferentes lugares y manteniendo un diario de bienestar subjetivo en una semana.

Pruebas específicas

- Supervisión de la presión arterial, durante 24 horas (ausencia de disminución por la noche).
- Electrocardiograma durante 24 horas (diagnóstico del ritmo cardíaco).

[71] Rea, W.J. (1997). Chemical Sensitivity: Tools of Diagnosis and Methods of Treatment, Vol.4, Lewis Publishers, Boca Raton.

[72] Documento de Consenso del Grupo de Trabajo sobre CEM, 2012. Colegio de Médicos de Austria (ÖÄK AG-EMF). https://www.sensibilidadquimicamultiple.org/2014/01/ehs-directrices-medicos-austria-2012.html

- Prueba de variabilidad del ritmo cardíaco VRC, durante 24 horas (diagnóstico del Sistema Nervioso Autónomo).

Pruebas de laboratorio

Pruebas básicas

- Primera orina de la mañana
  - Adrenalina
  - Noradrenalina
  - Cociente noradrenalina/adrenalina
  - Dopamina
  - Serotonina
- Primera orina de la mañana
  - 6-OH sulfato de melatonina
- Saliva
  - Cortisol (8am, 12am, 8pm)
- Sangre
  - Hemograma y hemograma diferencial
  - Glucosa en ayunas y glucosa sanguínea postprandial
  - HBA1c
  - THS

Pruebas adicionales-parámetros individuales específicos en función de los síntomas

- Orina por la mañana:
  - Histamina, glicina
  - Acido gamma aminobutírico
  - Glutamato
- Saliva
  - Alfa-amilasa A (a las 10horas)
  - Dehidroepiandrosterona DHEA (8am y 8 pm)
- Sangre
  - Homocisteína

- ATP intracelular
- Glutation intracelular (equilibrio redox)
- Malondialdehído (peroxidación lipídica)
- 8-hidroxideoxigunosina (oxidación del ADN)
- Interferon-gamma (IFNϒ)
- Interleucina-1 (IL-1)
- Interleucina-6 (IL-6)
- Interleucina-10 (IL-10)
- Factor de necrosis tumoral alfa (FNTA)
- NF-Kappa B
- Vitamina B2 (FAD y riboflavina) (sangre entera)
- Vitamina B6 (sangre entera)
- Vitamina D
- Ubiquinona (Q10)
- Selenio (sangre entera)
- Zinc (sangre entera)
- Magnesio (sangre entera)
- Perfil lipídico diferencial (sangre entera)

Lógicamente, hace falta que un médico formado en estas patologías sepa interpretar estos resultados.

Muchos de los marcadores sugeridos no podemos decir que sean patognomónicos de la SQM, pero sí que son característicos de patologías con una base pro inflamatoria, y con características degenerativas, crónicas y de hipersensibilidad. Todos estos rasgos hacen que varias patologías que cumplen estas características se engloben dentro de los llamados: Síndromes de Sensibilización Central.

Además, se cuenta con otra herramienta importante internacionalmente validada que asiste en el diagnóstico, es el **cuestionario QEESI**.

B4.3 Criterios de diagnóstico

Estos criterios se encuentran recogidos en el apartado A5. Diagnóstico del presente documento (pág. 28).

B5. CLASIFICACIÓN

La Guía del INSS, 2ª edición, en el punto 5.A.V CLASIFICACIÓN, página 129, habla del test QEESI resaltando en negrita la siguiente frase: «Su validad científica está muy limitada por basarse en las apreciaciones subjetivas del paciente».

Ante esta falsa afirmación hay que indicar que el test QEESI es una de las principales herramientas de diagnóstico recomendadas en el Documento de Consenso del Ministerio de sanidad sobre SQM del año 2011 y su posterior documento de actualización del año 2015, también del Ministerio de Sanidad. En ambos documentos se valida esta herramienta para el diagnóstico de la SQM como puede verse al leerlos. Y esto es porque a nivel internacional se trata de una herramienta que goza de gran prestigio en el ámbito médico, hasta tal punto que es la herramienta para el diagnóstico que se usa internacionalmente para hacer los estudios científicos en población afectada por SQM. **Por tanto, esta parcial guía del INSS, 2ª edición es el único documento que cuestiona la validez del cuestionario QEESI**[73], contradiciendo al Ministerio de Sanidad y al propio Ministerio de Trabajo y a la comunidad científica internacional que la utiliza como herramienta de diagnóstico principal en las publicaciones científicas que sobre SQM se publican.

Sorprende esta atrevida afirmación, porque en muchas áreas de la salud los cuestionarios son utilizados como una herramienta de apoyo importante junto con una historia y signos clínicos y son aceptados sin cuestionar nada.

Si el método de utilizar un cuestionario para un diagnóstico es válido y aceptado por la comunidad médica para diagnosticar por ejemplo una enfermedad que requiere medicación como una esquizofrenia, ¿Por qué no habría de ser válido un cuestionario orientado ambientalmente para diagnosticar otra enfermedad como la SQM? **¿O es que el método de cuestionario solo va a ser válido para diagnosticar unas enfermedades, pero no otras por motivos interesados?**

Por supuesto, el cuestionario podría no ser suficiente sino se acompañase de una historia clínica, anamnesis, signos físicos objetivables unido a las analíticas con valoración de diferentes parámetros… Pero el hecho de que sea recomendable aportar más datos para un buen diagnóstico no quiere decir en

[73] Ver: Enciclopedia Práctica de Medicina del Trabajo del Instituto Nacional de Seguridad y Salud en el Trabajo, 2018.

absoluto que la validez científica de este cuestionario esté limitada, tal como se pretende en esta guía.

Punto 5.A. VI, CRITERIOS TERAPÉUTICOS, página 129.

A este respecto, el Dr. W. Rea que lleva tratando durante más de 30 años a pacientes con SQM en EEUU, afirma:

«La eliminación de la inflamación crónica en el paciente con SQ, es extremadamente importante porque los procesos implicados consumen una gran cantidad de energía, causando así la debilidad y acidosis del tejido lo que estimula la producción de fibroblastos y genera el consumo de nutrientes».

"El objetivo primario de la terapia es reestablecer los mecanismos defensivos para un funcionamiento armonioso normal, de manera que se restaure la energía. Hay que mantener la caga tóxica lo más baja posible hasta q la mejoría sea estable. El paciente químicamente sensible debe mantenerse en un estado de desadaptación en el que su carga tóxica total disminuya y el estado de alarma esté activado, de manera que se pueda percibir la causa-efecto de toda exposición ambiental e intentar eliminar los agentes desencadenantes[74]».

Los médicos formados en Medicina Ambiental que llevan tratando durante años a afectados de SQM, utilizan distintas opciones terapéuticas en función de las características individuales de cada paciente, algunas de las más usadas son[75]:

- Evitación de agentes desencadenantes.
- Control ambiental.
- Reposición de nutrientes que asisten a la desintoxicación: vía preferente intravenosa.
- Tratamiento con inyecciones subcutáneas provocación/neutralización.
- Depuración con cámara térmica.
- Tratamiento endocrino.

[74] Rea, W.J. (1997). Chemical Sensitivity: Tools of Diagnosis and Methods of Treatment, Vol.4, Lewis Publishers, Boca Raton.

[75] Rea, W.J. (1997). Chemical Sensitivity: Tools of Diagnosis and Methods of Treatment, Vol.4, Lewis Publishers, Boca Raton.

B6. CRITERIOS TERAPÉUTICOS

«Las recomendaciones generales son evitar la reexposición a los agentes desencadenantes y la exposición a humos o irritantes, así como mejorar la ventilación y aireación de domicilios y áreas laborales. Pero esta medida tiene detractores, ya que al recomendar evitar la exposición se transmite un mensaje de causalidad que no está basado en las evidencias y que pueden hacer perdurar la sintomatología. En cualquier caso, en la práctica esta medida resulta difícil dada la ubicuidad de productos químicos en el ambiente, especialmente en medios urbanos[76]».

Al decir que la medida de la evitación tiene detractores no se está considerando que es **inmensamente mayoritaria la literatura científica que avala como mejor método de tratamiento la evitación.**

De hecho, el propio **Consenso Internacional sobre SQM de 1999** en el que se establecieron los criterios de definición de caso de la enfermedad establecen que:

- ✓ Los síntomas mejoran o se resuelven cuando los incitantes son eliminados.

Decir que la medida de la evitación tiene detractores es pretender hacer creer que hay un debate sobre este asunto cuando no es así en absoluto. Puede existir algún detractor amparado por otros motivos, no por la evidencia científica.

El Ministerio de Sanidad, en su Documento de Consenso del año 2011, así como en la Actualización de la Evidencia Científica del año 2015, contempla la retirada o la evitación de los factores desencadenantes como la medida terapéutica más validada ante esta enfermedad.

«En el ámbito de la Medicina del Trabajo, los trabajadores afectados por el síndrome de sensibilidad química múltiple, deben ser considerados como trabajadores especialmente sensibles y, en cumplimiento del artículo 25 **de la LPRL, se debe reforzar la aplicación de los principios de la acción preventiva descritos en los lugares de trabajo, evitando en lo posible la exposición a los agentes desencadenantes. Esto mejora los síntomas, disminuye el número de crisis y evita la aparición de nuevas intolerancias** (…) Como para cualquier persona trabajadora especialmente sensible, la

[76] Página 129 de la Guía del INSS, 2ª Edición.

adaptación del medio laboral a la persona con SQM debe realizarse de forma individualizada, respetuosa e integradora, valorando cada caso de forma independiente. **Las propuestas podrán ir desde medidas para mejorar la calidad del aire en la empresa (política de empresa libre de fragancias, cambio de uso de productos de limpieza, ventilación o reubicación de despacho…), hasta proponer cambio de puesto de trabajo a la persona afectada, o valorar la necesidad de una incapacidad laboral temporal en fases sintomáticas de agudización, o permanente, dependiendo de la gravedad de los síntomas y su profesión[77]».**

El apoyo a la aplicación de protocolos especiales para proteger a las personas con SQM en nuestro país viene también desde diversas instituciones públicas. Un ejemplo es la publicación del Protocolo de Sensibilidad Química Múltiple en las Unidades de Urgencias Hospitalaria de la Comunidad de Madrid, o el Protocolo de Mejora de Atención a las personas con Sensibilidad Química Múltiple elaborado por la Junta de Andalucía.

CONCLUSION

Consideramos importante poner de manifiesto las reflexiones que sobre esta enfermedad se han hecho por parte en la Enciclopedia Práctica de Medicina del Trabajo del INSST.

«En prevención primaria, conocer en más profundidad la SQM resulta fundamental pues puede tener como efecto colateral una mejora de las condiciones medioambientales de la población general. En cuanto a la prevención secundaria, la detección precoz en los circuitos de atención primaria y servicios de riesgo laboral, puede ser una buena medida para evitar la amplificación y cronificación del mecanismo de sensibilidad junto con la evitación de la exposición y reexposición a los agentes desencadenantes». (Pág. 240).

«Conviene hacer hincapié en que el sufrimiento de algunas de las personas afectadas puede llegar a ser importante como consecuencia de los padecimientos físicos de la enfermedad y de las

[77] Instituto Nacional de Seguridad y Salud en el Trabajo, dependiente del Ministerio de Trabajo. Enciclopedia Práctica de Medicina del Trabajo, diciembre *2018*. Pág. 240.

limitaciones de vida a que frecuentemente se ven sometidas, al reducir drásticamente su capacidad laboral y su autonomía personal por la necesidad de evitar aquellos entornos que, por propia experiencia, han comprobado que les causan reacciones indeseadas o adversas».
(Pág. 241).

En Europa el reconocimiento de la SQM y patologías asociadas viene de:

- ✓ La Resolución del Parlamento Europeo, de 4 de septiembre de 2008, sobre la Revisión intermedia del Plan de Acción Europeo sobre Medio Ambiente y Salud 2004–2010.
  Incluye a la SQM dentro del número creciente de enfermedades vinculadas a factores medioambientales y considera que la Medicina del Medio Ambiente tiene que ser apoyada y fomentada en el seno de la Unión Europea.

- ✓ En la Asamblea Parlamentaria del Consejo de Europa[78], se recoge la preocupación en el seno de la Unión Europea por la salud ambiental. Concretamente, en el punto 37 se dice:

«Para sumar a estas preocupantes recientes en salud ambiental, en los últimos años una serie de nuevos/as enfermedades o síndromes han hecho su aparición, tales como:

- MCS (sensibilidad química múltiple);
- SFC (síndrome de fatiga crónica);
- Síndrome de amalgama de mercurio dental;
- Hipersensibilidad a las radiaciones electromagnéticas;
- Síndrome del edificio enfermo;
- Fibromialgia».

Cada vez son mayores los pronunciamientos por parte de distintos organismos ante estas enfermedades emergentes tan complejas. Por ello, consideramos que intentar simplificar la magnitud de las consecuencias reales del padecimiento de estas patologías atribuyéndolas un factor psicológico sobre

[78] Doc. Doc. 11788. 20 January 2009. Environment and health: better prevention of environment related health hazards.

el que no cabe discusión, como se ha hecho en la Guía elaborada por el INSS, 2ª Edición, no conduce a ninguna parte, sino a prolongar el sufrimiento de los afectados mientras que aparecen casos nuevos porque se están cerrando los ojos ante una nueva realidad y un nuevo modelo de enfermedad.

B7. FACTORES PRONÓSTICOS

Es fundamental evitar todos los agentes químicos que pueden ser potencialmente dañinos para los afectados de SQM, es decir, es fundamental llevar un estricto programa de Control Ambiental.

Lo más importante es conseguir que la carga tóxica del afectado disminuya y que el individuo pueda mantener un estado de «desadaptación».

La experiencia clínica internacional dice que el primer paso del tratamiento es la evitación a objeto de que disminuya la carga toxica del individuo. Al comienzo del tratamiento, el paciente con SQ es muy frágil recayendo al entrar en contacto con multitud de incitantes tóxicos y no tóxicos, así como con alimentos o sustancias bilógicas inhaladas. Sin embargo, a medida que progresivamente se va reduciendo la carga corporal total del paciente y se restablecen sus mecanismos de defensa y nutrición, se acumula resistencia y esto hace que el afectado no sea tan sensible y reactivo aunque no realice tratamiento.

Respecto a la afirmación de la Guía del INSS, 2ª edición, de que la evitación a la reexposicion a agentes desencadenantes es una medida que tiene detractores (página 30) es una afirmación que solo pueden entenderse desde la más profunda ignorancia de esta enfermedad, además de que vuelve a contradecir las afirmaciones del Documento de Consenso del Ministerio de Sanidad sobre SQM, 2011, y su actualización de 2015 en la que se afirma la evitación como la principal herramienta terapéutica, al igual que al Instituto Nacional de Seguridad y Salud en el Trabajo que en la Enciclopedia Práctica de Medicina del Trabajo clama por considerar a los afectados de SQM como trabajadores especialmente sensibles que han de evitar todos los agentes desencadenantes y en casos extremos valorar su incapacidad laboral. Decir que el elemento terapéutico de la evitación tiene detractores es contradecir la propia definición internacionalmente aceptada.

Una vez más esta guía con pocas referencias científicas y pobremente fundamentada hace afirmaciones rotundas y falsas que han de ser rebatidas

por toda la literatura científica que contradice tales afirmaciones y por los médicos formados en esta patología emergente.

La mala calidad de vida se perpetuará precisamente cuando no se eviten estos agentes contaminantes aun a bajas dosis, ya que esto producirá un aumento de carga tóxica y un empeoramiento aun mayor, teniendo que permanecer prácticamente enclaustrados y luchando para no ser etiquetados de fóbicos solo por tener una enfermedad, poco estudiada todavía.

B8. ORIENTACIONES PARA VALORACIÓN INCAPACIDAD

Basándonos en todo lo expuesto, las personas con Sensibilidad Química Múltiple deberán ser valoradas teniendo en cuenta distintos criterios:

- Gravedad de su estado actual, que en muchos casos les impedirá trabajar temporalmente debido a su afectación física.
- Gravedad de su estado de forma cronificada, lo que le impedirá trabajar de forma permanente debido a su deterioro físico.
- Situación de obligada exposición a sustancias tóxicas, según el trabajo a desarrollar por el/la paciente. Imposibilidad de adaptación del puesto o el ambiente de trabajo, lo que seguirá repercutiendo en su estado de salud.

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Nota del Dr. Antonio Mª Pasciuto, Presidente de Assimas (www.assims.it), la Asociación italiana de Medicina, Ambiente y Salud; y miembro del Consejo Directivo de Europaem (www.europaem.eu), la Academia europea de Medicina Ambiental):

Nos indica que estas «enfermedades emergentes» son crónicas, multisistémicas y, en muchos casos, ambientales. Por ello es fundamental formar a médicos y profesionales de la salud en Medicina Ambiental con el fin de poder evaluar, actuar sobre sus causas y ayudar así a los pacientes.

ANEXOS

ANEXO I:

Documento del IPCS: Report of Multiple Chemical Sensitivities (MCS) Workshop. Berlin, Germany, 21-23 February 1996. IPCS: Interantional Programme on Chemical Safety.

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IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

REPORT OF MULTIPLE CHEMICAL SENSITIVITIES (MCS) WORKSHOP

Berlin, Germany, 21-23 February 1996

Organized in collaboration with the
German Federal Ministry of Health,
Federal Institute for Health Protection of
Consumers and Veterinary Medicine (BGVV)
and the Federal Environmental Agency (UBA)

United Nations Environment Programme

International Labour Organization

World Health Organization

REPORT OF THE WORKSHOP ON MULTIPLE CHEMICAL SENSITIVITIES (MCS)

BERLIN, GERMANY, 21-23 FEBRUARY 1996

August 1996

This report contains the views of an international group of experts and does not necessarily represent the decisions or the stated policy of the United Nations Environment Programme, the International Labour Organization, or the World Health Organization.

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

IPCS

This Workshop was organized by the International Programme on Chemical Safety (IPCS) in collaboration with the German Federal Ministry of Health, Federal Institute for Health Protection of Consumers and Veterinary Medicine (BGVV), and the Federal Environmental Agency (UBA). The Federal Environmental Agency coordinated the Workshop arrangements in Berlin. IPCS wishes to express its gratitude to these German Governmental Agencies for their active support of IPCS activities.

The Workshop outline programme appears as Annex A, the invited participants are listed in Annex B, and representatives and observers in Annex C.

The report was prepared by the Joint Rapporteurs, Professor H. Altenkirch and Dr L. Fishbein, in consultation with their fellow invited experts.

REPORT OF "MCS" WORKSHOP

Berlin, 21-23 February 1996

I. INTRODUCTION

A workshop of invited experts from a number of scientific disciplines was held on 21-23 February, 1996 in Berlin, Germany to discuss "Multiple Chemical Sensitivities" ("MCS"). The workshop was organized by the International Programme on Chemical Safety (IPCS), a cooperative programme of the United Nations Environment Programme (UNEP), the International Labour Organisation (ILO) and the World Health Organization (WHO), in collaboration with the German Ministry of Health (BMG), the Federal Institute for Health Protection of Consumers and Veterinary Medicine (BGVV), and the Federal Environmental Agency (UBA).

The workshop consisted of 18 introductory presentations by invited experts covering the expanse of European, US and Canadian perceptions of "MCS", various definitions of "MCS", toxicology, immunology, environmental illness, neurology, behavioral sensory irritation, clinical investigation and toxicodynamic, behavioral and psychological characteristics of "MCS". These presentations served as a stimulus for discussion of the major objectives of the workshop which were:

. to review information on "multiple chemical sensitivities" ("MCS")
. to determine whether or not "MCS" constitutes a syndrome
. to examine relationships with other "environmental illnesses" ("EI")
. to identify possible aetiological factors
. to discuss diagnosis, diagnostic testing, differential diagnosis and lines of treatment

During the workshop "ad hoc" panels were convened to review issues and report back to plenary sessions. The panels addressed diagnosis, epidemiology, and the applicability and appropriateness of the term "Multiple Chemical Sensitivities", and also indicated possible research priorities for general consideration in plenary session.

II. SUMMARY

HISTORY OF "MCS"

"Multiple Chemical Sensitivities" ("MCS"), a puzzling, poorly understood and contentious clinical entity emerging in the 1940's, with increased discussion in the 1980's, is often defined by reactivity to common environmental exposures at significantly lower exposure levels than those which would cause noticable illness in the general population and at levels which the preponderance of individuals tolerate quite well (Cullen, 1987; National Research Council, 1992; Terr, 1994; Sikorski et al., 1995).

The concept that "MCS" is a distinct entity caused by exposure to foods and chemicals originated in the work of Randolph in the 1940's and expanded in the 1960's (Randolph, 1956, 1962). In the disease model proposed by Randolph, "MCS" consists of multiple symptoms involving multiple organ systems due to an inability to adapt to chemicals with resulting responsiveness to extremely low concentrations after sensitization. According to this theory, symptoms can occur on exposure to chemicals or on withdrawal from exposure after an adaptive response has taken place (Randolph, 1956, 1962).

The term "Multiple Chemical Sensitivities" was introduced by Cullen (1987) and has also been referred to by many synonyms (introduced by physicians, clinical ecologists as well as the news media) (table 1). A wide range of individual symptoms (typically multiple and at various and multiple sites) are displayed by "MCS" patients (Sparks et al., 1994a,b). The main clinical features include the self-reported complaints of ill-defined symptoms. The lack of reproducible immunological or other laboratory findings have thwarted diagnostic testing. Despite numerous symptoms such as concentration and memory difficulties, respiratory tract irritation, abdominal, joint and muscle pain, nausea, dizziness, headache, fatigue, depression and irritability, physical examination and laboratory tests are generally normal. The illness tends to be a chronic disorder in which the patient may become increasingly disabled (Randolph, 1956, 1962, Doty et al., 1988, Ashford & Miller, 1991; Nethercott et al., 1993).

Clinically many "MCS" patients also report multiple food sensitivities and they may attempt to avoid various chemical substances and foods, as well as caffeine, alcohol and medications as a primary treatment modality (Randolph, 1956, 1962; Ashford & Miller, 1991, 1992).

Diagnostic criteria for "MCS" are lacking and there are no reliable data on the prevalence of individuals with chemical sensitivities. Definition of the phenomenon of "MCS" has been elusive (NRC, 1992).

Well-established descriptive diagnoses such as somatoform disorder, depression, asthma, migraine and post-traumatic stress disorder are believed by many practioners to account for symptoms in the majority of "MCS" cases. However, waxing and waning of symptoms with perceived or real chemical exposure is not an established component of any of these disorders except perhaps asthma and migraine. "MCS" has often been confused with the "sick-building syndrome" ("SBS") due to the sometimes similar constellation of exposures and symptoms and the fact that a subset of "SBS" patients appear to develop "MCS" (Ashford and Miller, 1991; Miller, 1994). "Chronic fatigue syndrome" ("CFS2) is a systemic disease that is accompanied by pronounced fatigue associated with fever, pharyngitis, myalgia, headache, cognitive impairment, insomnia and depression (Buchwald & Garrity, 1991; Buchwald et al., 1992), symptoms that are similar to those seen in "MCS". Thirty to 60% of those with "CFS" report some symptoms of chemical sensitivity.

Many opponents of "MCS" as an organic disease and a singular entity do not question the symptomatology of the patients but question whether these symptoms represent a direct toxic effect of chemicals. They hypothesize that "MCS" may not be a single entity but a manifestation of one or more physical or psychological illnesses that have been improperly diagnosed (Terr, 1993, 1994; Black, 1993; Staudenmayer et al., 1993; Sikorski et al., 1995, Gots, 1993, 1995; Wolf, 1994). Other physicians known as clinical ecologists diagnose patients with unexplained illnesses characterized by multiple, subjective symptoms that are attributed to chemical exposure (Randolph and Moss, 1980; Bell, 1982). However, some other some physicians including occupational medicine practioners, neurologists and others are also using the diagnostic label of "MCS" to describe patients of this type.

While the aetiology of "MCS" is unknown, the illness may be multifactorial. Proposed aetiologies for "MCS" include: toxicological; physiological; neurological; immunoloc; respiratory; olfactory-limbic sensitization; psychiatric or psychological; childhood abuse and porphyria (Bell et al., 1992; Sparks et al.,1994a,b; Harrison, 1995;Sikorski et al., 1995).

Suggested trigger agents of "MCS" have included a broad spectrum of chemicals. These include odorous and non-odorous volatile organic compounds (VOCs), solvents, pesticides, industrial chemicals, metals, consumer products (cosmetics, deodorants, perfumes, soaps, disinfectants, cleaning agents), new carpeting, and combustion products. Alleged sources include: construction materials, office equipment, supplies or furnishings (plastics, synthetic textiles),

tobacco smoke; indoor air (domestic), as well as contaminated community exposure to aerial pesticide sprays, air contamination from nearby industry, toxic waste dumps, ground-water contamination, ozone and miscellaneous community exposures (Randolph, 1956, 1962; Ashford & Miller, 1989, 1991). The list of trigger agents has been constantly expanding, and is not restricted to chemical agents. Physical entities such as electromagnetic fields (EMF) have also been recently reported to be linked to "MCS"-like symptoms (Gothe et al., 1995).

A large number of cases of "MCS" have been reported in the United States (Ashford & Miller, 1989, 1992; Rest, 1992; Miller, 1994; Sparks et al., 1994 a,b). However a survey conducted in 1994 has shown that "MCS" is of increasing public concern in many countries in the European Union (Ashford et al. 1995). As in North America, chemical sensitivity in Europe is an elusive and baffling condition. Compelling scientific evidence of a relationship between exposure to triggering agents and health effects is lacking (Ashford et al., 1995).

In the US, the phenomenon of "Multiple Chemical Sensitivities" has been the subject of numerous symposia, workshops (ISRPT, 1993,1995) and round table discussions (Sikorski et al., 1995); state governments (Ashford & Miller, 1989); federal agencies (Agency for Toxic Substances & Disease Registry) (ATSDR, 1994); the National Academy of Sciences (NRC, 1992) and a number of professional organizations via workshops and position papers (Association of Occupational and Environmental Clinics) (AOEC, 1992); (American College of Physicians) (ACP, 1989); and the American Medical Association (AMA, 1992). Acrimonious debate on "MCS" has been ongoing for nearly a decade in professional meetings and medical journals and in courtrooms (Miller, 1994).

III. REPORT OF OPENING REMARKS AND PRESENTATIONS

A. OPENING ADDRESSES

The workshop was opened with an address of welcome by Prof. A. Somogyi of the Federal Institute for Health Protection of Consumers and Veterinary Medicine (BGVV). He stressed that "MCS" is an international problem, one that warrants study by this group of international experts in Berlin meeting to discuss the phenomenon, to determine whether it could be defined, and form a framework for discussion and further scientific work. The importance of "MCS" to a broad spectrum of individuals (e.g., consumers) is recognized. It is unclear whether "MCS" is a psychogenic or toxicogenic phenomenon and it has been difficult to resolve this distinction by existing methods. The Workshop should try to shed light on the basic mechanisms

and genesis of the phenomenon known as "MCS" and perhaps address what the consumer should be protected against?

Mr. F.J. Bindert of the Federal Ministry of Health (BMG) then welcomed the participants on behalf of Mr. Seehofer, the Federal Minister of Health. Mr. Bindert raised the question of whether there is a connection between "MCS" and other illnesses linked to various agents and physical environments, e.g., sick-building syndrome and wood preservative syndrome. Like "MCS", these syndromes involve subjective complaints and patients lack clear signs of organ dysfunction. There is not a clear picture of the phenomenon as to whether psychomatic factors play a part. Subjects with "MCS" exhibit a lot of suffering. They join support groups and associations, do not want to be known to be suffering from a psychological disorder and some demand official acceptance of their condition and sick compensation. In terms of compensation, it is important to these individuals that the aetiology be physiologically induced. "MCS" symptoms affect a large number of people. Most individuals who are suffering are interested in prevention. For a relatively smaller number of people, individual therapy and prophylaxis may be possible if the causative agents could be identified. In this case the State would have to insist that these substances be identified and therefore removed. It is important to exchange international knowledge of experiences on the subject of "MCS" which will be useful in Germany and in public discussion. "MCS" is a relatively recent phenomenon and public discussion must be well-reasoned as the consequences of discussion of "MCS" can be far reaching.

Prof. Dr. H. Lange-Asschenfeldt, Federal Environmental Agency (UBA), next addressed the Workshop. He stated that "MCS" was not a general problem but affected a small number of individuals. In public discussion in the past, only environmental causes were noted. In Germany, the diagnosis of "MCS" is now being made more often. Afflicted patients can undergo serious economic change. Practioners are in a dilemma since there are no diagnostic criteria. The growing pressure from patients adds to the dilemma. Dr. Lange-Asschenfeldt stressed that the aims of the Workshop should be: 1) definition of terms; 2) education of the public should be encouraged and 3) diverse medical strategies should be outlined to the extent feasible.

Dr. E. Smith/WHO made the last opening presentation, welcoming participants on behalf of IPCS, and the executive heads of its cooperating organisations. IPCS had been established as a joint venture of UNEP, ILO, and WHO with the overall objective of establishing a scientific basis for evaluating human illness associated with exposure to chemicals in order to achieve sound management of chemicals and protect human health and the environment. The outputs of IPCS is available to all countries. The 1992 United Nations Conference in Rio de Janeiro on Environment and Development had emphasized the extreme importance of sound management of chemicals with

the active involvement of international agencies, national governments, and non-governmental organizations (NGOs). WHO has a large number of NGOs in official and working relations and two of these were represented by observers at the Workshop. Dr. Smith stressed the objectives of the Workshop and the need to reach structured conclusions and recommendations. The Workshop had been convened for a full exchange of views and opinions and was intended to result in a report by the invited experts reviewing the field of "MCS", and touching on environmental illnesses, with conclusions and recommendations.

B. PRESENTATIONS

The opening adddresses were followed by 4 sessions comprising 18 short presentations by invited experts.

Prof. H. Altenkirch (Spandau Hospital, Berlin), presenting "MCS" from a European perspective, reviewed the main features of "MCS". Reported in the US for almost 2 decades (under a large number of synonyms), "MCS" is being increasingly diagnosed in a number of European countries. Exposure to a wide range of chemicals of varying structures have been reported to result in patients exhibiting "MCS" (with over 500 papers on the subject published in the US alone). There are no diagnostic criteria set in European countries, and no specific epidemiological or other studies of this condition are in progress.

Prof. Altenkirch discussed purported causes in Germany of "MCS disease" involving wood preservatives (lindane and pentachlorophenol) where no scientific line of reasoning nor any standard for clinical assessment were found. Another current problem in Germany concerns disability claims submitted by employees of large department stores who had allegedly been exposed to low levels of pyrethroids in routine pest control procedures and consequently claimed to suffer from "MCS" symptoms. Individuals exposed to carpets containing pyrethroids (and/or treated with pyrethroids) are expected to be involved in further litigation in Germany.

Prof. Altenkirch discussed clinical investigations involving 23 persons on an in-patient basis who had been reported to BGA in 1993/1994 as cases of pyrethroid intoxication. Eight patients presented with "MCS" symptoms and showed no abnormalities in either laboratory findings nor in their physical examination. Available data did not indicate evidence of PNS or CNS impairment (Altenkirch et al., 1996).

He discussed various diagnostic criteria for "MCS" comparing this with established neurotoxicological disorders such as the Spanish oil neurotoxicity episodes of 1981-1982. "MCS syndrome" is not a neurotoxic disease but is a result of some sort of an initial chemical trauma. In

Prof. Altenkirch's experience, "MCS" is frequently a misdiagnosis, and exposure to chemicals is not the actual cause of the disease. "MCS" cases can actually be somatic and psychiatric illnesses and, in addition, overlap the symptomatology observed with "sick-building syndrome" ("SBS") and "chronic fatigue syndrome" ("CFS") cases.

Prof. Altenkirch discussed various hypotheses on the aetiology of "MCS" such as the olfactory and limbic system involvement (Bell et al., 1993). He listed ten research strategies suggested by the problems raised by "MCS". Foremost among these were: establishment of diagnostic criteria (possibly based on the criteria established by Cullen (1987)); consensus on psychological tests as well as clinical investigative methods including dermatological, allergic, immunological and neurological procedures; prospective and randomized double blind studies on "MCS" patients and a survey and critical evaluation of the different approaches to therapy that have been utilized to date.

Dr. R. Gots (Environmental Sensitivities Research Institute, US) discussed "MCS"from a US perspective and stressed that the fundamental issue is not whether or not the phenomenon of "MCS" really exists; rather it is whether it is primarily a psychogenic (an emotional response to a perceived chemical toxicity) or a toxicodynamic disorder (pathological interaction between chemical agents and organ systems). The causal question (e.g., whether "MCS" is a perceived toxicity or a physical disorder) is critical, first because it determines proper patient care, but also because it determines the nature of legal, societal and occupational response (e.g., possible compensation, litigation potential, workplace hygiene controls, rights under ADA (American Disabilities Act). It was stressed that how patients are treated depends on the underlying aetiology of the symptoms, e.g., a behavioral origin leads to behavioral therapy while a toxicodynamic aetiology may recommend avoidance, and exposure control methodologies.

Dr. Gots cited recognized examples of physical and psychogenic (emotional) causes of identical symptoms (e.g., headache, palpitations, fatigue, dizziness, nausea, etc) and stressed that determining whether the symptoms arise from dysfunctional organs or from mind-body relationships is neither trivial nor unnecessary. He contrasted the notion of an individually determined response (IDR) (somatic manifestation of an emotional response to an external or internal stimulus) with that which is organic or which are a combination of both. For example, for an external cause such as low-level non-allergenic chemicals, the IDR (behavioral) response could be fatigue, loss of memory, weakness, shortness of breath, etc. The organic response could be a mild irritant response. Individually determined responses may lead to a patient exhibiting symptoms or to the worsening of existing symptoms.

Dr. Gots noted that somatization, which is an endpoint (a set of symptoms arising from a wide variety of emotional factors, rather than a specific disorder) can mimic serious disorders such as asthma. Somatization appears to be increasing.

In a discussion of the toxicodynamic process versus psychogenic process and "MCS", Dr. Gots noted that there is no currently known mechanism whereby low levels of chemicals or chemicals of widely varied chemical structure could interact adversely with numerous organ systems. Neither immune dysfunction nor "toxic porphyria" (a recently advanced theory) would explain the multiple and varied symptomatology experienced by "MCS" patients. He stressed that behavioral mechanisms must serve as the intermediary between the sensory awareness and the sympomatology experienced. He further stressed the potential dangers of the misattribution of "poisoning" in the diagnosis of "MCS" which can yield to disability, wrong treatment approaches, contribution to societal chemophobia and the requirements to industry to make unreasonable and unattainable accomodations. Additionally, he expressed concern that such a misdiagnosis could set a precedent of a patient defined disorder unsupported by scientific facts. There are no consistent findings in the various "MCS" studies reported. Dr. Gots recommended that until the aetiology is determined, a more descriptive and less categorical title for "MCS" and one which is less implicative of causation might be "Environmentally Associated Symptoms" ("EAS").

Dr. F.C. Li (Laboratory Centre for Disease Control, Canada) discussing "MCS" from a Canadian perspective, indicated that there is no "single" or "commonly shared" perspective on "MCS" in Canada because of the relative lack of scientific information . Questions regarding the causation and effective management of "MCS" patients have stirred a great deal of controversy and debate. Nevertheless, "MCS" has been having important impacts in Canada. These include adverse physical, psychological, social and economic effects on "MCS" sufferers, and implications on the health care system, social services and the workplace.

Dr. Li highlighted some of the recommendations of the 1990 Environmental Sensitivities Workshop (Health & Welfare, Canada, 1990) and the 1992 "Multiple Chemical Sensitivities and the Relevance to Psychiatric Disorders" Workshop (Health Canada, 1993). The 1990 Canadian Workshop recommended that "disabilities should be rated functionally rather than diagnostically in considering eligibility for pensions/social assistance" and that "with those having subjective symptoms, it would be necessary to do double blind placebo controlled challenges"

To aid practitioners in their management of "MCS" the 1992 Canadian Workshop suggested a set of clinical diagnostic criteria for "possible", "more probable" and "most probable" MCS cases. Under the rubric of a "possible" "MCS" case, the National Research Council (1992) definition should be satisfied, (see p. 28). The diagnostic criteria for a "probable" "MCS" case are

: possible case plus improvement after reduction or elimination of suspected exposure and symptoms recur on re-exposure. The diagnostic criteria for "most probable" "MCS" case include: diagnosed by double-blind challenge(s) in a controlled environment (e.g., Environmental Control Unit) after appropriate de-adaptation.

Dr. Li stressed that there is no doubt that "MCS" patients are suffering from their symptoms, and that they should be treated with understanding and compassion. However, due to the many uncertainties surrounding "MCS" causation and treatment, it is necessary to be careful (e.g., health practioners, governments) and rational in formulating strategies for "MCS", and the temptation of substituting empathy and conjecture for evidence-based decision making must be resisted.

The key question that urgently needs to be addressed is that of "MCS" causation, and specifically, whether "MCS" is of toxicogenic (due to exposure to chemicals and other substances) or psychogenic (due to psychiatric or psychological factors) aetiology. This differentiation is important as each of these two causal mechanisms will lead along entirely different and divergent paths in the quest for knowledge on "MCS" aetiology and treatment.

Although some research studies have been conducted on "MCS" causation, they are however, still relatively sparse and have not been able to provide conclusive evidence. Dr. Li believed that the most direct and appropriate approach to resolving this toxicologic versus psychogenic causation question is to conduct well-controlled double-blind placebo challenge studies on "MCS" patients. The conduct of such challenge studies should be a top resarch priority . To enhance the eventual acceptance of study results, such challenge studies should be designed and implimented collaboratively by researchers with differing views on "MCS" aetiology. Government agencies may also be well-suited for coordinating these studies.

Dr. C. J. Gothe (AB Ekiatrika, Sweden) highlighted the similarities of "MCS" with examples of the "Environmental Somatization Syndrome"("ESS") (Gothe et al., 1995). He asked if "MCS" is a special type of poisoning or a psychogenic reaction of the persons presenting symptoms. According to his opinion, the pathogenesis is psychodynamic. "MCS" demonstrates such similarities with illnesses such as oral galvanism and electric hypersensitivity that they seem to be variants of the same disorder for which the designation "ESS" ("Environmental Somatization Syndrome") has been proposed. Patients with "ESS" (including "MCS") connect their complaints with exposure to tangible components of the external environment, reject alternative explanations of their symptoms, and tend to establish aggressive lobby groups asserting that the problems depend on environmental exposures. "ESS" is distinguished by mental contagiousness and a tendency to cluster. It has a poly-symptomatic touch dominated by fatigue, dizziness, and pains in

different parts of the body. Problems with sleep, concentration and memory are common, and the picture is often coloured by the alleged disease-inducing agent. The illness often starts distinctly in connection with serious life-strains which will be unnoticed without careful case histories.

Dr. L. Fishbein, (US) presented an overview of some definitions, causative agents, exposures and dilemmas associated with "MCS". The description and effects of chemical sensitivity disease (Randolph, 1962), case definition of "MCS" syndrome (Cullen, 1987), operational definition of "MCS" (Ashford and Miller, 1991), clinical ecologist's definition of environmental illness and the many names and synonyms associated with "MCS" (table 1) were all illustrated. A number of major tenets of clinical ecology were outlined including: a) responses occur to multiple, chemically unrelated substances, b) a toxic response to one chemical can lead to a "sensitivity" to all other chemicals, c) a chemical may induce widespread symptoms associated with all organ systems, d) in addition to the chemicals involved in the original exposure event, over time, more and more chemically unrelated substances may trigger symptoms ("spreading" phenomenon) and e) "petrochemicals" or synthetic organic chemicals somehow differ in their toxicological potential from "natural" chemicals.

Dr. Fishbein noted the tremendous spectrum of attributed chemicals and exposures including pesticides, solvents, metals, literally every class of odorous and non-odorous product encountered in outdoor and indoor contaminants; contaminated communities (e.g., from exposure to aerial pesticide spraying, air contamination from nearby industry, toxic waste dumps, ground water contamination, ozone and miscellaneous community exposures. Exposures are not limited to chemicals as electromagnetic fields (EMF) have also been recently implicated (Gothe et al., 1995).

The accepted bedrock toxicological principles such as : there is consistent or specific symptomatology for a given chemical; the degree of reaction must be proportionate to the exposure; symptoms can be elicited only by chemically related substances and there are objective measurable endpoints and reproducible results were noted. These principles were then contrasted with the major dilemmas surrounding "MCS" which included: many different environmental chemicals, foods and medications evoke multiple symptoms in "MCS" that do not correspond to either recognized allergic responses or known toxicities of the particular agent (s); and the provoking chemicals, exposures and symptoms in "MCS" are apparently limitless in number and type. The controversy surrounding "MCS" is heightened by confusion about the relationship of "MCS" to the "sick-building syndrome" ("SBS"), "chronic fatigue syndrome" ("CFS"), occupational illness, hypersensitivity diseases and toxicity from environmental pollution.

Dr. D.E. Ray (Medical Research Council Toxicology Unit, UK) discussed "MCS" from a mechanistic toxicological perspective stressing the initial need to identify preliminary factors

including: definition of the nature of the effects; susceptibility of the population; the definition of the causal agent(s) and its dose-response relationship. It is then often important to identify the mechanism of action of the agent.

In the case of "MCS" there is a lack of criteria for case definition and misdiagnosis is common. A clear distinction between organic and psychological causes is required. Individuals may be chemically poisoned and physicians may overlook chemical causation since putative causal agents are common in the working and domestic environment. Alternatively, a purely psychological condition might be precipitated by organic causes. Two types of exposure were stressed: causal exposures and subsequent exposures. Mechanistic explanations for "MCS" may arise if a subpopulation(s) could be identified where deficiencies in detoxification may exist. However it is important to realize that any such sub-population must be defined by something other than post-hoc diagnosis of "MCS", if this identification is to be of any value.

Because of the many problems involved in investigations of the "MCS" phenomenon, many toxicologists have been somewhat reluctant to become involved. It was noted that since unexpected forms of toxicity do occasionally appear, toxicologists must always examine such phenomenon in an open-minded manner. Clinicians, in contrast, aggressively searching for a cause of their patient's problems are more likely to need to employ "MCS" as an explanation since it is often impossible to determine causation in individual cases.

Dr. B. Heinzow, (Landesamt für Natur und Umwelt, LANU, Germany) described a 1994 survey of the presentation of "MCS" in a number of European countries which found that there were differences between countries perhaps based on cultural background and other factors. For Germany and other European Union countries, no clear definition of "MCS" has been established by the medical communities. The attitude towards "MCS" and its diagnosis differred markedly among countries. In general, the diagnosis of "MCS" did not follow stringent criteria as evidenced by the diagnosis of "MCS" frequently possessing an overlap with "chronic fatigue syndrome" (CFS), "fibromyalgia" and "sick-building syndrome" ("SBS").

Dr. Heinzow stressed the lack of definitive diagnostic criteria for "MCS" patients in Germany. For example, unvalidated diagnostic criteria and unconventional treatment applied by doctors coupled with patients desperately seeking any possible hint of a remedy for their illness were noted.

The most affected groups (and peculiar exposures) were found for the following EU countries and US: 1) Germany: wood preservatives/PCP, dental amalgam; Netherlands: PCP; 3) Denmark: hairdressers; and US: Gulf veterans, insecticides, carpets, mattresses, anesthetics. Other

significant chemical exposures suggested to be implicated with "MCS" in Germany include: dental materials, metals, solvents, formaldehyde and various insecticides.

Dr. Heinzow noted the psychodynamics of "MCS" citing this sequence following exposure : 1) symptoms-anxiety; 2) search for causality: media alert; 3) hypothesis: iatrogenic stigmatization; 4) therapeutic attempts : a) therapeutic failure: increased struggle, loss of trust, social withdrawal-isolation, depression, total avoidance-destruction.

It was stressed that most "MCS" cases in Europe are not sufficiently documented. In practice there is a discrepancy between the refusal of "classical physicians" and the medical acceptance of the "MCS Syndrome". A case definition of "MCS" is urgently needed and a questionnaire should be developed for diagnostic and research purposes.

Dr. C.S. Miller (University of Texas Health Science Center, US), presented the theme that medical understanding of chemicalsensitivity today is only beginning to develop. Biological plausability is dependent upon the scientific knowledge of the time. The illnesses of "MCS" patients and Gulf veterans could have an organic basis since so much is shared in common; the demographic diversity of groups reporting similar and subjective symptoms and intolerances following an exposure event; the temporal cohesiveness between onset of multiple intolerances and an exposure event; the internal consistency in these patients reporting intolerances to common airborne chemicals, various foods, drugs, caffeine and alcoholic beverages and the observations that many "MCS" patients who have avoided problem chemicals and foods report marked improvement or resolution of their symptoms.

Neither "MCS" nShe stated that neither "MCS" nor the "Gulf veterans' illnesses" fullfill criteria for being syndromes. Further, they are not explainable by any currently known mechanism for disease. Dr. Miller proposed that the similar phenomenologies of both conditions suggest that a new general mechanism or theory of disease involving chemically-induced loss of natural tolerance could be operative which could be described as "toxicant-induced loss of tolerance" ("TILT") (Miller, 1996).

Many cases of chemical sensitivity appear to involve a two-step process. A susceptible person initially exhibits loss of tolerance or sensitization (also referred to as initiation, "priming" or "induction") often following acute or chronic exposure to any of a wide range of environmental chemicals. Following this loss of tolerance, these now sensitive persons report that extremely low levels of common chemicals tolerated by the majority of the population trigger severe symptoms. Because of masking (e.g. acclimatization, addiction and apposition (overlapping symptoms resulting from temporally overlapping exposures) both physicians and patients may fail to

recognize that everyday low-level exposures may be triggering symptoms (Miller, 1994; Miller and Ashford, 1995).

Dr. Miller stressed that physicians urgently need a clinical approach for determining whether chemical intolerances are at the root of these patients' (e.g., "MCS", "Gulf veterans' illnesses") problems. Dr. Miller advocated that a controlled testing environment or Environmental Medical Unit (EMU) be employed as a research tool to address questions concerning causality. The EMU is a proposed hospital environment in which chemical exposures have been reduced to the lowest levels practicable via specialized air filtration and the use of construction materials and furnishings that do not emit chemicals into the air. The EMU would serve as a tool for ruling in or ruling out environmental sensitivities in the most direct and definitive manner possible. It was stressed that confirmation or refutation of illnesses of "MCS" patients and Gulf War veterans which are hypothesized as "toxicant-induced loss of tolerance" rests upon double-blind, placebo-controlled challenges conducted in an Environmental Medical Unit.

Dr. W.A. Nix (University Clinics, Mainz, Germany), stressed the similarity between features of "MCS" with "chronic fatigue syndrome" ("CFS") and that research strategies should be the same for both syndromes. He described the prevalence of psychosomatic symptoms in patients examined in an interdisciplinary "CFS"-clinic. Evaluation with an SCL-90-K questionnaire showed scores outside the normal range for somatization, obsessive compulsive disorders , depression and anxiety in patients who presented as their main complaint severe fatigue and in some cases, self-reported adverse reactions to environmental substances. The nessessity to screen for psychosomatic disorders in patients with a complaint of severe fatigue was stressed as well as the necessity to define subgroups for further evaluation of disease etiology under a bio-psycho-social disease concept.

It was further noted that "MCS" is not only a medical disease but a societal disease. It is difficult to differentiate the scientific and the pragmatic approach to assist the patient. All patients with "CFS" or "MCS" are evaluated at his Clinic with history, physical and mental status examinations. The goal is to determine the extent to which psychological problems are associated with these diseases and to find psychological parameters that disclose a predisposition to develop these symptoms and to see if laboratory parameters are of diagnostic value for these diseases.

Dr. P.S. Spencer (Oregon Health Sciences University, US), focused on recent research studies on unexplained illnesses of veterans associated with service during the Persian Gulf War (PGW). Unexplained illnesses refers to a constellation of symptoms designated as "PGW Unexplained Illness(es)" or "PGWUI". The long-term research goal is to develop a solid understanding of the nature of these conditions, their risk factors and their treatment and

prevention. The research focus concerns environmental factors encountered in military service that pose a threat principally to the neurological and musculoskeletal systems (fatigue, muscle and joint pain and cognitive complaints) of "PGWUI".

The overall research strategy outlined by Dr. Spencer is epidemiologically based involving: (a) case-control design, (b) clinical verification and (c) risk factor identification (exogenous and endogenous) (psychological, physical, chemical and biological). A major goal is thus to determine why some of the 700,000 veterans who were in the Persian Gulf for Desert Shield, Desert Storm and/or desert clean-up phases of the operation are now healthy (e.g., controls) while others (cases) have symptoms of "PGWUI". The primary research question is framed: are there differences between cases and controls in relation to individual subject factors and environmental exposures encountered in the Persian Gulf theater of war. Environmental exposures will be deduced by (a) stratifying subjects by their deployment period (e.g., Desert Shield only, Desert Storm only, desert clean-up only and combinations thereof), each of which is associated with a unique set of exogenous factors, (b) examining their geographical location in the Persian Gulf within the specified deployment periods and (c) assessing their duties and self-reported data on exposures in the Persian Gulf.

The difficulty of assessing and collecting unbiased data in the case of Persian Gulf veterans with unexplained illnesses (phase 1) was described. A major problem centered on different groups of veterans (different deployments as noted above) exhibiting differential exposures for different times. Phase 2 consisted of the deployment of a working case definition for "PGWUI" based in part on an analysis of 388 records of subjects in the Portland, Oregon component of the Veterans Administration (VA) Gulf Veterans Registry. This medical review provided valuable information on the leading symptoms from which a broad initial case-definition has been developed:

- symptom onset: during or after Persian Gulf war
- duration: 1 month or greater
- presence: within past 3 months
- symptoms: any of the following most frequently noted Registry symptoms ($> 10\%$) : (a) muscle-joint pain; (b) cognitive changes; (c) abdominal pain/diarrhea; (d) skin and/or mucous membrane lesions and (e) unexplained fatigue.

Dr. Spencer concluded that the association between exposures and unexplained illness whether it is "MCS" or "Persian Gulf War Syndrome" is difficult to assess because of sources of subject bias and the complexity of physical, psychological, chemical and biological exposures that occur. Studies seeking causal associations must take great care to identify and verify subject bias and to assess the plethora of environmental exposures that may have etiological significance.

Dr. G. Kobal (Institut fur Experimentelle und Klinische Pharmakologie und Toxicologie, Friedrich-Alexander Universitat, Erlangen-Nurnberg, Germany), discussed his studies of olfactory systems with patients with "MCS" and identified areas of the brain affected by olfactory agents. He further focused on intranasal chemoreceptors in patients with "MCS", subjective olfactory tests and acoustic rhinometry.

It is widely believed that intranasal chemoreceptive senses are involved in the pathophysiology of "MCS" since the characteristic symptoms of "MCS" are reprtedly triggered by very low concentrations of chemicals in the range of olfactory thresholds (Doty et al., 1988; Simon et al., 1990; Davidoff and Fogarty, 1994). Dr. Kobal described studies which highlighted changes of both the olfactory and trigeminal systems in "MCS" patients assessed by means of electrophysical correlates of chemoreceptors. Specifically, the focus of the studies were to determine whether patients with "MCS" exhibit differences in responses after they have been challenged to either room air or stimuli such as 2-propanol (Hummel et al., 1998). This question was addressed utilizing chemosensory-event-related potentials (CSERP) and subjective measures of olfactory function (e.g., odor discrimination and phenyl ethyl alcohol odor thresholds). CSERP were recorded in response to olfactory (H_2S) and trigeminal (CO_2) stimuli. CSERP (Kobal et al., 1992; Murphy et al., 1994) have also been demonstrated to be of potential use in the diagnosis of olfactory or neurological disorders (Hummel et al., 1995). Compared to the intergrative nature of psychological responses, CSERP appears to be less prone to influences such as response bias or changes in the subjects mood. CSERP encodes the intensity of a given stimulus but also permits the discrimination between trigeminal and olfactory characteristics of an odorant (Hummel and Kobal, 1992; Kobal et al., 1992).

Out of a total of 23 patients studied (mean age 47 years, 13 female, 10 male) diagnosed with "MCS" according to Cullen's criteria for "MCS" (Cullen, 1987), 20 % of patients presented symptoms regardless of the type of challenge suggesting the susceptibility of these patients to non-specific experimental manipulations. Changes in CSERP latencies indicated a change in the processing of both olfactory and trigeminal stimuli. While odor thresholds remained unchanged, the patients ability to discriminate odors decreased after exposure to room air, in contrast this decrease was less pronounced after exposure to 2-propanol. "MCS" patients responded to a

challenge with 2-propanol at concentrations around threshold values with changes of chemosensory perception which might increase their susceptibility to environmental volatile chemicals. Changes in the pattern of event related potentials were interpreted as the possible changes of the orientation of cortical generators, e.g., neuronal populations that were involved in the processing of chemosensory information (Hummel et al., 1996). Dr. Kobal concluded by stressing that future studies will have to demonstrate how these responses in "MCS" patients compare to those of healthy age and sex-matched controls.

Dr. A.C. Ludolph (Universitats Klinikum und Charite Poliklinik fur Neurologie, Berlin, Germany) addressed whether "MCS" is a neurotoxic disorder by considering the diagnostic criteria for clinical neurotoxicity. These are: 1) suspected compound must indeed be in the environment; 2) a dose-response relationship should be established; 3) after cessation of exposure, clinical progression stops and improvement is considered likely and 4) neurotoxic compounds induce a specific response which is characterized by a uniform pattern of vulnerability and thus a uniform clinical pattern.

Dr. Ludolph concluded that these criteria which are based on currently understood and accepted biological features of the nervous system presently do not support the hypothesis that "MCS" is a neurotoxic disorder. Dr. Ludolph stressed that to increase our knowledge of "MCS", the approach must be more systematic: 1) there must be agreement on diagnostic criteria for this "syndrome"; 2) more intensive efforts to identify compounds consistently associated with "MCS" should be made and 3) dose-response relationships, patterns of vulnerability and the natural course of the disease should be elaborated. Once these goals are at least partially achieved, controlled therapeutic attempts must be organized. He suggested that a priority might be to elucidate whether treatment of a depression or a behavioral therapy influences the symptomatology in "MCS".

Dr. H. Staudenmayer (Allergy Respiration Institute, US) described some of his experiences in working with "MCS" patients. He basically developed an algorithmic approach to discriminate individuals with verifiable chemical reactivity from patients with psychological or psychophysiological disorders (Staudenmayer et al., 1993). For example, double-blind provocation challenges with an olfactory marker were performed in an environmental chamber on each of 20 patients who believed that that they were reactive or hypersensitive to low-level exposure to multiple chemicals: (some patients had been previously evaluated and managed by the tenets of "clinical ecology" and diagnosed as having "MCS"). A variety of chemicals (e.g., formaldehyde, natural gas, cleaners, combusted kerosene, fuel oil, trichloroethane, trichloroethylene, freon, denatured alcohol, printer's ink, oil paint, and insecticides) were employed one or more per subject dependent on an individual's clinical history. Clean air challenges with an olfactory marker

were used as placebo or sham controls. As a group probability analyses of patient symptom reports from 145 chemical and clean air challenges failed to show sensitivity (33.3%), specificity (64.7%), or efficiency (52.4%). Individually none of these patients demonstrated a reliable response pattern across a series of challenges.

Dr. Staudenmayer reported a series of patients presenting with "MCS" who suffered major childhood trauma such as physical or sexual abuse. These highly significant life stressors were difficult to elicit, requiring months of intensive psychotherapeutic interaction. In these patients, the prevalence of physical and sexual childhood abuse was significantly higher ($p < 0.05$) among the cohort of women who attributed their symptoms to environmental or chemically related illness. The data suggested to him that somatization may reflect sequelae of childhood abuse and may play an important role in the illness experienced by women who believe that they are sensitive to environmental chemicals (Staudenmayer et al., 1993).

Dr. Staudenmayer described neuropsychologic measures (EEG, scalp EMG) that were employed during relaxation in individuals who attribute medical and psychologic symptoms to chemical exposures ("universal reactors") compared to subjects with primary psychologic disorders and with a control group (Staudenmayer and Selner, 1990). High levels of EMG scalp activity were observed in a greater number of "universal reactors" than with subjects in the other groups ($p < 0.001$).

Dr. M. Huppe (Universitat Wurzburg, Germany) raised the question of whether environmental stress research can contribute to understanding psychological processes in "MCS". Stress is considered to be a somatic and a psychic reaction related to environmental conditions. How is behavior influenced by environmental factors ("stressors")? In the case of "MCS" such stressors could be chemical or environmental agents. Dr. Huppe described some characteristics of stress. Stress is a temporally protracted longer reaction to environmental conditions and is usually associated with negative mood states such as fear and anxiety. Stress is a process (not a state) which initiates coping as illustrated by two well known nuclear power accidents in Three Mile Island and in Chernobyl. Depending on individual coping strategies, psychic reactions in individuals exposed in the accidents differed greatly. Coping is directed to the environmental factor or to psychic processes of the person. Coping may be positive and reduce stress reactions or it may be negative and increase stress reactions. Currently stress coping strategies are most frequently addressed by questionnaires. Important individual characteristics that modify coping with stress include: psychophysiological state, perception of controlability, personal traits such as neuroticism, annoyance or coping strategies and demographic variables such as age and sex.

The main characteristics of environmental agents that cause "MCS" were illustrated: a) they are external and perceptible, b) the intensity is low, c) they are not new to the patients, d) they are often not contollable and they elicit negative emotional responses.

Dr. Huppe suggested that from the viewpoint of a psychologist, research is needed in the development and use of challenge tests or tests of reactivity. The psychological evaluation of experimental challenge tests should include assessments of mood state, including emotions and somatic feelings and coping with stress. There is a need for sensitive psychological methods for the assessment of symptoms or psychic states since the described manifestations of "MCS" are predominantly subjective. There is an obvious need for control subjects who do not suffer from the symptoms described by "MCS" patients.

Dr. S. Dewey (Forschungszentrum Borstel, Germany) described a number of cases studies and operating procedures of the Environmental Health Consultation Center (Umweltmedizinische Beratunsstelle/UMB) in Hamburg) and the Medical Clinic of the Forschungszentrum Borstel. The procedures of the UMB are based on the approach that there should be some effort at medical and environmental research and consideration between first contact and final counselling of the patient. The predominant environmental problem encountered at the UMB was that of indoor pollution (wood preservatives, pesticides, formaldehyde and solvents). The symptoms generally involved the upper respiratory tract and the skin as well as complaints of fatigue. The "likely" or "very likely" relationship between the environmental exposure and health problems was considered to be only 15% in 254 reported cases with a ratio of 2:1 women to men, while 16% were judged "possible: and 53% were considered unlikely.

Of 31 patients who submitted to the medical clinic of the Forschungszentrum Borstel with diagnosis of food allergy/intolerance, 3/31 had proven food allergy; 3/31 had an intolerance to aspirin and food preservatives and in nearly half of the patients, psychiatric/psychosomatic disorders were the main diagnosis.

Dr. Dewey stressed that in regard to "MCS", existing case definitions and diagnostic criteria are insufficient. Thus he felt that "MCS" should not be applied as a diagnosis in medical practice. A significant portion of "MCS" cases are misdiagnosed with the majority of these patients apparantly having common psychiatric/psychosomatic disorders. It was emphasized however that the experienced complaints are real whatever the etiology may be and hence there is an urgent need for sufficient therapeutic strategies.

Dr. V.M. Weaver (Johns Hopkins University School of Public Health, US) discussed the evaluation and treatment of an "MCS" patient and stressed that the clinical goals were to rule out specific disorders, reduce symptoms and increase function in a patient. Patient evaluation includes

a comprehensive history with a review of past medical records, and a physical examination with specific focus to the affected organ system(s). Laboratory evaluation should be individualized, dependent on past testing and patient symptoms and, although standard baseline tests are helpful, exhaustive testing is not. The evaluation is principally designed to exclude disease requiring other specific medical therapy.

A post evaluation discussion with the patient is important. If "MCS" is an issue, its characteristics should be discussed frankly stressing that the cause is unknown but treatment options are available. According to Dr. Weaver the focus should be on symptoms rather than aetiologic considerations. Although treatment modalities can vary greatly, the most important is the supportive care approach and should be utilized in all "MCS" patients. Since many "MCS" patients do not trust the medical community, entrenched patient beliefs should not be aggressively challenged initially. Dr. Weaver emphasized that a great deal of patience is required by both physician and patient to develop a working relationship and establish trust in the face of a chronic condition surrounded by uncertainty and controversy.

Dr. Weaver noted that a number of therapies are being utilized in "MCS" patients including: supportive care; behavioral techniques including desensitization and psychotherapy; chemical avoidance and clinical ecology regimens such as provocation-neutralization protocols. The extent to which avoidance (particularly long-term avoidance) should be used is an extremely contoversial issue. In general there is great concern regarding the severe isolation that results when patients attempt total chemical avoidance, particularly since evidence of organ damage is lacking. It was stressed that the supportive approach is a primary treatment modality that should be employed for all "MCS" patients. The clinical ecology regimens have no role in the treatment of "MCS" patients since many of these regimens have known serious side effects and have not been studied for efficacy in contolled clinical trials.

Dr. H. Kipen (Environmental and Occupational Health Sciences Institute; University of Medicine & Dentistry of N.J-Robert Wood Johnson Medical School, US) briefly synopsized the issues which surround "MCS". The following points were stressed: 1) while clinical ecology offered a relatively easy target, it is noted that most "MCS" patients have not seen a clinical ecologist who may give patients understanding or misunderstanding; 2) we simply do not know what causes "MCS", the underlying mechanisms, toxicology, etc; 3) while we attempt to understand suspected causes of "MCS" we should investigate it as prevalent phenomenon independent of causation, and 4) it should be stressed that "MCS" overlaps with other syndromes particularly "chronic fatigue syndrome" ("CFS"), the symptoms of which are seen in a high percentage of "MCS" patients. (Fiedler et al., 1996).

Dr. Kipen suggested that the key question with regard to "MCS" is : are we studying causes (which are not easily verifiable) or a clinical phenomenon? He noted that "MCS" is best seen as a syndrome which may have a number of underlying causes or one underlying CNS biological cause which can keep much different company in terms of the accompanying major symptoms. In many ways research and conceptions of CFS can serve as useful models for how one might approach "MCS". Dr. Kipen emphasized that research in "MCS" is greatly hindered by the lack of a working or accepted definition which can be relatively uniformly applied by either experts or non-experts. Contentious issues to resolve in developing a definition(s) include: the role of psychiatric and medical co-morbidity (especially the methods for seeking and scope of the former); the importance of chemical initiation of the syndrome as opposed to subsequent triggering of symptoms (listing the key symptoms which could probably be accomplished as it was for "CFS") and the role of severity/disability as a qualification. Such a definition would facilitate varied clinical research and could be based on a combination of clinical and questionnaire instrument information. Scores on multiple scales of "MCS-ness" as proposed by Neutra et al., (1995) may be more useful for identification of patients/subjects than an unidimensional list of criteria.

Prof. H. Altenkirch (Spandau Hospital, Berlin) presented a video of 3 cases in which patients described "multiple chemical sensitivity syndrome" in their own words. In clinical neurology, videos are often used to present case histories and stimulate discussions on differential diagnosis. These 3 case histories presented, underscored the significance of differential diagnosis and the correct aetiological allocation of symptoms.

For all 3 patients, the presenting complaints were "MCS" symptoms and diagnostic criteria described by Cullen (1987) which were met. There were no abnormalities found in the physical neurological examination. Nonetheless, all three had different diseases that could be distinguished by differential diagnosis. These were: case 1: paranoid development and substance abuse (opiates); case 2: cerebral seizures with focal epilepsy and sleep -associated secondary generalized grand mal seizures and case 3: bipolar affective disorder with uniform symptoms. In all 3 cases the individual disease urgently required treatment, however adequate therapy did not take place.

In one illustrative case, a 30-year-old man reported that since 1989 he had been exposed to pesticides (organophosphates and permethrin) which were sprayed onto his clothes and bed linen in his bedroom. His symptoms consisted of fatigue, feeling of weakness, abdominal pain, light headedness, strong headaches, difficulty concentrating and memory loss. He observed

oversensitivity to fresh paint, solvents, pesticides and sprays which made him tired and restless and forced him to leave the room as quickly as possible.

The clinical neurological examination as well as all additional investigations including neurophysiological findings and neuroimaging showed no abnormalities. Cholinesterase and pyrethroid levels in serum and urine were normal. A sample of a wooden picture frame of a painting that the patient brought from his bedroom showed no indication of pesticides. Further inquiries revealed that his mother wanted to poison him to deny his inheritance. Additional investigations revealed that the patient had demanded prescriptions for opiates from different physicians. Final diagnosis: suspicion of paranoid development; suspicion of substance abuse (opiates).

IV. DESCRIPTION AND DEFINITIONS OF "MCS"

There is an apparent ever increasing demand by various social, political and economic forces in a number of countries that "MCS" be defined medically, even though scientific studies to date have not identified pathogenic mechanisms for the condition or any consistent objective diagnostic criteria (Sparks et al., 1994 a,b). Regulatory, legislative and occupational control responses are also dependent upon the critical distinction between psychogenic and organic aetiologies that might underpin a definition of "MCS" (Miller, 1994; Gots, 1995). The growing polarization of scientists, physicians and medical associations regarding the scientific basis of "MCS" (e.g., whether the syndrome or phenomenon is a psychogenic or a toxicodynamic disorder) coupled by the profusion and escalating number of synonyms attached to "MCS" (table 1), as well as the increasing public and media confusion concerning "MCS" has been frequently noted in many countries.

A number of definitions of "MCS" have been previously proposed. Cullen (1987) proposed the following definition of "MCS": 1) the initial symptoms acquired in relation to an identifiable environmental exposure (s), 2) symptoms involve more than one organ system, 3) symptoms recur and abate in response to predictable stimuli, 4) symptoms are elicited by low-level exposures to chemicals of diverse classes and 5) no standard test of organ system function can explain symptoms. Cullen's definition of "MCS" (primarily for research purposes) is currently the most widely used clinical definition for this condition.

Ashford and Miller (1992) proposed the following operational definition of "MCS" for diagnostic purposes, a definition that is based upon challenge testing: " The patient with "MCS" can be discovered by removal from the suspected offending agents and by rechallenge, after an

appropriate interval, under strictly controlled environmental conditions. Causality is inferred by the clearing of symptoms with removal from the offending environment and recurrence of symptoms with specific challenge". For research purposes, such testing shoulf be conducted using double-blind, placebo-controlled challenges.

The National Research Council definition is as follows: " 1) Sensitivity to chemicals. By sensitivity we mean symptoms or signs related to chemical exposures at levels tolerated by the population at large that is distinct from such well recognized hypersensitivity phenomena as I_gE-mediated immediate hypersensitivity reactions, contact dermatitis, and hypersensitivity pneumonitis. 2) Sensitivity may be expressed as symptoms and signs in one or more organ systems. 3. Symptoms and signs wax and wane with exposures. It is not necessary to identify a chemical exposure associated with the onset of the condition. Pre-existent or concurrent conditions, e.g., asthma, arthritis, somatization disorder or depression should not exclude patients from consideration" (National Research Council,1992).

The Ontario Ministry of Health Committee (1985) definition is as follows : Environmental hypersensitivity is a chronic (i.e., continuing for more than three months) multisystem disorder, usually involving symptoms of the central nervous system and at least one other system. Affected persons are frequently intolerant to some foods and they react adversely to some chemicals and to some environmental agents, singly or in combination, at levels generally tolerated by the majority. Affected persons have varying degrees of morbidity, from mild discomfort to total disability. Upon physical examination, the patient is normally free from any objective findings. Although abnormalities of complement and lymphocytes have been recorded, no single laboratory test, including serum I_gE is consistently altered. Improvement is associated with avoidance of suspected agents and symptoms recur with re-exposure".

Nethercott et al., (1993) proposed the following case definition for "MCS": 1) the symptoms are reproducible with exposure, 2) the condition is chronic, 3) low-level exposure results in manifestations of syndrome, 4) symptoms improve or resolve when incitants are removed and 5) responses occur to multiple, chemically unrelated substances.

In discussion, a number of participants proposed the consideration of different terminology to replace "MCS". For example, Dr. Gothe (Sweden) proposed the term "ESS" ("Environmental Somatization Syndrome") be employed to emphasize the uniform character of the syndrome which he outlined was related to chemical and physical components of the environment as well as ergonomic stress. The pathologic picture was consistent in that almost any symptoms might occur in "ESS"; different combinations of symptoms exhibited by "MCS"patients are common in "ESS" and the symptomatology was influenced by the alleged disease inducing agent. An additional

reason for consideration of a change in the definition for "MCS" was to address the fact that non-chemical triggers, e.g., electromagnetic fields (EMF) have been suggested as the cause of an "MCS" type of illness in Scandinavia (Gothe et al., 1995).

Dr Gots (US) recommended that until the aetiology is determined, a more descriptive and less categorical title for "MCS" and one which is less suggestive of causation would be "Environmentally Associated Symptoms" ("EAS").

Dr. Miller (US) offered the term "Multiple Chemical Intolerances" ("MCI") to circumvent the causation debate, and proposed that this term would still capture the most distinctive clinical feature of the phenomenon.

Following discussion of these proposals the term "Idiopathic Environmental Intolerances" ("IEI") was suggested to be employed in place of "MCS" for salient reasons delineated below and this was endorsed by the majority of participants of the Workshop. It should be noted that the term idiopathic is defined to mean that the condition is unclear or of unknown causation (pathogenesis).

DEFINITION

The majority of invited experts* supported the suggestion for the term "Idiopathic Environmental Intolerances" ("IEI") which would cover a number of disorders sharing similar symptomatologies including what is described as "MCS". A working definition was formulated as follows:

- acquired disorder with multiple recurrent symptoms
- associated with diverse environmental factors tolerated by the majority of people
- cannot be explained by any known medical or psychiatric disorders.

Diverse environmental factors includes: chemical (e.g., volatile organic compounds (VOCs)), biological (e.g., molds), physical (EMR) and psychological (e.g., stress).

There are no specific tests to establish the presence of "IEI". Certain tests are considered to be of no confirmatory value in clinical assessment, including the following: immunological testing, porphyria testing, neuroimaging, biological monitoring and alternative medicine methodologies.

V. AETIOLOGIES

It is well recognized that the lack of a uniform case definition for individuals with "MCS" has greatly hampered the investigation of aetiology. The criteria for study eligibility have varied depending on the target population (Terr, 1993; Sparks et al., 1994 a,b; Harrison, 1995; Sikorski et al., 1995). Aetiologic hypotheses have focused generally on either a primary physiologic or psychiatric aetiology to explain how chemicals produce the many polysymptomatic responses frequently noted in "MCS" patients. The aetiologies that have been suggested for "MCS" are:

. toxicological/physiological
. immunological
. neurological
. psychological/psychiatric
. respiratory
. olfactory-limbic
. violence in childhood
. porphyria

A. Immunologic hypothesis

It has been established in both animals and human beings that a number of environmental and occupational chemical exposures may affect the immune system with a variety of cellular and cell-mediated immunological effects (Gleichman et al., 1989; Sullivan, 1989; Bellant, 1991). For many years, proponents of "MCS" have focused on immunological mechanisms to explain the aetiology and pathogenesis of "MCS" (Rea, 1977; Rea et al., 1979; Levin and Byers, 1987). However published articles on investigations of the immunological status of "MCS" patients have found no consistent abnormalities in immunoglobulins, complement, lymphocytes, or B-cell or T-cell subsets; no evidence of increased autoantibodies, lymphocyte count, helper or suppressor cells, B or T cells and TAI^{+} or interleukin-2+ cells when compared to control subjects (Terr, 1986, 1993). Taken in sum, there is no currently compelling evidence that "MCS" is an immunological disorder (Terr, 1986; Albright and Goldstein, 1992; Simon et al., 1993; Sikorski et al., 1995). Further, patients with "MCS" have not been shown to have an unusual propensity to make autoantibodies, and their clinical symptoms and absence of any organ or tissue pathology provide no support for the autoimmune theory (Terr, 1993). However it has been noted that

immunological testing of "MCS" has been confined to a limited set of markers; future studies using other markers may be revealing.

B. Neurogenic Inflammation Hypothesis

"MCS" have been hypothesized to represent an amplification of the non-specific immune response to low-level irritants, since many individuals with "MCS" report a heightened sense of smell or develop symptoms at low levels of environmental exposure. Altered function of c-fibers, respiratory epithelium, or neuroepithelial interaction has been postulated to result in increased symptom reporting correlated with physiological abnormalities (Bascom, 1992; Meggs, 1993). A group of subjects with "MCS" have been reported to have significantly higher nasal resistance and respiratory rates (Doty et al., 1988). The neurogenic inflammation hypothesis remains principally untested and its relevance to the etiology of "MCS" remains to be determined (Harrison, 1995; Sikorski et al., 1995).

C. Olfactory-limbic hypothesis (model)

The olfactory nerves with their receptors in the nose, link the external chemical environment to the amygdala, hippocampus, hypothalmus and other parts of the limbic system. The limbic system ("primitive smell brain") is a phylogenetically ancient part of the brain present in all mammals. Since there is no blood-brain barrier at olfactory receptors, it is postulated that various substances can enter the olfactory bulbs via retrograde transport within the olfactory neurons. The olfactory bulbs lie in close proximity to the limbic area and supply much of the neural imput. Lesions in the limbic region have been suggested to be associated with many symptoms in patients reported with "MCS", e.g., irrational fears, feelings of strangeness or unreality, sadness, a sensation of being out of touch with or out of control of one's feelings and thoughts. Sensitization or kindling of olfactory-limbic pathways by acute or chronic exposure has been proposed as a putative mechanism for chemical sensitivity (Bell et al., 1992; Miller, 1992, 1994; Miller and Ashford, 1992; Ashford and Miller, 1995). In this hypothesized model for "MCS", sensitization to chemicals or foods parallels the phenomenon of time-dependent sensitization from drugs or non-drug stressors with heightened sensitivity to stimuli, gradual improvement following withdrawal , and reactivation of symptoms following reexposure (Bell, 1994; Harrison, 1995). The olfactory-limbic model remains to be further tested (Sikorski et al., 1995).

D. Psychiatric hypothesis

A large number of investigators in North America and Europe have concluded that many, if not most "MCS" patients, do not differ significantly from psychiatric patients who do not perceive their symptoms to have environmental triggers. Available studies to date suggest that "MCS" is not a distinctive diagnosis or syndrome. Some feel that the diagnosis of "MCS" has been incorrectly applied to too many patients. Individuals with "MCS" may be a heterogenous group of patients with various psychiatric disorders, either the cause of related or secondary to "MCS", such as depression, anxiety and a variety of somatoform disorders (e.g., phobias, hypochondrias, conversion disorder), somatization disorders and other common psychiatric disorders (Brodsky, 1984, 1987; Stewart and Ruskin, 1985; Schottenfeld, 1987; Staudenmayer and Selner, 1987; Terr, 1986, 1989; Black, 1993; Sparks et al., 1994 a,b; Harrison, 1995; Sikorski et al., 1995). It may also be the expression of a subconscious troubled by early life events such as childhood abuse (Staudenmayer, 1993). On the other hand, one cohort of rigorously defined "MCS" cases, assessed by standardized instruments, showed only a 26% prevalence of diagnosable psychiatric disorders (Fiedler et al., 1996).

Other investigators have argued that psychiatric and psychologic disorders may be a consequence, rather than a cause of "MCS" (Davidoff, 1992). The explanation that primary or misdiagnosed psychiatric disease may be the actual cause of "MCS" has been largely predicated on clinical experience lacking standardized case definitions, examiner blinding and appropriate comparison groups. However it should be also noted that some studies have demonstrated the role of psychologic mechanisms in the manifestation if not the etiology of "MCS" in individuals with the syndrome (Sparks et al., 1994 a,b; Harrison, 1995). It is generally acknowledged that considerable controversy continues to surround the aetiology, case definition, diagnosis and treatment of individuals with "MCS".

VI. DISCUSSION OF IDENTIFICATION AND DIAGNOSIS

There are neither widely accepted theories of underlying mechanisms nor validated clinical criteria for the diagnosis of "MCS", nor for "IEI". Clinical assessment should be designed primarily to rule out conditions requiring specific therapy. This involves a comprehensive history, physical examination, psychological/psychiatric assessment and laboratory testing designed to identify explanatory conditions which are deemed essential to uncover alternative diagnoses that require specific treatments. These clinical assessment procedures should be sufficiently

comprehensive to establish or rule out all other occupational and non-occupational disease conditions in the differential diagnosis.

There are no specific tests to establish the presence of "IEI". Certain tests are considered to be of no current confirmatory value in clinical assessment, including the following: immunological testing, porphyria testing, neuroimaging, biological monitoring and alternative medicine methodologies. The descriptor "IEI" should be used only after a thorough examination of patients and careful consideration of alternative explanations. Focused, interdisciplinary approaches for the diagnosis and treatment should be sought (including good quality toxicological, psychological/psychiatric and analytical advice) in order to provide more effective treatment of the patient.

VII. RESEARCH - PAST, PRESENT -

A. Human Research Priorities

"Idiopathic Environmental Intolerances" ("IEI"), as the name implies, describes an illness with an unknown aetiology but which nevertheless may be associated with, and often attributed by the patient or physician to, exposure to environmental factors. In this context, environmental factors is a broad term that includes external physical (e.g., electromagnetic radiation) and psychological (e.g., stressors) agents as well as a plethora of exogenous chemicals in air, water and food that are perhaps most often considered in relation to this malady. The aetiology of the disorder presumably may be exogenous, endogenous, or some combination of the two. Discriminating between these possibilities is a top research priority since the result will indicate whether "IEI" is psychological or organic (toxicological) in nature. Settlement of this cardinal issue will serve to identify the future direction of "IEI" research.

The key experiment is to determine in a double-blind challenge study whether subjects with "IEI" successfully discriminate between exposures to environmental factors (including those to which illness is attributed) and placebos. Chemicals (e.g., VOCs) might usefully serve as experimental agents given their frequency of association with "IEI", the possibility of administering substances of known purity, dosage and treatment duration, and the convenience of experimental design. If the subjective response (appearance of symptoms) of test subjects is able to discriminate between exposure to test chemicals and placebos, in a blinded design this would suggest the operation of a toxicological mechanism in which culpable agents interact with tissue targets to trigger a receptor-mediated pathophysiological reponse. Confidence in the existence of

this mechanism would increase greatly if the severity of the response was shown in individuals to be related to the dosage and if the response could be blocked by a competing substance (none currently known). If, on the other hand subjects were unable to distinguish between exposure to test chemical and placebos, this would suggest the operation of psychophysiological factors which did not require exogenous chemical activation of a tissue receptor site.

The selection and handling of test subjects is an important consideration. In general, cooperative patients reporting a constellation of robust symptoms should be selected as cases for study. While the proposed experiments can be conducted using individual cases with subjects serving as their own control, comparison of responses between subjects requires a population with uniform characteristics. For example, given that women between the ages of 30 and 40 years appear at high risk for "IEI", this is a convenient population from which cases might be drawn. Factors such as ethnicity and socioeconomic status might also be controlled. Matched subjects would serve as controls in the event these were incorporated into the study (vide infra). Ideally, cases should have a recent (e.g., up to 5 years) onset of "IEI" but be asymptomatic prior to chemical challenge. Cases may be justifiably studied after environmental factors believed to obscure the alleged trigger have been removed if the effects of the ("unmasking") procedure itself are understood. In some instances, it may be possible for the test procedures to take place in a familiar setting (e.g., general atmosphere) rather than in a booth or specially constructed environmental chamber/room, especially if the effects of these environments in the absence of the test articles are unknown. Procedures should be carried out with standardized protocols and with repeated challenges. Detailed methodologies have been proposed (US NIEHS "MCS" Workshop, to be published).

Strength might be added to the experimental design with the introduction of control groups: (a) one serving as a negative control would consist of matching, healthy subjects with no complaints of environmental chemical intolerance, (b) the other serving as a positive control group in which expected responses could be demonstrated. Positive controls, which might include subjects with known intolerance for caffeine or alcohol (disulfuram), serve to demonstrate to others that the observer is able to demonstrate a predictable response to a test agent.

Measures of responses to environmental challenges should include objective physiological changes in test subjects and controls. Examples include: EEG, EKG, blood pressure, skin galvanic responses and psychological measures. More elaborate methods, such as SPECT or functional MRI are not needed at this phase of investigation but may be useful as research tools to evaluate mechanisms underlying subject responses. Unvalidated measures, such as certain immunological and toxicological screens should be avoided.

1. Subjects Able To Distinguish Between Test Agents & Placebos

Subjects who are able successfully to distinguish between chemical triggers of symptomatology and non-provoking placebos provide evidence of the possible existence of an interaction between exogenous triggers and target tissue sites. Attempts to strengthen this association should be sought by demonstrating that the time to onset and/or severity of symptomatology correlates with dose, again using negative and positive control groups, the latter showing the expected presence of dose-dependent phenomenology. Demonstration that cases exhibit symptomatology in proportion to the concentration of test articles used in the challenge would provide compelling evidence that physiological changes are in part mediated by interaction of the offending substances with tissue targets.

Further research might focus on the characterization of organ changes underlying prominent symptoms. For example, complaints of cognitive dysfunction (spaciness, concentration and memory difficulties) would merit studies using brain imaging methods. Muscle and joint complaints might call for investigational studies of circadian cortisol patterns.

For mechanistic investigations, cases with "IEI" might usefully be studied alongside non-IEI subjects with chemical intolerances who display physiological (e.g., pregnant women) or pathophysiological changes (subjects dosed with disulfuram or serotonin-reuptake inhibitors).

Any objective demonstration of a human response to a wide range of chemicals below the threshold for either conventional toxicological effects or subjective detection would pose difficult challenges for toxicologists, which would then need to be addressed. Questions that might be posed include: (1) Is there a generalized reduction of xenobiotic metabolism in "IEI" cases because of genetic polymorphism (e.g., P450 subtypes, A-esterases, multi-drug-resistance genes). If so, why are effects not compound-specific (mirroring those seen in normal subjects at higher doses? (2) Are there novel toxic target sites/mechanisms in "IEI"? If so, how might they be responsive to a wide range of disparate chemicals?

2. Subjects Unable To Distinguish Between Test Agents & Placebos

Cases who are unable to discriminate by symptomatology on repeated challenge between test agents and placebos provide putative evidence that "IEI" is a psychological disorder which, while potentially stimulated by the presence of chemicals, employs no toxicological mechanism to effect the perceived pathophysiological response.

In this event, the overarching concern would be the mechanism by which environmental factors, or the perception thereof, induces a pathophysiological response. High on the list of possibilities are conditioned or other learned responses: of these, the possible existence of a specific event in the past which initiated susceptibility to the subsequent presentation of environmental triggers would merit priority consideration. For example, an environmentally intolerant subject may have been exposed to an agent (e.g., pesticide, combat stress, hyperthermia) that resulted in the unequivocal induction of adverse health effects which, after recovery, are subsequently recapitulated by diverse environmental stimuli normally tolerated by the populace. This type of conditioned response might initially be sought by an epidemiological approach in which either prospectively or retrospectively selected subjects are studied in a population-based approach Populations suitable for such studies should be cooperative and homogenous for retrospective study (e.g., sick-building occupants) or prospective study (e.g., personnel hired into the chemical industry or as pesticide applicators). A key question is the presence or absence of a putative conditioning event; a priori, this might be a distressing transient reaction to a chemical poisoning or a transient psychological stress situation that was temporally associated with an innocuous chemical exposure.

Subjects with a psychological basis for "IEI" might be usefully studied alongside individuals with other distinct psychological disorders, which can be triggered on demand by environmental cues (e.g., carbon dioxide, spiders) other than the factors (e.g., other chemicals) under study in "IEI". For example, comparative physiological monitoring of brain and somatic functions in subjects with "IEI" and arachnophobia might serve to reveal commonalities in these endogenously generated disorders. Research on basic personality dynamics may also help to identify individual susceptibility factors.

3. Other Research Priorities

Once the nature of "IEI" has been elucidated, appropriate models should be developed in suitable laboratory species. An animal model of "IEI" would be a valuable tool (1) to research the relationship between biochemical and behavioral changes, (2) to use as a test-bed for the development of effective therapeutic intervention. Approaches to the development of animal models have been discussed elsewhere (US EPA, 1994).

3. Recommendations on Epidemiology

For research studies, the broad definition of "IEI" has to be further refined. Subdefinitions have to be formed according to specific research interests and needs and situations in different countries. Epidemiologic studies reflect health and disease in populations as opposed to individual cases. Epidemiology includes careful observation,counts of well-defined cases and the demonstration of relationships between cases and risk factors.

Epidemiologic studies are needed:

1) to find out the prevalence and incidence of "IEI" and define those individuals who meet the case definition of "IEI" with respect to demographic factors such as gender, age and sex.

2) to address the question whether the prevalence of the phenomenon in a particular group is increased or decreased and what is the baseline for such statements. If there is a change, to what is it attributable? For example: a) prevalence is influenced by a high interest towards this phenomenon in medicine or only locally due to local reasons; b) the medical community is not well informed and neglects the problem; c) the medical community is hesitant about the diagnosis as it does not believe this phenomenon to be a medical problem; d) the prevalence is influenced by media effects.

3) to assess the need for further research based on the "burden of illness" (e.g., prevalence and severity of illness) documented in these studies.

4) to identify cases for further critical scientific workup. From this patient-grou, persons could be selected who fullfill criteria for studies as outlined in the research recommendations.

5) to test hypothesized causal relationships between "IEI" and various proposed causative risk factors (mechanisms). Experimental, case-control, cohort and/or cross-sectional designs could be employed.

6) to study the natural history and prognosis of "IEI" and evaluate the efficacy and effectiveness of advocated therapeutic interventions.

7) to define the relationship between subcategories of "IEI" and between "IEI" and other idiopathic conditions such as "CFS".

VIII. PRACTICAL IMPLICATIONS AND PRIORITIES

Part (c) of the "IEI" case definition excludes any known medical or psychiatric disorder as an explanation for the symptoms. A number of Workshop participants expressed a wide range of interpretations as to what constitutes a known medical or psychiatric disorder. Known disorders could be interpreted broadly to include asthma, depression, or even somatoform disorder. On the other hand, known disorders may be restricted to those with a well defined primary aetiology, e.g., hypothyroidism, allergic asthma, or simple phobia. The broader the exclusion criteria, the greater the risk of defining away conditions that might have an exogenous chemical aetiology. In order to be useful, any exclusion criteria should be tightly defined.

Dr. Ray (UK) suggested that if "IEI" is found to be a valid entity, then the presence of a minority ("IEI") population with very markedly greater susceptibility to environmental chemicals then the normal population (for whom current safety margins are calculated) would have far reaching practical and financial consequences. In such a situation, possible strategies would involve either specific therapeutic measures based on toxicological mechanisms or avoidance of exposure to "IEI" sufferers or, alternatively, the setting of new low safety limits so as to protect all individuals. If, however, "IEI" is found not to be a valid entity, the action can be restricted to appropriate psychological treatment for individual sufferers.

In addition to the direct health implications of "IEI", there are two important implications for conventional chemical toxicology:

1. Where "IEI" is prevalent in a population, then it becomes difficult to carry out conventional toxicological investigations of the health effects in such a population. It is generally possible to detect adverse effects across a population because the lowest exposure quartile will show minimal changes. The presence of a significant subpopulation with "IEI" (objective or subjective) would lead to positive effects even in the lowest quartile, thereby diluting the power of any analysis. Any survey of such a population would therefore have to carry a selection of questions designed to seggregate "IEI"-like responders from the normal population.

2. Overenthusiastic diagnosis of "IEI" without paying sufficient attention to the elimination of conventional diagnoses would lead to underestimation of conventional, specific, toxic effects and also to inappropriate therapy.

Dr. Miller (US) suggested that because of the possibility that "Idiopathic Chemical Intolerances" could have an organic basis in some individuals, it is important that, in the interim, while research to settle these questions is underway, patients be provided adequate access to sympathetic caregivers and those social support services and accomodations needed to prevent personal hardship.

It should be noted that Dr. Kipen, following the Workshop Meeting, expressed his dissent to the conclusions as follows: "While there was widespread support of the invited participants for most of the components of the report and conclusions, the central idea of whether or not a name change should occur was not unanimously agreed upon. Those opposed to the name change, included Dr. Kipen, the chair of the workshop, among others. It is further understood that the term "idiopathic" has a number of meanings, and that the definition used for purposes of this workshop is that the condition is of unclear or unknown pathogenesis".

Following the Workshop Meeting, Dr. Miller suggested "that the conclusions and recommendations would have been far stronger (no name change, no attempt to exclude psychological diagnoses from consideration as possible manifestations of MCS) had the participation been more balanced".

IX. CONCLUSIONS AND RECOMMENDATIONS

The following Conclusions and Recommendations were endorsed by the majority of invited participants.

A. Conclusions

It is recognized that there are patients who report a variety of unexplained environmental intolerances. It is acknowledged that these patients do suffer and that they need compassion and professional help.

The term "Multiple Chemical Sensitivities" ("MCS") should be discontinued because it makes an unsupported judgement on causation. Although there exist several definitions of what has been called "MCS", it cannot be regarded as a clinically defined disease. There are neither

accepted theories of underlying mechanisms nor validated clinical criteria for diagnosis. A relationship between exposures and symptoms is unproven.

A more appropriate descriptor is "Idiopathic Environmental Intolerances" ("IEI"). This term incorporates a number of disorders sharing similar symptomatologies, including what is described as "MCS". The descriptor may be qualified by the putative origin of the disorder, e.g., "IEI (chemical)".

A working definition of this disorder is that it is:

- an acquired disorder with multiple recurrent symptoms
- associated with diverse environmental factors tolerated by the majority of people
- not explained by any known medical or psychiatric/psychologic disorder

Clinical assessment should be designed to rule out conditions requiring specific therapy. Appropriate evaluation should be based on a biopsychosocial understanding of the patient. This involves history, physical examination, psychological/psychiatric assessment, and laboratory testing designed to identify explanatory conditions. This is essential to avoid misdiagnosing conditions that require specific treatments.

There are no specific tests to establish the presence of "IEI". Certain tests are considered to be of no confirmatory value in clinical assessment, including the following: immunological testing, porphyria testing, neuroimaging, biological monitoring and alternative medicine methodologies.

Effective treatment has not been validated in controlled clinical trials. It will probably evolve from an understanding of the nature (e.g., psychogenic, toxicogenic) of "IEI". For example a demonstratable psychogenic origin would demand psychological/psychiatric intervention; a toxicogenic origin would call for exposure minimization. There is no justification for aggressive and potentially harmful methodologies (e.g., chelation therapy) or other purported detoxification procedures (e.g., vitamins, mineral supplementation, herbal therapy or sauna detoxification).

In the present state of uncertainty concerning "IEI" causation, and therefore appropriate treatment, approaches based on understanding and supportive care are necessary. In addition there are two common approaches, exposure avoidance and psychological/psychiatric therapy. In some instances the implementation of methods to avoid or minimize exposure to possible environmental triggers may be appropriate; however, isolation of patients from the general environment may have adverse consequences. Psychological/psychiatric approaches currently include self-regulation

(relaxation, biofeedback), behavioural therapy (desensitization), psychopharmalogical treatment, cognitive therapy and insight-oriented therapy, tailored to the individual's condition.

Human research is urgently needed to determine the nature (e.g., psychogenic, toxicogenic) of "IEI" since the outcome will influence public policy and clinical practice for IEI prevention and treatment respectively. The key question is whether subjects with "IEI" are able to discriminate in double-blind placebo-controlled challenge studies between reported environmental (e.g., chemical) triggers and placebos. Ability to discriminate suggests a toxicological (i.e., chemical-receptor) mechanism. Inability to discriminate would suggest a psychogenic (e.g., conditioned or other learned) mechanism.

B. Recommendations

1. Diagnosis

- The descriptor "IEI" should be used only after a thorough examination of patients and careful consideration of alternative explanations.

- Focused, interdisciplinary approaches for the diagnosis and treatment of these patients should be sought in order to provide more efficient and effective treatment. These include good quality toxicological and analytical advice.

2. Research

Research on IEI should be given high priority.

- Challenge studies to distinguish psychogenic from toxicogenic or other responses are deemed essential and urgent. These are necessary to define the nature and origins of environmental intolerances so that effective treatment, public health protection and policies can be developed and implemented. Such studies are research prerequisites which must precede further mechanistic studies.

- Epidemiological research should be directed at the prevalance of relevant symptoms and correlates such as demographics, time trends and the concurrent presence or absence of

known and unexplained conditions (e.g., Chronic Fatigue Syndrome (CFS), "Gulf War Veterans' Illnesses"). Risk factors could be sought in case control studies.

3. Communication and Cooperation

- Scientific research on IEI will lead to an improved understanding of environmental hazards that should lead to improved risk communication. Public information should be based on established facts and not on speculation.

- Cooperation should be established between all responsible health care systems, institutions and insurers, in order to coordinate approaches to patients with IEI.

- WHO should promote continuous exchange of knowledge and international cooperation on research into "IEI".

TABLE 1 NAMES ASSOCIATED WITH "MULTIPLE CHEMICAL SENSITIVITIES"

- ALLERGY TOXEMIA
- AUTOINTOXICATION
- CEREBRAL ALLERGY
- CHEMICAL AIDS
- CHEMICAL HYPERSENSITIVITY SYNDROME
- CHEMICALLY INDUCED IMMUNE DYSREGULATION
- CHEMICAL SENSITIVITY
- CLINICAL ECOLOGY SYNDROME
- ECOLOGICAL ILLNESS/DISEASE
- ECO-SYNDROME
- ENVIRONMENTAL ILLNESS
- ENVIRONMENTAL HYPERSENSITIVITY
- ENVIRONMENTAL MALADAPTATION
- ENVIRONMENTAL SOMATIZATION SYNDROME
- ENVIRONMENTAL STRESS SYNDROME
- HYPERSUSCEPTIBILITY
- IMMUNE DYSFUNCTION SYNDROME
- NON-SPECIFIC HYPER-RESPONSIVENESS
- ORGANIC BRAIN SYNDROME
- ORGANIC SOLVENT SYNDROME
- PETROCHEMICAL PROBLEM
- PERSIAN GULF WAR SYNDROME
- PSEUDO-ALLERGY
- TOTAL ALLERGY SYNDROME
- TWENTIETH CENTURY DISEASE
- UNIVERSAL ALLERGY

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ANNEX A

MCS Workshop[1]
21-23 February 1996, Berlin

Organised in collaboration by the International Programme on Chemical Safety (UNEP-ILO-WHO), the Federal Ministry of Health (BMG), the Federal Institute for Health Protection of Consumers and Veterinary Medicine (BGVV), and the Federal Environmental Agency (UBA).

OUTLINE PROGRAMME

Wednesday, 21 February

Registration
Opening Session - Official Speakers
Mr F.J. Bindert, Federal Ministry of Health (BMG)
Prof. A. Somogyi, Federal Institute for Health Protection of Consumers and Veterinary Medicine (BGVV)
Prof. H. Lange-Asschenfeld, Federal Environmental Agency (UBA)
Dr E. Smith, IPCS - Objectives of the Workshop - Administrative announcements
Appointment of Chairman, Vice-Chairman and Rapporteurs

SHORT PRESENTATIONS BY INVITED EXPERTS
Introductory

Prof. H. Altenkirch - "*MCS; a European perspective*"
Dr R.Gots - "*MCS; a US perspective*"
Dr F.Li - "*MCS; a Canadian perspective*"

Toxicology, immunology, environmental illnesses

Dr C-J. Göthe
Dr L. Fishbein
Dr E. Ray
Dr B.Heinzow
Dr C. Miller

Neurology, behavioral, sensory irritation

Prof. W.A. Nix
Dr P.S. Spencer
Prof. G.Kobal
Dr A.C. Ludolph
Dr H. Staudenmayer
Dr M. Hüppe

[1]A WHO Workshop is a meeting for the exchange of technical and scientific information. The emphasis is on free discussion, exchange of ideas, and practical application of skills and principles.

Clinical investigation and diagnosis

Dr S.Dewey
Dr V.M. Weaver
Prof. H.M. Kipen
Prof. H. Altenkirch

General discussion; identification of issues

Thursday, 22 February

Discussion in plenary session and in *ad hoc* panels

Friday, 23 February

Discussion
Outline of report
Conclusions and recommendations
End of Workshop

ANNEX B

MCS WORKSHOP - 21-23 February 1996

Invited experts

Prof. H. Altenkirch, Spandau Hospital, Department of Neurology, Humboldt University, Berlin, Germany (**Joint Rapporteur**)
Dr S. Dewey, Medizinische Klinik, Forschungsinstitut, Borstel, Germany
Dr L. Fishbein, Fairfax, Virginia, United States (**Joint Rapporteur**)
Dr C.-J.B. Göthe, AB Ekiatrika, Stockholm, Sweden
Dr R.E. Gots, Environmental Sensitivities Research Institute, Rockville, Maryland, United States
Dr B. Heinzow, Landesamt für Natur und Umwelt, Kiel, Germany
Dr M. Hüppe, Lehrstuhl für Psychologie der Universität, Würzburg, Germany
Prof. H. Kipen, Environmental & Occupational Health Sciences Institute, State University of New York, Piscataway, New Jersey, United States (**Chairman**)
Prof. G. Kobal, Institut für experimentelle und klinische, Pharmakologie und Toxikologie, Friedrich-Alexander-Universität, Erlangen, Germany
Dr F. Li, Health Protection Branch, Health Canada, Ottawa, Canada
Prof. A.C. Ludolph, Universitätsklinikum Charité, Universitätsklinikum und Poliklinik für Neurologie, Berlin, Germany
Prof. C. Miller, Environmental & Occupational Medicine, Department of Family Practice, University of Texas Health Science, San Antonio, Texas, United States
Prof. W.A. Nix, Universitätsklinikum, Klinik und Poliklinik für Neurologie, Mainz, Germany
Dr D.E. Ray, Medical Research Council Toxicology Unit, University of Leicester, Leicester, United Kingdom
Prof. P.S. Spencer, Center for Research on Occupational and Environmental Toxicology Oregon Health Sciences University, Portland, Oregon, United States
Prof. H. Staudenmayer, Allergy Respiration Institute, Denver, Colorado, United States
Dr V.M. Weaver, Division of Occupational Health, Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland, United States

Secretariat

Dr I. Paulini, Federal Environmental Agency (UBA), Berlin, Germany
Dr E. Smith, International Programme on Chemical Safety, World Health Organization, Geneva Switzerland

ANNEX C

Representatives and Observers

Federal Ministry of Health (BMG), Berlin, Germany
Mr F.J. Bindert
Dr J. Blasius
Dr W. Töpner

Federal Institute for Health Protection of Consumers and Veterinary Medicine (BGVV), Berlin, Germany
Dr K.E. Appel
Dr A. Hahn
Dr G. Heinemeyer
Dr W. Lingk
Prof. A. Somogyi

Federal Environmental Agency (UBA), Berlin, Germany
Prof. H. Lange-Asschenfeld
Prof. W. Schimmelpfennig
Dr B. Seifert

Federal Ministry of the Environment, Nature Conservation & Nuclear Safety, Bonn, Germany
Dr R. Türck

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Dr D. Arndt

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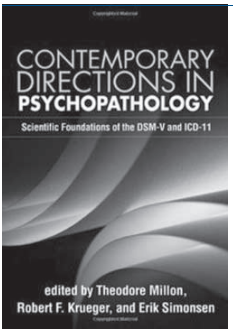
ANEXO II:

The British Journal of Psychiatry (2011) 198, 160–164.

Book reviews

Edited by Allan Beveridge, Femi Oyebode and Rosalind Ramsay



Contemporary Directions in Psychopathology: Scientific Foundations of the DSM–V and ICD–11

Edited by Theodore Millon, Robert F. Krueger & Erik Simonsen. Guilford Press. 2010. US$85.00 (hb). 636pp. ISBN: 9781606235324

The present volume contains 30 chapters by a variety of experts, dealing with conceptual issues that need to be considered in preparation for the next revision of our classifications. The great change in psychiatric classification came with DSM–III, which consisted of 265 mental disorders and replaced clinical descriptions – where the task of the clinician was to recruit the patient to the nearest description – with the Chinese menu, now familiar to us all. Lee Robins pointed out that the rule laid down was that any given symptom could only appear in one disorder. She concluded: 'I thought then, and I still do, that the rule was not a good one, because it deviates from the practice in the rest of medicine, where many diseases share symptoms' (p. 268). Thus, although previously anxious symptom had been seen as an integral part of what was then 'neurotic depression', anxiety now had to be reassigned to anxiety disorders. Sadly, the arbitrary diagnostic rules built into our classification systems impose tunnel vision on many clinicians, who tend to reify the disorders described and no longer appear to notice symptoms which are there before them. Since then, successive versions of the DSM have added 89 new disorders, and abandoned diagnostic hierarchies, so giving birth to 'comorbidity'. Recently work has been divided into topic groups, but 'each working group was reluctant to give up their rights to a particular domain, even when it might have been better categorised elsewhere' (p. 61).

When the American Psychiatric Association began to consider changes in preparation for DSM–V the problems seemed to be that many patients were found to have multiple comorbidity, that many more were diagnosed as 'not elsewhere classified', and that the categorical dichotomies of the DSM system might be supplemented by a dimensional system to allow various degrees of severity of a disorder to be recognised. Ortigo and others argue for a prototype diagnostic system, where each diagnosis would be rated on a 5-point scale, ranging from a poor to a perfect match to a prototype (p. 377).

Maj (p. 263) considers two questions, whether mental disorders are really as common as community surveys suggest that they are, and whether comorbidity can really be so common. He argues that there can be no firm answer to the first problem, and makes cogent objections to the latter. Zachar & Kendler (p. 127) distinguish between 'disease realists', who consider that there are qualitative differences between true diseases and normality, between which Nature has beneficently provided joints, and empiricists, who reject these assumptions, and seek to make connections between observable phenomena. For them, validity refers not to whether a disease is really there, but to what kinds of inferences one can make about a patient on the basis of a particular diagnosis. The differences between these fundamentally different approaches to classification echo throughout the volume.

Many of the papers by psychologists clearly take the latter approach, for example those by Krueger's group on the meta-structure of the diagnoses produced by the DSM–IV system. Yet unless the metastructure can be radically simplified the comorbidity problem is insoluble, and rival working groups will jealously hold on to their symptoms. The editors do not attempt to draw any general conclusions at the end, and indeed it would be impossible to do so.

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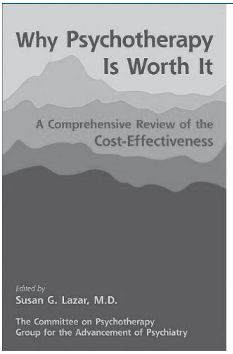

Psychotherapy Is Worth It: A Comprehensive Review of the Cost-Effectiveness

Edited by Susan G. Lazar. American Psychiatric Publishing. 2010. US$60.00 (pb). 359pp. ISBN: 9780873182157

Like a well-known cosmetic advert, this book makes psychotherapy beautiful: a book that proves we are worth it! As in all slogans there is some truth mixed with spin.

The book is divided by diagnosis and most chapters follow a logical format. Why is the condition important? For example, Rosenblatt states that anxiety disorders are 'one of the most expensive disorders', accounting for 31% of mental health costs at US$46.6 billion in one year. This makes a compelling argument that mental health desperately needs cost-effectiveness studies. But there is too little on the quality criteria for health economics papers to allow readers to critique the studies effectively.

The methodology is basically a simple search strategy plus literature reviews. Here is where the promise is more than the reality: the authors simply use 'cost' as a principal search term and produce lots of studies about the overall costs of disorders with estimates of cost reduction. There are very few studies using established methodologies to assess cost-effectiveness. The best studies are summarised with tables to allow comparisons.

The sting is often in the tail, for example in the conclusions to the anxiety chapter:

> Although there are increasing data that specifically measure the cost-effectiveness of psychotherapy for the anxiety disorders, a strong case can be made . . . simply by considering the available data documenting the high costs of these illnesses and data indicating the cost of effective treatment. (p. 116)

Given the book's subtitle, such an inexhaustive approach is disappointing but perhaps inevitable as we know already there are not enough health economics studies to fill a whole book. Nevertheless, this is a good compendium of research and is generally up to date. The discussions have a strong US bias, but unlike many books of this type there is a reasonable coverage of non-American studies. The emphasis on diagnosis, however, limits the book too much, although a good chapter on medical conditions mitigates this.

For anyone trying to convince service commissioners that non-drug treatments are effective this book is invaluable. It argues cogently that psychotherapy can be cost-effective, but that is a big step from saying that it always will be, as cost-effectiveness depends crucially on how a service is delivered.

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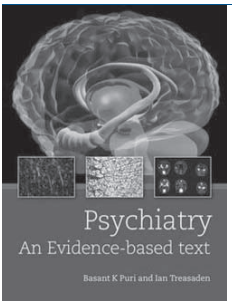

Psychiatry: An Evidence-Based Text

Edited by Basant K. Puri & Ian Treasaden.
Hodder Education. 2009.
£125.00 (hb). 1323pp.
ISBN: 9780340950050

This is the newest addition to the standard texts for trainees preparing for the MRCPsych examination in the UK and Ireland. The breadth of topics covered is impressive and includes a history of psychiatry, basic psychology, statistics, neurosciences (including neuroimaging and anatomy), mental disorders, and medical and psychological management. The book touches on clinical specialties, management of mental health services and legal and ethical aspects of psychiatry, as well as subjects infrequently covered in other texts: emergency psychiatry, chronic pain and palliative care. Some of the chapters are supplemented with a reading list.

The book makes abundant use of tables, images and summary boxes. The sections on basic psychology and psychological therapies are likely to be sufficient for those preparing for the MRCPsych exam. This may sweeten the pill of the hefty price tag and obviate the need for additional textbooks. In the chapters covering mental illness, common pathologies are covered alongside the less common ones: psychosexual disorders and paraphilia. The sections on functional disorders are extensive and, rather perturbingly, the chapter on multiple chemical sensitivities is considerably longer than the one on schizophrenia. The ICD–10 and DSM–IV criteria are provided for some disorders but omitted in others. This may prove frustrating to those preparing for exams who wish to have all the relevant information to hand.

Despite these few shortcomings, this book will provide a solid reference source which can confidently take its place next to its more established rivals.

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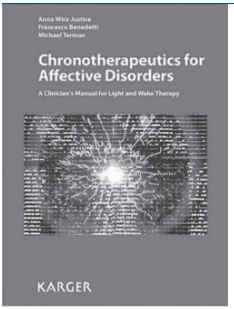

Chronotherapeutics for Affective Disorders: A Clinician's Manual for Light and Wake Therapy

By Anna Wirz-Justice, Francesco Benedetti & Michael Terman.
Karger. 2009.
US$48.00 (pb). 116 pp.
ISBN: 9783805591201

This book has three stated aims. The authors present the theory behind chronobiological treatments for affective disorder, document evidence of their efficacy and provide a step-by-step guide to clinicians as to how these therapies might be implemented. My main criticism of the book is that the balance between these three areas may not be optimal.

Manuals should probably instruct readers in how to do something rather than explain in depth why they should do it. However, whereas the guide to the implementation of chronotherapeutic techniques is detailed, the theory underlying these techniques merits expansion and I felt that evidence for their effectiveness was significantly lacking. For example, the efficacy of bright light treatment for non-seasonal depression is affirmed in fewer than 100 words, with only two references. In some European countries, chronotherapeutics are quite widely used and in Milan it is apparently routine for in-patients on medication for non-seasonal depression to receive light therapy and a single session of late-night wake therapy at the start of treatment. By contrast, in the UK, the authors would be preaching chronotherapeutics to the unconverted; most psychiatric professionals will need to know why they are using a treatment, not least because they might be asked by the patient.

Despite these criticisms, I found the book to be useful and engaging. It is well written and elegantly illustrated and it links to an informative website (www.cet.org) for the Center for Environmental Therapeutics, a non-profit agency dedicated to education and research in environmental therapies. The difficulties inherent in researching and promoting such therapies, in contrast to the international resources of the pharmaceutical industry, are noteworthy.

Most psychiatrists will have patients with unipolar or bipolar depression who are resistant to other treatments and this book may help to see them, literally, in a different light. There is a very useful level of detail about light therapy, including ways of estimating the best time of day at which it can be prescribed, since this varies between individuals. Helpful illustrative schedules are

given for using light therapy alone, wake therapy plus light therapy and wake therapy plus light therapy plus sleep phase advance. There are informative sections on the use of melatonin and the practicalities of light therapy, including recognition that motivated and knowledgeable night nurses are required to competently implement some of the chronotherapeutic techniques with in-patients.

Overall, I feel that clinicians who work with patients with affective disorders should gain new and significant insights from reading this book.

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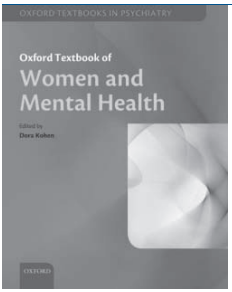

Oxford Textbook of Women and Mental Health

Edited by Dora Kohen.
Oxford University Press. 2010.
£75.00 (pb). 352pp.
ISBN: 9780199214365

I wanted to like this book; I knew and respected Professor Kohen although I did not always agree with her. Healthy debate has, however, always formed an important part of the Royal College of Psychiatrists' Women in Psychiatry Special Interest Group, to which Professor Kohen brought her extensive intellect and unique perspective.

The book is advertised by the publisher as including chapters by leading experts in their respective fields providing 'the most authoritative information available'. There are contributions from academics in Canada, England, India, Ireland, Switzerland and Turkey. Some are indeed leading experts; however, others are not and despite their best efforts in some chapters this shows.

Although I enjoyed reading many of the chapters, I found the overall structure of the book rather confused. Part 1 focuses on 'Fundamental aspects: women and mental health'. This was an enjoyable section covering issues such as stigma, violence and ethnicity. I was pleased to see a chapter on lesbianism and mental health, an area much neglected in contemporary research despite the health inequalities experienced by lesbians. I particularly enjoyed the useful introduction to biological sex differences relating to mental health, but was disappointed that this was not followed up with specific coverage of gender differences in prescribing (although this was actively considered in the section on intellectual disability later in the book).

I found Part 2, 'Clinical aspects: women and mental health', less coherent. Under the heading of mental illness a number of disorders such as anxiety, depression, borderline personality disorder and schizophrenia are considered, yet post-traumatic stress disorder is not; this was addressed as a 'special clinical topic' in Part 3. There is a specific section on perinatal psychiatric disorders and, importantly, parental psychiatric disorders are also considered. Specific focus is also given to substance misuse, eating disorders and women with intellectual disabilities. I was surprised not to find a section on the mental health difficulties and challenges faced by older women.

I support the arguments of this book; it highlights, from a multidisciplinary perspective, some of the essential issues facing women in the context of their daily lives and how these issues relate to their mental health. I welcome an approach that considers women's different roles as carers, parents, workers and partners. Overall the chapters were succinct, well written and comprehensive. I accept that no book can cover all areas of such a broad topic, but in parts the coverage was lacking. If you expect a 'practical' text focused on service delivery, then you will be disappointed but if you accept that this is not a practical guide, then this book is a noteworthy addition to the literature.

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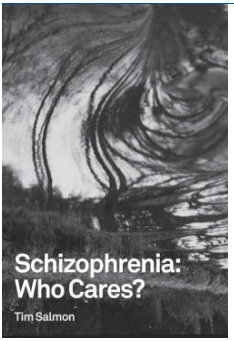

Schizophrenia: Who Cares?

By Tim Salmon.
Artaxerxes Press. 2010.
£12.00 (pb). 178pp.
ISBN: 9780956507006

I found this book to be a bit of a long gripe at times, but nonetheless a salutary one. Before embarking on it I kept in mind three questions: Will it provide comfort/advice/guidance to other carers? Will it make mental health professionals more aware of the plight of the carer? Will it offer insights on what carers actually need in terms of support? The answer to all three questions is yes, in parts.

The book relates a 20-year history of a father not only struggling to come to terms with his son's schizophrenia, prompting guilty, soul-searching questions, but also having to cope with the idiosyncrasies of the caring system, which apparently often failed both him and his son. Father deserves admiration for the courage, resilience and sheer utter resolve not to abandon a son in distress, even when he behaved in an appalling, bewildering and risky manner, living between the extremes of 'constant worry, increasing anxiety and heart-in-mouth horror'. Salmon describes the incomprehensible institutional routines, the Kafkaesque bureaucratic system, constant changes in policy and personnel, and the 'impersonal system of care', which fails to take into account the inability of a person with a mental illness to navigate its forms and procedures, constantly fails to deliver despite good intentions and high-sounding but empty rhetorical words (consultation, empowerment, normalisation, accessibility, flexible pathways,

well-being agenda, therapeutic optimism, preventing revolving doors, early intervention, social inclusion) and, in the words of the author, all that 'brouhaha'. More often than not he was left having to do all the provision himself.

In terms of ideas helpful to services Salmon does offer some insights. He stresses the need to involve carers more effectively when drawing care plans that are feasible and implementable, an awareness that people with schizophrenia are particularly sensitive to defensiveness, insincerity or discomfort in staff and more likely to react in a violent or bizarre manner when faced with uncaring professionals, and the need for straight and frank communication when establishing a prognosis and therapeutic hopes.

Although at times I was uncomfortable at his comments expressing a hint of resentment against other 'creeds and races' (both patients and staff) who often populate admission wards and poor estates, and the deference he showed the medical profession as opposed to other mental health workers, I do agree with the overriding message that we have a long way to go to work alongside carers in a mutually sharing system of care. I would recommend this book for care coordinators and those interested in more responsive and engaged services.

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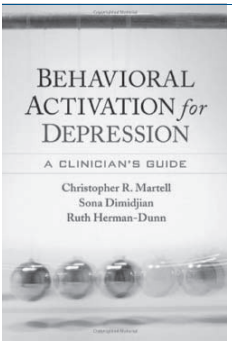

Behavioural Activation for Depression: A Clinician's Guide

By Christopher R. Martell, Sona Dimidjian & Ruth Herman-Dunn. Guilford Press. 2010. US$35.00 (hb). 224pp. ISBN: 9781606235157

As the authors comment in this very accessible book, they are sometimes confronted by the objection that behavioural activation 'sounds too simplistic'. It is indeed a very clear and straightforward model for helping people who experience depression. Nevertheless, coaching a client into accepting that what they need to do in order to feel better in their mood is to begin to identify and indulge in more 'antidepressant behaviours' can be a challenging task; but it is a rewarding one. In fact, for me the great advantage of the model is that it is remarkably easy to follow. For some, of course, this may be its downfall. After all, is a psychological therapy not supposed to be complicated to learn, couched in mystifying language and (these days anyway) contain the word 'cognitive' in its title?

Behavioural activation starts from the premise that in order to feel better it is necessary to 'act' better; that mood and activity are inextricably related to each other; that as a person becomes more depressed they stop engaging in activities that were once pleasurable, utilise escape or avoidance behaviours which service to keep them stuck in a rut, such as shutting themselves away in their room and not answering the phone; pull away from their world and potential sources of antidepressant reinforcement, and as a consequence feel more down. Behavioural activation really works, as the authors have demonstrated in their research, and there is evidence that it is as effective as 'full' cognitive–behavioural therapy. It is now in the National Institute for Health and Clinical Excellence guidance for depression. It is being increasingly used, as I know first-hand, as a front-line therapy by workers in primary care mental health. As a client of the authors once very succinctly put it: 'So are you saying that cognitive therapists believe that the head teaches the hands, whereas the BA (behavioural activation) approach assumes that the hands teach the head?' That is a great way of describing something which is essentially a very practical way of learning how to feel better.

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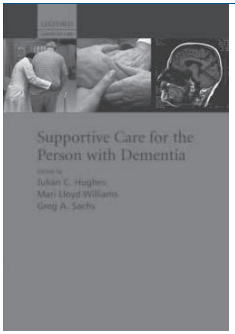

Supportive Care for the Person with Dementia

Edited by Julian Hughes, Mari Lloyd-Williams & Greg Sachs. Oxford University Press. 2009. £59.95 (hb). 330pp. ISBN: 9780199554133

This is a book covering the care for people with dementia, from diagnosis to death. The 'supportive care' of the title refers to a model developed to guide the comprehensive support of people with a variety of long-term, life-shortening conditions. The approach owes a lot to the philosophy of palliative care in its attention to biological, psychological, social and spiritual needs but these considerations are extended, within supportive care, to encompass diagnosis, curative and life-prolonging treatments as well as palliation and dying. The book itself is one of a series of volumes focused on different diseases and is the first to apply this framework to dementia.

One of the delights of the book is the range of writings, with no fewer than 32 chapters packed into its 300 or so pages, including many contributions from well-known names as well as some newer voices. There are chapters from psychiatrists and old age physicians, general practitioners and palliative care specialists, psychologists, philosophers and many more besides. The mix is greatly enriched by contributions from individuals with dementia and family members of people with dementia, as well as chapters on often neglected topics such as Huntington's dementia and dementia in low-income countries. Overall the content

provides an excellent and broad-based distillation of up-to-date knowledge. I imagine that for every open-minded reader it will provide fresh insights and new titbits of knowledge.

I blew hot and cold about the supportive care framework. The first chapter provides a seductive start for those of us who tire of the self-righteous positioning of biomedical and person-centred approaches. It holds out a promise of an all-singing, all-dancing way of ensuring that people with dementia get the services they deserve: 'a complete mixture of biomedical dementia care, with good quality, person-centred, psychosocial, and spiritual care under the umbrella of holistic palliative care throughout the course of the person's experience' (p. 7). But a recipe for something so ambitious is impossible to deliver. The final chapter eloquently summarises the strata of understanding that make up the model, but the third layer, the so-called logistical steps through which the model is put into practice, is sidestepped on the basis that application is context dependent. Frustrating! However, grand aspirations can be infectious and I find myself looking forward to a future volume reporting the improvements in care that have been introduced as a result of applying this approach.

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Psychiatry: An Evidence-Based Text

Floriana Coccia

BJP 2011, 198:161.
Access the most recent version at DOI: 10.1192/bjp.bp.110.080200

ANEXO III:

Recopilación realizada por A. Donnay de documentación científica realizada hasta 1999 que investigan y concluyen que la enfermedad de SQM es una enfermedad física. www.mcsrr.org

Bibliographie MCS - Physische Ursache

Bibliographie aller 311 wissenschaftlichen Artikel, Editorials, Bücher, Buchkapitel und Berichte, die bis September 1999 erschienen sind und eine physische Ursache von MCS unterstützen und/oder solche, die Erkenntnisse über psychiatrische Funde kritisieren. (Publikationen in Zeitschriften von Klinischen Ökologen oder Briefe an Herausgeber ausgenommen)

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Anmerkung:
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ANEXO IV:

Recopilación A. Steinemann.

Research on Multiple Chemical Sensitivity (MCS)

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This document lists citations and abstracts for peer-reviewed journal articles that support a physiological basis for MCS. We would appreciate knowing if and how this document has been useful to you. Please send email to: mcsdoc@gmail.com.

Abdel-Rahman A., Shetty A.K., Abou-Donia M.B. 2002. Disruption of the blood-brain barrier and neuronal cell death in cingulate cortex, dentate gyrus, thalamus, and hypothalamus in a rat model of Gulf-War syndrome. *Neurobiology of Disease* 10(3): 306-26.

We investigated the effects of a combined exposure to restraint stress and low doses of chemicals pyridostigmine bromide (PB), N, N-diethyl-m-toluamide (DEET), and permethrin in adult male rats, a model of Gulf-War syndrome. Animals were exposed daily to one of the following for 28 days: (i) a combination of stress and chemicals (PB, 1.3 mg/kg/day; DEET, 40 mg/kg/day; and permethrin, 0.13 mg/kg/day); (ii) stress and vehicle; (iii) chemicals alone; and (iv) vehicle alone. All animals were evaluated for: (i) the disruption of the blood-brain barrier (BBB) using intravenous horseradish peroxidase (HRP) injections and endothelial barrier antigen (EBA) immunostaining; (ii) neuronal cell death using H&E staining, silver staining, and glial fibrillary acidic protein (GFAP) immunostaining; and (iii) acetylcholinesterase (AChE) activity and m2-muscarinic acetylcholine receptors (m2-AChR). Animals subjected to stress and chemicals exhibited both disruption of the BBB and neuronal cell death in the cingulate cortex, the dentate gyrus, the thalamus, and the hypothalamus. Other regions of the brain, although they demonstrated some neuronal cell death, did not exhibit disruption of the BBB. The neuropathological changes in the above four brain regions were highly conspicuous and revealed by a large number of HRP-positive neurons (21-40% of total neurons), a decreased EBA immunostaining (42-51% reduction), a decreased number of surviving neurons (27-40% reduction), the presence of dying neurons (4-10% of total neurons), and an increased GFAP immunostaining (45-51% increase). These changes were also associated with decreased forebrain AChE activity and m2-AchR (19-25% reduction). In contrast, in animals exposed to stress and vehicle or chemicals alone, the above indices were mostly comparable to that of animals exposed to vehicle alone. Thus, a combined exposure to stress and low doses of PB, DEET, and permethrin leads to significant brain injury. The various neurological symptoms reported by Gulf-War veterans could be linked to this kind of brain injury incurred during the war.

Abel-Rahman A., Abou-Donia S., El-Masry E., Shetty A., Abou-Donia M. 2004. Stress and combined exposure to low doses of pyridostigmine bromide, DEET, and permethrin produce neurochemical and neuropathological alteration in cerebral cortex, hippocampus, and cerebellum. *Journal of Toxicology and Environmental Health Part A* 67(2): 163-92.

Exposure to a combination of stress and low doses of the chemicals pyridostigmine bromide (PB), DEET, and permethrin in adult rats, a model of Gulf War exposure, produces blood-brain barrier (BBB) disruption and neuronal cell death in the cingulate cortex, dentate gyrus, thalamus, and hypothalamus. In this study, neuropathological alterations in other areas of the brain where no apparent BBB disruption was observed was studied following such exposure. Animals exposed to both stress and chemical exhibited decreased brain acetylcholinesterase (AChE) activity in the midbrain, brainstem, and cerebellum and decreased m2 muscarinic acetylcholine (ACh) receptor ligand binding in the midbrain and cerebellum. These alterations were associated with significant neuronal cell death, reduced microtubule-associated protein (MAP-2) expression, and increased glial fibrillary acidic protein (GFAP) expression in the cerebral cortex and the hippocampal subfields CA1 and CA3. In the cerebellum, the neurochemical alterations were associated with Purkinje cell loss and increased GFAP immunoreactivity in the white matter. However, animals subjected to either stress or chemicals alone did not show any of these changes in comparison to vehicle-treated controls. Collectively, these results suggest that prolonged exposure to a combination of stress and the chemicals PB, DEET, and permethrin can produce significant damage to the cerebral cortex, hippocampus, and cerebellum, even in the absence of apparent BBB damage. As these areas of the brain are respectively important for the maintenance of motor and sensory functions, learning and memory, and gait and coordination of movements, such alterations could lead to many physiological, pharmacological, and behavioral abnormalities, particularly motor deficits and learning and memory dysfunction.

Abdel-Rahman A., Dechkovskaia A.M., Goldstein L.B., Bullman S.H., Khan W., El-Masry E.M., Abou-Donia M.B. 2004. Neurological deficits induced by malathion, DEET, and permethrin, alone or in combination in adult rats. *Journal of Toxicology and Environmental Health Part A* 67(4): 331-56.

Malathion (O,O-dimethyl-S-[1,2-carbethoxyethyl]phosphorodithionate), DEET (N,N-diethyl-m-toluamide), and permethrin [(+/-)-cis/trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylic acid (3-phenoxyphenyl) methyl ester] are commonly used pesticides. To determine the effects of the dermal application of these chemicals, alone or in combination, the sensorimotor behavior, central cholinergic system, and histopathological alterations were studied in adult male Sprague-Dawley rats following a daily dermal dose of 44.4 mg/kg malathion, 40 mg/kg DEET, and 0.13 mg/kg permethrin, alone and in combination for 30 d. Neurobehavioral evaluations of sensorimotor functions included beam-walking score, beam walk time, inclined plane, and grip response assessments. Twenty-four hours after the last treatment with each chemical alone or in combination all behavioral measures were impaired. The combination of DEET and permethrin, malathion and permethrin, or the three chemicals together resulted in greater impairments in inclined performance than permethrin alone. Only animals treated with a combination of DEET and malathion or with DEET and permethrin exhibited significant increases in plasma butyrlcholinesterase (BChE) activity. Treatment with DEET or permethrin alone, malathion and permethrin, or DEET and permethrin produced significant increases in

cortical acetylcholinesterase (AChE) activity. Combinations of malathion and permethrin or of DEET and permethrin produced significant decreases in midbrain AChE activity. Animals treated with DEET alone exhibited a significant increase in cortical m2 muscarinic ACh receptor binding. Quantification of neuron density in the dentate gyrus, CA1 and CA3 subfields of the hippocampus, midbrain, brainstem, and cerebellum revealed significant reductions in the density of surviving neurons with various treatments. These results suggest that exposure to real-life doses of malathion, DEET, and permethrin, alone or in combination, produce no overt signs of neurotoxicity but induce significant neurobehavioral deficits and neuronal degeneration in brain.

Abou-Donia M.B 2003. Organophosphorus ester-induced chronic neurotoxicity. *Archives of Environmental Health* 58(8): 484-97.

Organophosphorus compounds are potent neurotoxic chemicals that are widely used in medicine, industry, and agriculture. The neurotoxicity of these chemicals has been documented in accidental human poisoning, epidemiological studies, and animal models. Organophosphorus compounds have 3 distinct neurotoxic actions. The primary action is the irreversible inhibition of acetylcholinesterase, resulting in the accumulation of acetylcholine and subsequent overstimulation of the nicotinic and muscarinic acetylcholine receptors, resulting in cholinergic effects. Another action of some of these compounds, arising from single or repeated exposure, is a delayed onset of ataxia, accompanied by a Wallerian-type degeneration of the axon and myelin in the most distal portion of the longest tracts in both the central and peripheral nervous systems, and is known as organophosphorus ester-induced delayed neurotoxicity (OPIDN). In addition, since the introduction and extensive use of synthetic organophosphorus compounds in agriculture and industry half a century ago, many studies have reported long-term, persistent, chronic neurotoxicity symptoms in individuals as a result of acute exposure to high doses that cause acute cholinergic toxicity, or from long-term, low-level, subclinical doses of these chemicals. The author attempts to define the neuronal disorder that results from organophosphorus ester-induced chronic neurotoxicity (OPICN), which leads to long-term neurological and neurobehavioral deficits. Although the mechanisms of this neurodegenerative disorder have yet to be established, the sparse available data suggest that large toxic doses of organophosphorus compounds cause acute necrotic neuronal cell death in the brain, whereas sublethal or subclinical doses produce apoptotic neuronal cell death and involve oxidative stress degeneration in brain.

Abou-Donia M.B., Wilmarth K.R., Abdel-Rahman A.A., Jenseen K.F., Oehme F.W., Kurt T.L. 1996. Increased neurotoxicity following concurrent exposure to pyridostigmine bromide, DEET, and chlorpyrifos. *Fundamentals of Applied Toxicology* 34(2): 201-22.

The operating environment of the service personnel during the Persian Gulf War involved psychological, biological, and chemical elements including exposure to pesticides such as the insect repellent DEET (*N,N*-diethyl-*m*-toluamide) and the insecticide chlorpyrifos (*O,O*-diethyl*O*-3,5,6-trichloropyridinyl phosphorothioate) and to pyridostigmine bromide (PB, 3-dimethylaminocarbonyloxy-*N*-methylpyridinium bromide) that was administered as a prophylactic agent against possible nerve gas attack. The present study was designed to determine the toxicity produced by individual or coexposure of hens 5 days/week for 2 months to 5 mg PB/kg/day in water, by gavage; 500 mg DEET/kg/day, neat, sc; and 10 mg chlorpyrifos kg/day in corn oil, sc. Coexposure to various binary treatments produced greater neurotoxicity

than that caused by individual exposures and was characterized by severe neurologic deficit and neuropathological alterations. Also, neurotoxicity was further enhanced following concurrent administration of the three chemicals. Severe inhibition of plasma butyrylcholinesterase (BuChE) activity was produced in hens treated with PB (activity 17% of control) compared to those treated with chlorpyrifos (activity 51% of control) or DEET (activity 83% of control). BuChE inhibition was further increased in binary and tertiary treatment groups compared to individual treatment groups. In contrast, a significant inhibition of brain acetylcholinesterase (AChE) was produced in hens administered chlorpyrifos alone (activity 67% of control), while those given chlorpyrifos in combination with other compounds exhibited a significant inhibition of brain AChE activity ranging from 43 to 76%. Brain neurotoxicity target esterase (NTE) was not inhibited in any of the individual treatment groups or PB/DEET, but was significantly inhibited and had activity expressed as a percentage of control in groups administered combined chlorpyrifos with PB of 73% or DEET of 74% and in the tertiary treatment group of 71%. We hypothesize that test compounds may compete for xenobiotic metabolizing enzymes in the liver and blood and may also compromise the integrity of the blood–brain barrier, leading to an increase in their "effective concentrations" in the nervous system to levels equivalent to the toxic doses of individual compounds. This is consistent with the present observation of increases in (1) the inhibition of brain AChE and NTE, (2) the extent of neurologic dysfunction, and (3) the severity and frequency of neuropathologic lesions in the combined treatment groups compared to those administered individual compounds..

Abou-Donia M.B., Dechkovskaia A.M., Goldstein L.B., Shah D.U., Bullman S.L., Khan W.A. July 2002. Uranyl acetate-induced sensorimotor deficit and increased nitric oxide generation in the central nervous system in rats. *Pharmacology, Biochemistry, and Behavior* 72(4): 881-90.

We investigated the effects of uranyl acetate on sensorimotor behavior, generation of nitric oxide and the central cholinergic system of rats. Male Sprague-Dawley rats were treated with intramuscular injection of 0.1 and 1 mg/kg uranyl acetate in water, daily for 7 days. Control animals received equivalent amount of water. The treatment was stopped after the seventh injection because the animals in the 1-mg/kg group appeared lethargic. The animals were maintained for an additional observation period of 30 days. The study was initiated as a dose-finding study that covered doses of 10 and 100 mg/kg, as well. However, all the animals in the 100-mg/kg treatment group died after the third and fourth injections, and all animals given 10 mg/kg died after the fifth and sixth injections. On day 30 following the cessation of treatment, the sensorimotor functions of the animals in the 0.1- and 1-mg/kg treatment groups were evaluated using a battery of tests that included measurements of postural reflexes, limb placing, orientation to vibrissae touch, grip time, beam walking and inclined plane performance. The animals were sacrificed the same day and the cerebral cortex, brainstem, cerebellum and midbrain were dissected. The levels of nitric oxide as marker for increased oxidative stress, and the integrity of the cholinergic system as reflected in acetylcholinesterase (AChE) activity and m2 muscarinic acetylcholine receptors ligand binding, were determined. The data from behavioral observations show that there was a dose-related deficit at the 0.1- and 1-mg/kg treatment groups for inclined plane performance. Both doses reduced grip time, but there was no significant difference between the two doses. Similarly, both beam-walk score and beam-walk time were impaired at both doses as compared with the controls. A significant increase in nitric oxide was seen at 0.1 mg/kg dose in cortex and midbrain, whereas brainstem and cerebellum

showed an insignificant decrease at both the doses. Similarly, there was no significant change in nitric oxide levels in kidneys and liver of the treated animals as compared with the controls. There was a significant increase in AChE activity in the cortex of the animals treated with 1 mg/kg uranyl acetate, but not in other brain regions. Ligand binding densities for the m2 muscarinic receptor did not show any change. These results show that low-dose, multiple exposure to uranyl acetate caused prolonged neurobehavioral deficits after the initial exposure has ceased.

Abou-Donia M.B., Dechkovskaia A.M., Goldstein B., Abdel-Rahman A., Bullman S.L., Khan W.A. 2004. Co-exposure to pyridostigmine bromide, DEET, and/or permethrin causes sensorimotor deficit and alterations in brain acetylcholinesterase activity. *Pharmacology, Biochemistry, and Behavior* 77(2): 253-62.

Military personnel deployed in the Persian Gulf War (PGW) were exposed to a combination of chemicals, including pyridostigmine bromide (PB), DEET, and permethrin. We investigated the dose-response effects of these chemicals, alone or in combination, on the sensorimotor performance and cholinergic system of male Sprague-Dawley rats. Animals were treated with a daily dermal dose of DEET and/or permethrin for 60 days and/or PB (gavage) during the last 15 days. Neurobehavioral performance was assessed on day 60 following the beginning of the treatment with DEET and permethrin. The rats were sacrificed 24 h after the last treatment for biochemical evaluations. PB alone, or in combination with DEET, or DEET and permethrin resulted in deficits in beam-walk score and longer beam-walk times compared to controls. PB alone, or in combination with DEET, permethrin, or DEET and permethrin caused impairment in incline plane performance and forepaw grip strength. PB alone at all doses slightly inhibited plasma butyrylcholinesterase activity, whereas combination of PB with DEET or permethrin increased its activity. Brainstem acetylcholinesterase (AChE) activity significantly increased following treatment with combinations of either DEET or permethrin at all doses, whereas the cerebellum showed a significant increase in AChE activity following treatment with a combination of PB/DEET/permethrin. Co-exposure to PB, DEET, and permethrin resulted in significant inhibition in AChE in midbrain. PB alone or in combination with DEET and permethrin at all doses increased ligand binding for m2 muscarinic acetylcholine receptor in the cortex. In addition, PB and DEET together or a combination of PB, DEET, and permethrin significantly increased ligand binding for nicotinic acetylcholine receptor. These results suggest that exposure to various doses of PB, alone and in combination with DEET and permethrin, leads to sensorimotor deficits and differential alterations of the cholinergic system in the CNS.

Abu-Qare A.W., Abou-Donia M.B. 2001. Combined exposure to sarin pyridostigmine bromide increased levels of rat urinary 3-nitrotyrosine and 8-hydroxy-2'deoxyguanosine, biomarkers of oxidative stress. *Toxicology Letters* 123(1): 51-58.

In this study concentrations of markers of oxidative stress 3-nitrotyrosine and 8-hydroxy-2'-deoxyguanosine (8-OhdG) were determined in rat urine following a single oral dose of pyridostigmine bromide (PB) 13 mg/kg and a single intramuscular dose of sarin 80 microg/kg alone or in combination. Urine samples were collected 16, 24, 48, 72, and 96 h following dosing. Control urine samples of five rats treated with normal saline were also collected at the same time intervals. A combined dose of PB and sarin significantly increased levels of 3-nitrotyrosine and (8-OhdG) starting 48 h after dosing. An increase in the concentration of these markers was not

detected following a single dose of PB or sarin alone. Maximal increase in 3-nitrotyrosine and 8-OhdG was detected 48 h after administration of a combination PB and sarin. The results indicate that concurrent exposure to PB and sarin could generate free radical species that may cause oxidative stress in rats. The results may have significant impact if veterans were expose to sarin following an oral dose of PB.

Abu-Qare A.W., Abou-Donia M.B. 2001. Biomarkers of apoptosis: release of cytochrome c, activation of caspase-3, induction of 8-hydroxy-2'-deoxyguanosine, increased 3-nitrotyrosine, and alteration of p53 gene. *Journal of Toxicology and Environmental Health Part B, Critical Reviews* 4(3): 313-32.

Biomarkers rely on biochemical, histological, morphological, and physiological changes in whole organisms. Their use is becoming an important tool to examine changes at cellular and molecular levels, especially in nucleic acids and proteins. Biomarkers are used to measure exposure to a toxic agent, to detect severity of any toxic response, and to predict the possible outcome. Information on the mechanisms of action of toxicants can allow the development of potential biomarkers of effect and thus improvement of the risk assessment processes. Use of biomarkers as a tool to predict induction of apoptosis allows identification of biological signs that may indicate increased risk for disease. In cells undergoing apoptosis, the release of cytochrome c from the mitochondria to the cytoplasm and the activation of caspase-3, a key enzyme to execution stage of apoptotic pathway, have been studied as biomarkers of cell death (apoptosis). Products of DNA fragmentation that either accumulate in the cellular tissues or are excreted in the urine are useful markers of DNA damage. The induction level of urinary or cellular level of 8-hydroxy-2-deoxyguanosine and 3-nitrotyrosine has been used as a marker to measure extent of DNA oxidative damage. Furthermore, alteration or overexpression of the p53 gene was considered an indication of apoptosis. This article reviews some of the aspects of biomarkers of apoptosis, indicating relevance of their uses to predict apoptosis following exposure to environmental toxicants.

Abu-Qare A.W., Abou-Donia M.B. 2008. In vitro metabolism and interactions of pyridostigmine bromide, N,N-diethyl-m-toluamide, and permethrin in human plasma and liver microsomal enzymes. *Xenobiotica* 38(3): 294-313.

The *in vitro* human plasma activity and liver microsomal metabolism of pyridostigmine bromide (PB), a prophylactic treatment against organophosphate nerve agent attack, *N*,*N*-diethyl-*m*-toluamide (DEET), an insect repellent, and permethrin, a pyrethroid insecticide, either alone or in combination were investigated. 2. The three chemicals disappeared from plasma in the following order: permethrin > PB > DEET. The combined incubation of DEET with either permethrin or PB had no effect on permethrin or PB. Binary incubation with permethrin decreased the metabolism of PB and its disappearance from plasma and binary incubation with PB decreased the metabolism of permethrin and its clearance from plasma. Incubation with PB and/or permethrin shortened the DEET terminal half-life in plasma. These agents behaved similarly when studied in liver microsomal assays. The combined incubation of DEET with PB or permethrin (alone or in combination) diminished DEET metabolism in microsomal systems. 3. The present study evidences that PB and permethrin are metabolized by both human plasma and liver microsomal enzymes and that DEET is mainly metabolized by liver oxidase enzymes.

Combined exposure to test chemicals increases their neurotoxicity by impeding the body's ability to eliminate them because of the competition for detoxifying enzymes.

Anderson R.C., Anderson J.H. 1999. Sensory irritation and multiple chemical sensitivity. *Toxicology and Industrial Health* 15(3-4): 339-45.

Many of the symptoms described in Sick Building Syndrome (SBS) and multiple chemical sensitivity (MCS) resemble the symptoms known to be elicited by airborne irritant chemicals. Irritation of the eye, nose, and throat is common to SBS, MCS, and sensory irritation (SI). Difficulty of breathing is often seen with SBS, MCS, and pulmonary irritation (PI). We therefore asked the question: can indoor air pollutants cause SI and/or PI? In laboratory testing in which mice breathed the dilute volatile emissions of air fresheners, fabric softeners, colognes, and mattresses for 1 h, we measured various combinations of SI and PI as well as airflow decreases (analogous to asthma attacks). Air samples taken from sites associated with repeated human complaints of poor air quality also caused SI, PI, and airflow limitation (AFL) in the mice. In previous publications, we have documented numerous behavior changes in mice (which we formally studied with a functional observational battery) after exposure to product emissions or complaint site air; neurological complaints are a prominent part of SBS and MCS. All together, these data suggest that many symptoms of SBS and MCS can be described as SI, PI, AFL, and neurotoxicity. All these problems can be caused by airborne irritant chemicals such as those emitted by common commercial products and found in polluted indoor air. With some chemical mixtures (e.g., emissions of some fabric softeners, disposable diapers, and vinyl mattress covers) but not others (e.g., emissions of a solid air freshener), the SI response became larger (2- to 4-fold) when we administered a series of two or three 1-h exposures over a 24-h period. Since with each exposure the intensity of the stimulus was constant yet the magnitude of the response increased, we concluded that there was a change in the sensitivity of the mice to these chemicals. The response was not a generalized stress response because it occurred with only some mixtures of irritants and not others; it is a specific response to certain mixtures of airborne chemicals. This is one of the few times in MCS research that one can actually measure *both* the intensity of the stimulus *and* the magnitude of the response and thus be allowed to discuss sensitivity changes. The changing SI response of the mice might serve as a model of how people develop increasing sensitivity to environmental pollutants. Intensive study of this system should teach us much about how people respond to and change sensitivity to airborne irritant chemicals.

Ashford N.A. 1999. Low-level chemical sensitivity: implications for research and social policy. *Toxicology and Industrial Health* 15(3-4): 421-47.

There is increasing evidence that human exposure to levels of chemicals once thought to be safe—or presenting insignificant risk—are, in fact, harmful. So-called low-level exposures are now known to be associated with adverse biological effects including cancer, endocrine disruption, and chemical sensitivity. This requires that we change both (1) the way we design research linking chemicals and health, and (2) the solutions we devise to address chemically caused injury. The new and emerging science of low-level exposure to chemicals requires appropriate social policy responses which include regulation of toxic substances, notification of those exposed, and compensation and reasonable accommodation to those affected. Research and social policy need to be focused towards two distinct groups: (1) those individuals who could

become chemically intolerant as a result of an initiating exposure, and (2) those individuals who have already become chemically intolerant and are now sensitive to chemicals at low levels.

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. *Archives of Environmental Health* 1998 53(5): 347-53.

Chemical intolerance, or reported illness from odors of common environmental chemicals (e.g., car exhaust, pesticides), is emerging as an important environmental and public health-care issue. Epidemiologic methods provide relevant heuristic devices for studies of complex disorders, such as chemical intolerance. The authors examined personal and reported parental cardiopulmonary disease prevalence rates in a community sample of chemically intolerant and control individuals. A county government (Tucson, Arizona) employee and kin subset (N = 181; 113 households) completed standard health questionnaires. Investigators determined chemical intolerance (n = 41/181) from self-reports of individuals who felt "moderately" to "severely" ill from exposure to at least three of five chemicals (i.e., car exhaust, pesticides, paint, new carpet, and perfume) on a Chemical Odor Intolerance Index. The authors chose the control group (n = 57/181) on the basis of self-reports of "never" feeling ill on the Chemical Odor Intolerance Index. The chemically intolerant group, which primarily comprised women (78% versus 51% of controls, $p < .05$), was significantly more likely to report-and to have sought--medical attention for heart problems, bronchitis, asthma, and pneumonia. Reports of heart problems in the chemically intolerant index cases and the occurrence of heart disease in both of their parents were significant (Fisher's $p < .05$). The chemically intolerant individuals were also significantly more likely to report maternal histories of chest problems (e.g., inhalant allergens, tuberculosis) than controls. The findings of the study suggested that the chemically intolerant individuals (a preponderance of whom were women [sex-related risk]) were more likely to have (a) reported cardiopulmonary problems (i.e., greater health risk); (b) actively sought medical care for these problems (i.e., increased medical utilization); and (c) reported more parental illnesses-particularly heart disease, asthma, and diabetes (i.e., genetic risk). Additional community-based studies of chemical intolerance are needed.

Baldwin C.M., Bell I.R., O'Rourke M.K. 1999. Odor sensitivity and respiratory complaint profiles in a community-based sample with asthma, hay fever, and chemical odor intolerance. *Toxicology and Industrial Health* 15(3-4): 403-409.

This is a community-based study of odor sensitivity and respiratory complaints for persons reporting asthma (*n*=14/141), hay fever (*n*=72/140), and chemical odor intolerance (CI) (*n*=41/181). CI, a symptom of multiple chemical sensitivity (MCS), was determined from self-ratings of feeling `moderately' to `severely' ill using the Chemical Odor Intolerance Index (CII). Index odors included perfume, pesticide, drying paint, new carpet odor, and car exhaust. Six additional odors [natural gas, disinfectants, chlorinated water, room deodorizers, and environmental tobacco smoke (ETS)] were also assessed in the health and environment survey. Asthmatics reported feeling `frequently' to `almost always' ill from the CII index odors of drying paint, new carpet odor, perfume, and cleaning agents compared to nonasthmatics. People with hay fever documented feeling `frequently' to `almost always' ill from pesticides, drying paint, and car exhaust compared to individuals without hay fever. The CI cited illness from air freshener,

natural gas and chlorinated water, in addition to the index odors of perfume, paint, pesticides, new carpeting and auto exhaust. All three groups were significantly more likely to report feeling ill from ETS. People with asthma were significantly more likely to report lower lung complaints, such as wheeze and dyspnea. People with hay fever cited more chest tightness. The CI were significantly more likely to report upper and lower respiratory symptoms. Given this overlap in respiratory complaints, it could be that CI may serve to amplify these traditional immune-related disorders and/or suggest that having asthma or hay fever could make one more vulnerable to CI.

Bascom R., Meggs W.J., Framptom M., Hudnell K., Kilburn K., Kobal G., Medinsky M., Rea W. 1997. Neurogenic inflammation: with additional discussion of central and perceptual integration of nonneurogenic inflammation. *Environmental Health Perspective* 105 (Suppl. 2): 531-37.

The Working Group on Neurogenic Inflammation proposed 11 testable hypotheses in the three domains of neurogenic inflammation, perceptual and central integration, and nonneurogenic inflammation. The working group selected the term people reporting chemical sensitivity (PRCS) to identify the primary subject group. In the domain of neurogenic inflammation, testable hypotheses included: PRCS have an increased density of c-fiber neurons in symptomatic tissues; PRCS produce greater quantities of neuropeptides and prostanoids than nonsensitive subjects in response to exposure to low-level capsaicin or irritant chemicals; PRCS have an increased and prolonged response to exogenously administered c-fiber activators such as capsaicin; PRCS demonstrate augmentation of central autonomic reflexes following exposure to agents that produce c-fiber stimulation; PRCS have decreased quantities of neutral endopeptidase in their mucosa; exogenous neuropeptide challenge reproduces symptoms of PRCS. In the domain of perceptual and central integration, testable hypotheses included: PRCS have alterations in adaptation, habituation, cortical representation, perception, cognition, and hedonics compared to controls; the qualitative and quantitative interactions between trigeminal and olfactory systems are altered in PRCS; higher integration of sensory inputs is altered in PRCS. In the domain of nonneurogenic inflammation, testable hypotheses included: increased inflammation is present in PRCS in symptomatic tissues and is associated with a heightened neurosensory response; PRCS show an augmented inflammatory response to chemical exposure. The working group recommended that studies be initiated in these areas.

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. *Biological Psychiatry* 32(3): 218-42.

This paper reviews the clinical and experimental literature on patients with multiple adverse responses to chemicals (Multiple Chemical Sensitivity Syndrome-MCS) and develops a model for MCS based on olfactory-limbic system dysfunction that overlaps in part with Post's kindling model for affective disorders. MCS encompasses a broad range of chronic polysymptomatic conditions and complaints whose triggers are reported to include low levels of common indoor and outdoor environmental chemicals, such as pesticides and solvents. Other investigators have found evidence of increased prevalence of depression, anxiety, and somatization disorders in MCS patients and have concluded that their psychiatric conditions account for the clinical picture. However, none of these studies has presented any data on the effects of chemicals on

symptoms or on objective measures of nervous system function. Synthesis of the MCS literature with large bodies of research in neurotoxicology, occupational medicine, and biological psychiatry, suggests that the phenomenology of MCS patients overlaps that of affective spectrum disorders and that both involve dysfunction of the limbic pathways. Animal studies demonstrate that intermittent repeated low level environmental chemical exposures, including pesticides, cause limbic kindling. Kindling (full or partial) is one central nervous system mechanism that could amplify reactivity to low levels of inhaled and ingested chemicals and initiate persistent affective, cognitive, and somatic symptomatology in both occupational and nonoccupational settings. As in animal studies, inescapable and novel stressors could cross-sensitize with chemical exposures in some individuals to generate adverse responses on a neurochemical basis. The olfactory-limbic model raises testable neurobiological hypotheses that could increase understanding of the multifactorial etiology of MCS and of certain overlapping affective spectrum disorders.

Bell I.R., Warg-Damiani L., Baldwin C.M., Walsh M.E., Schwartz G.E. 1998. Self-reported chemical sensitivity and wartime chemical exposures in Gulf War veterans with and without decreased global health ratings. *Military Medicine* 163(11): 725-32.

This cross-sectional telephone survey study assessed prevalence rates of current chemical sensitivity, frequency of chemical odor intolerance, and self-reported Persian Gulf chemical exposures among 41 randomly sampled Department of Veterans Affairs outpatients who were Persian Gulf War (PGW) and PGW-era veterans. The participants were drawn from an initial random list of 100 veterans, of whom 28 PGW and 20 era veterans had correct telephone data on file. Of those contacted, 86% of PGW veterans (24/28) and 85% of era veterans (17/20) agreed to participate. Significantly more PGW veterans with poorer global health after military service reported considering themselves now "especially sensitive to certain chemicals" (86%, 12/14) than did the PGW veterans or era veterans in stable health (both comparison groups 30%, 3/10). Among PGW veterans, the subset with worse health associated with marked increases in chemical odor intolerance since their military service had a significantly higher odds ratio for exposure to multiple chemicals, notably wartime pesticides and insect repellent, than did comparison groups. The high rate of chemical sensitivity of PGW veterans with deteriorated health is almost three times that in PGW-era veterans and in elderly primary care outpatient veterans at the same Department of Veterans Affairs medical center and in community-based civilian samples (i.e., 30%). These preliminary findings suggest the need for further study of chemical sensitivity, including tests for acquired increases in neural sensitizability to multiple low-level chemicals, in ill PGW veterans

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. *Archives of Environmental Health*. 48(1): 6-13.

The present survey of young adult college students investigated the prevalence of self-reported illness from the smell of the five following common environmental chemicals (cacosmia): (1) pesticide, (2) automobile exhaust, (3) paint, (4) new carpet, and (5) perfume. Sixty-six percent of 643 students reported feeling ill from one or more of the five chemicals; 15% identified the smell of at least four chemicals as making them ill. Ratings of illness from pesticide correlated weakly

but significantly with ratings for the largest number of individual symptoms (9 of 11); daytime tiredness and daytime grogginess both correlated at high levels of significance with illness ratings (on a 5-point scale) for four of the five chemicals. The most cacosmic group (CS) included significantly more women (79%) than the noncacosmic group (NS) (49%); women overall were more cacosmic than men ($p < .001$), even with the significant covariate of depression. Ratings of cacosmia correlated only weakly with scores for depression ($r = 0.16$), anxiety ($r = 0.08$), and trait shyness ($r = 0.18$) in the total sample. On stepwise multiple regression with cacosmia score as the dependent measure, shyness accounted for 5.8% of the variance, while depression, anxiety, sense of mastery, and repression did not enter the equation. Histories of physician-diagnosed hay fever, but not asthma, were more frequent in the CS (16%) than in the NS group (5%). Without the confounds of chronic illness or specific treatment programs, these data are similar to patterns described clinically for a subset of patients with multiple chemical sensitivities (MCS), including previous data on increased nasal resistance in MCS. The findings also suggest a limited relationship between degree of self-reported cacosmia and trait shyness, possibly on the basis of limbic hyper-reactivity. Psychological variables did not otherwise account for any of the variance in self-rated illness from chemical odors in this nonclinical sample.

Bell I.R., Schwartz G.E., Baldwin C.M., Hardin E.E. 1996. Neural sensitization and physiological markers in multiple chemical sensitivity. *Regulatory Toxicology and Pharmacology* 24(1), pt. 2: S39-47.

This paper summarizes the key features of the olfactory-limbic, neural sensitization model for multiple chemical sensitivity (MCS) and presents relevant data on chemically intolerant human subjects from laboratory studies using quantitative electroencephalography, polysomnography, neuropsychological tests, cardiovascular measurements, and blood markers. MCS is a poorly understood chronic, polysymptomatic condition in which some prior controlled research studies have failed to find evidence to differentiate active from placebo tests. Closer examination of past MCS research, however, reveals that studies have failed to incorporate the design and methodological approaches necessary to test for nonimmunological sensitization. Time-dependent sensitization (TDS) is a well-documented phenomenon in the pharmacology literature involving the progressive increase in a given response by the passage of time between the initial and subsequent exposures to a substance or a stressor. As in MCS, multiple, chemically unrelated agents can trigger TDS. Females time-sensitize more readily than do males. Pharmacological and nonpharmacological (stress) stimuli can cross-sensitize. Dopaminergic pathways in the brain and the hypothalamic–pituitary–adrenal axis are likely involved in TDS. Data on the symptomatology of MCS point to central nervous system involvement, including limbic regions that receive input from both olfactory (odor) and trigeminal (irritant) pathways. Limbic and mesolimbic brain regions are among the most sensitizable to repeated, intermittent environmental stimuli. Sensitizable individuals can show no difference or lesser responses to a test substance on initial exposure, but later exhibit much greater increases in responsivity on the next exposure after a period of days. For future research, it is essential to distinguish chemical intolerance symptoms such as derealization, sudden mood changes, musculoskeletal pain, menstrual dysfunction, and uncontrollable sleepiness from chemical phobia and avoidance behaviors. This model permits hypothesis-driven research on MCS and has major implications

for interpretation of apparently positive and negative tests for “true” as opposed to “perceived” sensitivity to low levels of environmental chemicals.

Bell I.R., Baldwin C.M., Schwartz G.E.R. 2001. Sensitization studies in chemically intolerant individuals: implications for individual difference research. *Annals of the New York Academy of Sciences* 933:38-47.

Chemical intolerance (CI) is an individual difference trait in which persons report feeling ill in multiple physiological systems from low levels of a wide range of chemically unrelated environmental substances. This paper discusses the neural sensitization model for progressive host amplification of polysymptomatic responses elicited by chemical exposures following an initiating event. The sensitization model accommodates hypotheses for initiating and eliciting CI in human populations that involve both environmental chemicals and physical or psychological stressors. Recent studies in this laboratory have demonstrated sensitization in individuals with CI over repeated sessions for dependent variables such as electroencephalographic (EEG) activity and diastolic blood pressure. Psychological distress variables alone do not explain these findings. Individuals with CI and/or vulnerability to sensitization share specific characteristics, for example, female gender, certain genetic background (offspring of alcohol-preferring parents), and personal preference for high sugar/carbohydrate intake. Overall, the data suggest that the 15-30% of the general population who report heightened CI are highly sensitizable. Sensitizability may serve an adaptive, sentinel function in threatening environments with poor signal-to-noise ratios. However, as sensitization gradually shifts operating set points of physiological systems out of the normal range in response to allostatic load, this process may contribute to the development of chronic, polysymptomatic health conditions such as multiple chemical sensitivity and/or fibromyalgia. Individual response specificity and stereotypy rather than toxicant properties may determine which types of central, autonomic, and/or peripheral nervous system dysfunctions manifest at subclinical and clinical levels.

Brandt-Rauf P.W., Andrews L.R., Schwarz-Miller J. 1991. Sick-hospital syndrome. *Journal of Occupational Medicine*.33(6): 737-39.

An outbreak of complaints consisting primarily of eye and respiratory tract irritation accompanied by headache, dizziness, fatigue, and nausea occurred among the operating room personnel of a large metropolitan hospital. This initially was attributed to infiltration of diesel exhaust emissions into the ventilation system. However, following correction of this problem and subsequent unrevealing air monitoring, symptoms persisted and were noted in personnel in adjacent areas of the hospital as well. An industrial hygiene and medical evaluation was undertaken. Monitoring for carbon monoxide, formaldehyde, and anesthetic gases and review of medical records and patient examinations were unrevealing, and the problem resolved gradually over several weeks. This outbreak represents a case of building-associated illness among health professionals in a hospital setting that was triggered by a single, identifiable noxious exposure but was sustained despite any apparent ongoing noxious exposures

Bronstein A.C. 1995. Multiple chemical sensitivities—new paradigm needed. *Journal of Toxicology*: *Clinical Toxicology* 33(2): 93-94.

The current principles of toxicology, immunology and allergy do not provide a coherent explanation of a chemical sensitivity lacking reproducible and measurable physiologic or biochemical changes. A new paradigm is needed as a scientific model for multiple chemical sensitivities.

Brooks S.M., Weiss M.A., Bernstein I.L. 1985. Reactive airways dysfunction syndrome. Case reports of persistent airways hyperreactivity following high-level irritant exposures. *Journal of Occupational Medicine* 27(7): 473-76.

Two individuals developed an asthma-like illness after a single exposure to high levels of an irritating aerosol, vapor, fume, or smoke. Symptoms developed within a few hours. A consistent physiologic accompaniment was airways hyperreactivity, with the two subjects showing positive methacholine challenge tests. No documented preexisting respiratory illness was identified, nor did subjects relate past respiratory complaints. Respiratory symptoms and airways hyperreactivity persisted for at least four years after the incident. The incriminated etiologic agents all shared a common characteristic of being irritant in nature. Bronchial biopsy specimens showed an airways inflammatory response. This report suggests that acute high-level irritant exposures may produce an asthma-like syndrome in some individuals, with long-term sequelae and chronic airways disease. Nonimmunologic mechanisms seems to be operative in the pathogenesis of this syndrome.

Brown-DeGagne A.M., McGlone J. 1999. Multiple chemical sensitivity: a test of the olfactory-limbic model. *Journal of Occupational and Environmental Medicine* 41(5): 366-77.

Thus far, no neuropsychological study has examined the cognitive profile of multiple chemical sensitivity (MCS) within the framework of Bell's Olfactory-Limbic Model. It predicts that cognitive weaknesses will be associated more with limbic (i.e., frontal and/or temporal lobe) than with non-limbic (i.e., posterior cortex) brain regions. Matched MCS, asthma, and healthy control groups (n = 63) were tested on cognitive measures with localizing value. Between-group comparisons found that the MCS group performed as well as controls on all cognitive tasks. Within-group comparisons found that both the MCS and asthma groups performed significantly more poorly on tasks that were sensitive to frontal and temporal regions than to posterior regions. Additional research is needed before concluding that the Olfactory-Limbic Model adequately describes the cognitive strengths and weaknesses of MCS. Confounding factors such as medication use and chronic illness need to be considered.

Buchwald D., Garrity D. 1994. Comparison of patients with chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities. *Archives of Internal Medicine* 154(18): 2049-53.

Chronic fatigue syndrome (CFS), fibromyalgia (FM), and multiple chemical sensitivities (MCS) are conditions associated with fatigue and a variety of other symptoms that appear to share many clinical and demographic features. Our objectives were to describe the similarities and differences among patients with CFS, FM, and MCS. Additional objectives were to determine

how frequently patients with MCS and FM met the criteria for CFS and if they differed in their health locus of control. METHODS: Demographic, clinical, and psychosocial measures were prospectively collected in 90 patients, 30 each with CFS, FM, and MCS. Patients were recruited from a university-based referral clinic devoted to the evaluation and treatment of chronic fatigue and three private practices. Variables included demographic features, symptoms characteristic of each condition, psychological complaints, a measure of health locus of control, and information on health care use. RESULTS: Overall, the three patient groups were remarkably similar in demographic characteristics and the presence of specific symptoms. Patients with CFS and FM frequently reported symptoms compatible with MCS. Likewise, 70% of patients with FM and 30% of those with MCS met the criteria for CFS. Health care use was substantial among patients with CFS, FM, and MCS, with an average of 22.1, 39.7, and 23.3 visits, respectively, to a medical provider during the prior year. Health locus of control did not differ among the three populations. CONCLUSIONS: In general, demographic and clinical factors and health locus of control do not clearly distinguish patients with CFS, FM, and MCS. Symptoms typical of each disorder are prevalent in the other two conditions.

Caress S.M., Steinemann A.C. 2003. A review of a two-phase population study of multiple chemical sensitivities. *Environmental Health Perspectives* 111(12): 1490-97.

Summarizes the findings of a two-phase study of the prevalence and etiology of multiple chemical sensitivities (MCS). Exploration of the lifestyle alterations produced by MCS; potential linkage between MCS and other disorders; estimation of the number of people who have MCS.

Caress S.M., Steinemann A.C. 2004. Prevalence of multiple chemical sensitivities: A population-based study in the southeastern United States. *American Journal of Public Health* 94(5): 746-47.

We examined the prevalence of multiple chemical sensitivities (MCS), a hypersensitivity to common chemical substances. We used a randomly selected sample of 1582 respondents from the Atlanta, GA, standard metropolitan statistical area. We found that 12.6% of our sample reported the hypersensitivity and that, while the hypersensitivity is more common in women, it is experienced by both men and women of a variety of ages and educational levels. Our prevalence for MCS is similar to that (15.9%) found by the California Department of Health Services in California and suggests that the national prevalence may be similar.

Caress S.M., Steinemann, A.C. 2009. Prevalence of fragrance sensitivity in the American population. *Journal of Environmental Health* 71(7): 46-50.

This study determined the percentages of individuals who report adverse effects from exposure to fragranced products in the U.S. population and in subpopulations of those with asthma or chemical sensitivity. Data were collected through telephone interviews from two geographically weighted, random samples of the continental U.S. in two surveys during 2002-2003 and 2005-2006 (1,057 and 1,058 cases, respectively). Respondents were asked if they find being next to someone wearing a scented product irritating or appealing; if they have headaches, breathing difficulties, or other problems when exposed to air fresheners or deodorizers; and if they are irritated by the scent from laundry products, fabric softeners, or dryer sheets that are vented outside. Results aggregated from both surveys found that 30.5% of the general population reported scented products on others irritating, 19% reported adverse health effects from air

fresheners, and 10.9% reported irritation by scented laundry products vented outside. This study reveals that a considerable percentage of the U.S. population reports adverse health effects or irritation from fragranced products, with higher percentages among those with asthma and chemical sensitivity.

Caress S.M., Steinemann A.C. 2009. Asthma and chemical hypersensitivity: prevalence, etiology, and age of onset. *Toxicology and Industrial Health* 25(1): 71-78.

This study investigates asthma's national prevalence and potential overlap with chemical hypersensitivity. It also examines asthma's etiology, age of onset, and demographic characteristics. Data were collected from a geographically weighted random sample of the continental U.S. (1058 cases), in four seasonal cohorts (2005–2006). The study found that 12.9% of the sample report asthma, 11.6% report chemical hypersensitivity, and 31.4% of those with asthma report chemical hypersensitivity. Among asthmatics, 38% report irritation from scented products, 37.2% report health problems from air fresheners, and 13.6% report their asthma was caused by toxic exposure. Asthma cases affected each racial/ethic group in roughly the same proportion, with nearly 50% classified as childhood onset.

Caress S.M., Steinemann A.C. 2004. A national population study of the prevalence of multiple chemical sensitivity. *Archives of Environmental Health* 59(6): 300-305.

The article presents information on the findings of a telephone survey conducted to find the prevalence of hypersensitivity to low levels of common chemicals in the American population. Chemical hypersensitivity--often called multiple chemical sensitivity (MCS)--is also referred to as toxicant-induced loss of tolerance or environmental illness. It is typically acknowledged to be a condition characterized by acute reactions that occur after exposure to even low levels of common chemical products such as fragrances, household cleaners, fresh paints, newsprint, pesticides and other products that contain petrochemicals. MCS can produce a wide range of symptoms, and individuals with the hypersensitivity can encounter great difficulty functioning in normal working and living environments. Although a limited number of epidemiological studies have investigated the regional prevalence of chemical hypersensitivity in the U.S., its national prevalence is speculative. The National Academy of Sciences estimated that up to 15% of the U.S. population experiences some degree of hypersensitivity to common chemicals.

Caress S.M., Steinemann A.C. 2005. National prevalence of asthma and chemical hypersensitivity: an examination of potential overlap. *Journal of Occupational and Environmental Medicine* 47(5): 518-22.

Objective: The objective of this study was to investigate the linkage between asthma and chemical hypersensitivity.
Methods: The authors conducted a population study with a random sample of 1057 geographically weighted cases to determine the prevalence of both asthma and chemical hypersensitivity in the American population and to explore their co-occurrence.
Results: A total of 14.1% of the respondents reported being diagnosed with asthma and 11.2% reported a hypersensitivity to chemicals. Of those with asthma, 27.2% also reported being hypersensitive to chemicals and 7.4% reported also being diagnosed with multiple chemical

sensitivities (MCS). Of those diagnosed with MCS, 42% reported also being diagnosed with asthma. Additionally, 29.7% of those with asthma said air fresheners caused breathing difficulties, and 37.2% found scented products irritating.
Conclusions: The results indicate that there is significant overlap between some forms of asthma and chemical hypersensitivity.

Caress S.M., Steinemann A.C., Waddick C. 2002. Symptomatology and etiology of multiple chemical sensitivities in the southeastern United States. *Archives of Environmental Health* 57(5): 429-36.

A questionnaire was administered to individuals who had reported a hypersensitivity to common chemical products in an earlier epidemiological study in the Atlanta, Georgia, metropolitan area. The questionnaire investigated the nature of the symptoms and factors that potentially initiated hypersensitivity and subsequently triggered reactions. Also examined were associated lifestyle modifications and the relationships of hypersensitivity with other illnesses. The authors found that a majority of hypersensitive individuals (52.2%) experienced either "severe" or "somewhat severe" symptoms. The most common triggers of symptoms were cleaning products (88.4%), tobacco smoke (82.6%), perfume (81.2%), pesticides (81.2%), and car exhaust (72.5%). Only 1.4% of the subjects had a prior history of emotional problems, whereas 37.7% developed such problems after the emergence of their hypersensitivity. Lifestyle modifications varied; 76.8% changed their household cleaning/personal hygiene products, 47.8% began using water and/or air filtration systems, and 13% found it necessary to change residence. Although hypersensitivity was more common in females than males, the condition affects individuals in all categories of race/ethnicity, age, household income, and educational level.

Davidoff A.L., Keyl P.M., Meggs W.J. 1998. Development of multiple chemical sensitivities in laborers after acute gasoline fume exposure in an underground tunneling operation. *Archives of Environmental Health* 53(3):183-89.

Reports on the presence and nature of chemical sensitivities and other indices of illness in a cohort of workers excavating a subway tunnel located under a former gasoline station. Chemical sensitivities among the gasoline over-exposed sample; Abnormal findings after the tunnel shut down; Characteristics of tunnel workers with increased sensitivities and reference multiple chemical sensitivities syndrome and general population sample.

DeRosa C.T., Hicks H.E., Ashizawa A.E., Pohl H.R., Mumtaz M.M. 2006. A regional approach to assess the impact of living in a chemical world. *Annals of the New York Academy of Sciences* 1076:829-38.

In the United States, some 80,000 commercial and industrial chemicals are now in use of which over 30,000 are produced or used in the Great Lakes region. Thus, the environmental quality within the Great Lakes basin has been compromised particularly with respect to persistent toxic substances (PTS). Information derived from wildlife studies, prospective epidemiological and toxicological studies, databases, demographics, and Geographical Information Systems (GIS) demonstrate significant public health implications. Studies of human populations indicate: (a) elevated body burden levels of PTSs, (b) decrease in gestational age, (c) low birth weight (LBW), (d) greater risk of male children with birth defects (OR = 3.01), (e) developmental and

neurological deficits, (f) increased risk of infertility, (g) changes in sex ratio, and (h) fluctuations in thyroid hormones. These findings have been identified in vulnerable populations, such as the developing fetus, children, minorities, and men and women of reproductive age who are more susceptible because of their physiologic sensitivity and/or elevated exposure to toxic chemicals. Typically such health effects are assessed on a chemical specific basis; however, most human populations are exposed to hazardous chemicals as mixtures in air, water, soil, and biota. In this article we present an assessment of the potential for joint toxic action of these substances in combinations in which they are typically found. These evaluations represent an integration of all available scientific evidence in accordance with the "NAS paradigm" for risk assessment. In aggregate, our evaluations have demonstrated a need for community-based frameworks and computational techniques to track patterns of environmentally related exposures and associated health effects.

Donnay, A.H. 1999. On the recognition of multiple chemical sensitivity in medical literature and government policy. *International Journal of Toxicology* 18(6): 383-92.

The history of chemical sensitivity in America is reviewed from the first description published by Edgar Allan Poe in 1839, to its first medical definition as a symptom of neurasthenia in 1869, its rediscovery as allergic toxemia in 1945, its redefinition in 1987 as multiple chemical sensitivity (MCS), and its overlap in the 1990s with chronic fatigue syndrome, fibromyalgia syndrome, and Gulf War syndrome (GWS). More than half of the over 500 peer-reviewed articles on MCS support an organic basis for MCS, whereas less than one-quarter support a psychiatric basis. The same 2:1 difference is seen in the numbers of MCS researchers writing these articles and the number of journals publishing them. A psychogenic interpretation of MCS also is specifically rejected in the latest formal position statement on the subject, a 1994 consensus of the American Lung Association, American Medical Association (AMA), U.S. Environmental Protection Agency (US EPA), and U.S. Consumer Product Safety Commission (US CPSC) (U.S. Government Printing Office 1994-523-217/81322). This and other government recognition of MCS in policy, research, and scientific conferences are summarized. Dozens of federal, state, and local authorities accept MCS as a legitimate disease and/or disability that deserves reasonable accommodation in housing, employment, and public facilities. Official recognition is expected later in 1999 when the U.S. Centers for Disease Control and Prevention (CDC) announces a formal definition of MCS and the federal Interagency Workgroup on MCS releases its long-awaited final report, 4 years in the making. Given that epidemiological data from three states puts the prevalence of chemical sensitivity at 16 to 33% of the general population, 2 to 6% of whom have already been diagnosed with MCS, this truly is a hidden epidemic that deserves the priority attention of public health researchers and policy makers. Industrial toxicologists are encouraged to work on reducing and eliminating the use of synthetic fragrances, chemical sensitizers, and other irritants in consumer products and occupational settings.

Elberling J., Linneberg A., Dirksen A., Johansen J.D., Frølund L., Madsen F., et al. 2005. Mucosal symptoms elicited by fragrance products in a population-based sample in relation to atopy and bronchial hyper-reactivity. *Clinical and Experimental Allergy* 35(1): 75-81.

Background: Exposure to perfume and fragrance products may, in some individuals, cause symptoms from the eyes and airways. The localization, character and risk factors of such symptoms in the general population are unknown.
Objective: To investigate both the localization and character of symptoms from the eyes and airways elicited by fragrance products, and the associations between such symptoms and skin prick test reactivity (atopy), methacholine bronchial hyper-reactivity (BHR), allergic rhinitis and asthma.
Methods: A questionnaire on mucosal symptoms elicited by fragrance products was posted to 1189 persons who had participated in a Danish population-based study of allergic diseases in 1997/1998. The study included measurement of BHR, atopy, forced expiratory volume in 1 s (FEV1), and serum eosinophilic cationic protein (serum ECP).
Results: The response rate was 79.6%. Symptoms from the eyes or airways elicited by fragrance products were reported by 42%. BHR (adjusted odds ratio 2.3, 95% confidence interval 1.5–3.5) was independently associated with symptoms from the eyes and airways elicited by fragrance products. There were no significant associations between these symptoms and atopy, FEV_1 or serum ECP.
Conclusions: Mucosal symptoms from the eyes and airways were common in this population. BHR was a significant and independent predictor of these symptoms. The lack of association with atopy suggested that IgE-mediated allergic mechanisms do not play a major role in the development of these symptoms.

Farrow A., Taylor H., Northstone K., Golding J. 2003. Symptoms of mothers and infants related to total volatile organic compounds in household products. *Archives of Environmental Health* 58(10): 633-41.

The authors sought to determine whether reported symptoms of mothers and infants were associated significantly with the use of household products that raised indoor levels of total volatile organic compounds ($TVOC_s$). Data collected from 170 homes within the Avon Longitudinal Study of Parents and Children (ALSPAC: a large birth cohort of more than 10,000) had determined which household products were associated with the highest levels of $TVOC_s$. The latter data were collected over a period that approximated 6 mo of pregnancy and the infants' first 6 mo of life. This paper presents (a) the mothers' self-reports of the use of these products in their homes and (b) self-reported medical symptoms of mothers and infants postnatally. Higher TVOC levels were associated with air freshener and aerosol use. Infant diarrhea and earache were statistically significantly associated with air freshener use, and diarrhea and vomiting were significantly associated with aerosol use. Headache experienced by mothers 8 mo after birth was significantly associated with the use of air fresheners and aerosols; maternal depression was significantly associated with the use of air fresheners. The results of the study suggest a link between the use of products that raise indoor levels of $TVOC_s$ and an increased risk of certain symptoms among infants and their mothers.

Fernandez M., Bell I.R.,.Schwartz G.E. 1999. EEG sensitization during chemical exposure in women with and without chemical sensitivity of unknown etiology. *Toxicology and Industrial Health* 15(3-4): 305-12.

This study tested the sensitization model proposed by Bell et al. [Bell I.R., Miller C.S. and Schwartz G.E. An olfactory-limbic model of multiple chemical sensitivity syndrome: possible relationship to kindling and affective spectrum disorders. Biol. Psychiatry 1992: 32: 218-242] to study chemical sensitivity. The sensitization model indicates that a pharmacological stimulus or a traumatic event which elicits a strong response can sensitize limbic and/or mesolimbic pathways; and subsequent less intense trauma or stimuli, in the same or different modality, can elicit an amplified response. Three groups of subjects were tested: (1) women who reported chemical sensitivity and no sexual abuse (chemically sensitive, CS); (2) sexually abused (SA) women without chemical sensitivity; and (3) healthy women without chemical sensitivity or sexual abuse history (normal, N). All subjects were exposed to odorant and nonodorous control stimuli once a week for 3 weeks. Electroencephalographic activity was recorded while subjects sniffed the odorant and control stimuli. Results of the study revealed that both the CS and the SA group showed electroencephalogram (EEG) alpha sensitization across experimental sessions, while the N group showed little change over time. Additionally, EEG findings revealed that the CS group generated significantly greater alpha activity than the other two groups. Finally, while the groups were different on measures of psychological distress, these differences did not diminish the EEG findings. In summary, these findings suggest that intermittent exposure to chemicals elicits sensitization in CS and SA women without chemical sensitivity, supporting our expectations that chemical sensitivity is, in part, a manifestation of time-dependent sensitization (TDS). Additionally, these EEG findings indicate that CS women are unlike SA and healthy women in the amount of EEG alpha activity they generate. Finally, these findings indicate that psychological factors as assessed in this study do not explain electrophysiological differences between chemically and non-chemically-sensitive women.

Gibson P.R., Elms A.N., Ruding L.A. 2003. Perceived treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity. *Environmental Health Perspectives* 111(12): 1498-1504.

Provides some information about the perceptions of multiple chemical sensitivities patients regarding a large number of interventions. Examination of the types of the perceived efficacy of the treatments used by people with MCS; Analysis of the lengths of helpful and harmful effects of time-limited therapies.

Gilbert M.E. 1995. Repeated exposure to lindane leads to behavioral sensitivities and facilitates electrical kindling. *Neurotoxicolgy and Teratology* 17(2): 131-41.

Repeated intermittent exposure to some chemicals produces behavioral sensitization and seizure induction through a kindling mechanism. Although many pesticides are convulsant at high dosages, the persistent neurological effects of chronic low level exposure are unclear. The impact of intermittent exposure to lindane on behavioral seizure development and subsequent electrical kindling was assessed in the present study. Rats were administered lindane (0 or 10 mg/kg, po) for 30 days, or 3 times/week for 10 weeks. Enhanced behavioral responsiveness to lindane

(myoclonic jerks, clonic seizures) emerged over the course of dosing and persisted 2 to 4 weeks after the last dose. The incidence of generalized convulsions was increased from 0% to 15% between the first and final day of dosing. In addition, electrographic recordings from the amygdala revealed brief rhythmic bursts and isolated interictal spike and wave discharge in the absence of overt behavioral seizures. Electrical kindling of the amygdala, beginning 4 to 6 weeks after the final dose, was facilitated. In contrast, prior administration of a single convulsive dose of lindane (20 mg/kg) was without effect on kindling development. These data indicate that repeated exposure to subconvulsant doses of lindane produces a persistent alteration in the central nervous system as evidenced by an enhanced susceptibility to kindled seizures. The pattern of behavioral development whereby the sensitivity is built up gradually over time is suggestive of a chemical kindling mechanism. Savings in the number of stimulation sessions required to induce electrical kindling following a history of lindane treatment provides further evidence that prior lindane exposure may lead to a state of partial kindling. Thus, intermittent subconvulsive lindane treatment induces alterations in limbic excitability that persist for at least 1 month.

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

Environmental exposures to very low levels of airborne chemicals are associated with adverse symptoms, often affecting multiple organ systems, in the phenomenon of chemical sensitivity (CS). Recent surveys suggest a significant prevalence of chemically sensitive subjects in the United States, but the mechanism linking exposure to symptoms remains unclear, despite the advancement of a variety of theoretical models. In many of these models, exposure of the nasal respiratory system to an airborne agent is the first step in the pathway leading to symptoms. In this article, we advance the hypothesis that interactions between environmental chemicals and the vomeronasal organ (VNO) may play a role in the etiology of CS. The VNO, a bilateral, tubular organ located in the nose, serves in animals as part of a sensitive chemosensory system; however, evidence suggesting that the VNO retains a functional role in the adult human is controversial. Reported characteristics of the human VNO relevant to CS, including location, prevalence, selective sensitivity to airborne chemical exposure, and capacity to produce systemic effects, are discussed within the context of this ongoing debate. Beyond relevance to CS, the demonstration of an active, adult VNO could have significant impact on environmental toxicology.

Haley R.W., Billecke S., La Du B.N. 1999. Association of low PON1 type Q (type A) arylesterase activity with neurologic symptoms complexes in Gulf War veterans. *Toxicology and Applied Pharmacology* 157(3): 227-33.

Previously Haley et al. described six possible syndromes identified by factor analysis of symptoms in Gulf War veterans and demonstrated that veterans with these symptom complexes were more neurologically impaired than age-sex-education-matched well controls. They also uncovered strong associations (relative risks 4-8) suggesting that these symptom complexes were related to wartime exposure to combinations of organophosphate pesticides, chemical nerve agents, high concentration DEET insect repellant, and symptoms of advanced acute toxicity after taking pyridostigmine. Here we have shown that compared to controls, ill veterans with the

neurologic symptom complexes were more likely to have the R allele (heterozygous QR or homozygous R) than to be homozygous Q for the paraoxonase/arylesterase 1 (PON1) gene. Moreover, low activity of the PON1 type Q (Gln192, formerly designated type A) arylesterase allozyme distinguished ill veterans from controls better than just the PON1 genotype or the activity levels of the type R (Arg192, formerly designated type B) arylesterase allozyme, total arylesterase, total paraoxonase, or butyrylcholinesterase. A history of advanced acute toxicity after taking pyridostigmine was also correlated with low PON1 type Q arylesterase activity. Type Q is the allozyme of paraoxonase/arylesterase that most efficiently hydrolyzes several organophosphates including sarin, soman, and diazinon. These findings further support the proposal that neurologic symptoms in some Gulf War veterans were caused by environmental chemical exposures.

Heuser G., Mena I., Alamos F. 1994. NeuroSPECT findings in patients exposed to neurotoxic chemicals. *Toxicology and Industrial.Health* 10: 561-71.

Exposures to neurotoxic chemicals such as pesticides, glues, solvents, etc. are known to induce neurologic and psychiatric symptomatology. We report on 41 patients--16 young patients (6 males, 10 females, age 34 +/- 8 yrs.) and 25 elderly patients (9 males, 16 females, age 55 +/- 7 yrs). Fifteen of them were exposed to pesticides, and 29 to solvents. They were studied with quantitative and qualitative analysis of regional cerebral blood flow (rCBF), performed with 30 mCi of Xe-133 by inhalation, followed by 30 mCi of Tc-HMPAO given intravenously. Imaging was performed with a brain dedicated system, distribution of rCBF was assessed with automatic ROI definition, and HMPAO was normalized to maximal pixel activity in the brain. Results of Xe rCBF are expressed as mean and S.D. in ml/min/100g, and HMPAO as mean and S.D. uptake per ROI, and compared with age-matched controls--10 young and 20 elderly individuals. table: see text] We conclude that patients exposed to chemicals present with diminished CBF, worse in the right hemisphere, with random presentation of areas of hypoperfusion, more prevalent in the dorsal frontal and parietal lobes. These findings are significantly different from observations in patients with chronic fatigue and depression, suggesting primary cortical effect, possibly due to a vasculitis process.

Jammes Y., DelPierre S., DelVolgo M.J., Humbert-Tena C., Burnet, H. 1998. Long-term exposure of adults to outdoor air pollution is associated with increased airway obstruction and higher prevalence of bronchial hyperresponsiveness. *Archives of Environmental Health* 53(6): 372-77.

The authors studied the association between long-term exposure (i.e., > 10 y) to outdoor air pollution and the severity of obstructive pulmonary disease and prevalence of bronchial hyperreactivity to Beta 2 agonists in two groups of adult patients who were of similar ages and who had similar smoking habits. The subjects lived in downtown districts or in the outer suburbs of Marseilles, the neighborhood that contained air samplers. The regions were similar with respect to sulfur dioxide levels, but levels of nitric oxides and particulate matter (10 millimeters or less) were higher in the downtown area than the suburbs. The authors assessed airway obstruction, as determined by a decrease in forced expiratory volume in 1 s, mean forced expiratory flow measured between 25% and 75% of vital capacity, and an elevated value of central airway resistance. The authors tested the changes in these variables induced by inhalation

of a Beta 2 agonist. Baseline lung function was altered more significantly in both male and female patients who lived in downtown Marseilles than in those who resided in the suburbs, and the differences persisted regardless of the season during which the study occurred. Prevalence of bronchial hyperreactivity and symptoms of asthma (but not of rhinitis) were higher in the downtown than suburban male subjects. The results of this study suggest that an association exists between actual environmental exposure to outdoor air pollution (i.e., nitrogen oxides and/or particulate matter of 10 millimeters or less) and respiratory effects in sensitive adults represented by patients with chronic obstructive pulmonary disease or asthma.

Johansson A., Löwhagen O., Millqvist E., Bende M. 2002. Capsaicin inhalation test for identification of sensory hyperreactivity. *Respiratory Medicine* 96(9): 731-35.

Patients with upper and lower airway symptoms and with pronounced sensitivity to chemical odours, such as perfumes, flower scents and tobacco smoke, have been suggested to have sensory hyperreactivity (SHR). The symptoms have been difficult to identify with physiological measurements and the effects of various medications are doubtful. However, these patients have been found to be more sensitive to inhalation of capsaicin than healthy people. The aim of this study was to establish limit values with the capsaicin inhalation test in patients with SHR. METHODS: Ninety-five consecutive patients with upper and lower airway problems, who were admitted for allergy testing, underwent a capsaicin inhalation test with three different concentrations. The number of coughs was registered during each challenge. Score systems were used for symptoms and influence on social life of sensitivity to odours. In relation to scored symptoms, the patients were grouped as SHR or not, and compared with 73 healthy controls. RESULTS: All patients and controls coughed on capsaicin in a dose-dependent manner. Symptom score of odour sensitivity in patients was positively correlated to the response of the test. Out of 95 patients, 15 (16%) were scored to SHR. Patients with SHR reacted more to the capsaicin inhalation test than the other patients and the healthy controls. The limit values for a positive capsaicin inhalation test for the SHR were determined to be 10, 35 and 55 coughs at 0.4, 2.0 and 10 microM capsaicin, respectively. CONCLUSION: The capsaicin inhalation test well reflects the degree of airway sensitivity to chemicals and to what extent the social life is influenced. The cut-off values of the test can distinguish patients with pronounced sensitivity to odours.

Joffres M.R., Sampalli T., Fox R.A. 2005. Physiologic and symptomatic responses to low-level substances in individuals with and without chemical sensitivities; a randomized controlled blinded pilot booth study. *Environmental Health Perspectives* 113(9): 1178-83.

We conducted a pilot study using a randomized, single-blind, placebo-controlled exposure among 10 individuals with and 7 without reported chemical sensitivities in a dedicated testing chamber. Objectives of the study were to explore the length of the adaptation period to obtain stable readings, evaluate responses to different substances, and measure the level and type of symptomatic and physiologic reactions to low-level exposures. Reported and observed symptoms, electrodermal response, heart rate, skin temperature, surface electromyogram, respiratory rate, contrast sensitivity, and the Brown-Peterson cognitive test were used and compared between cases and controls and between test substances (glue, body wash solution, dryer sheet) and control substances (unscented shampoo and clean air). Subjects witb chemical

sensitivities (cases) took longer to adapt to baseline protocols than did controls. After adaptation, despite small study numbers, cases displayed statistically significant responses (all measures, /> < 0.02) in tonic electrodermal response to test substances compared with controls and compared with the control substance. Symptoms were also higher in cases than in controls for the body wash solution {p = 0.05) and dryer sheets ip = 0.02). Test-retest showed good agreement for both symptoms and tonic electrodermal responses (McNemar's test, p = 0.32 and p = 0.33, respectively). Outside of skin conductance, other measures had no consistent patterns between test and control substances and between cases and controls. This study shows the importance of using an adaptation period in testing individuals with reported chemical sensitivities and, despite small numbers, raises questions about underlying mechanisms and level of reactivity to low-level chemical exposures in sensitive individuals.

Kelly K.J., Prezant D.J. 2005. Bronchial hyperreactivity and other inhalation lung injuries in rescue/recovery workers after the world trade center collapse. *Critical Care Medicine* 33 (Suppl 1): S102-S106.

Background: The collapse of the World Trade Center (WTC) on September 11, 2001 created a large-scale disaster site in a dense urban environment. In the days and months thereafter, thousands of rescue/recovery workers, volunteers, and residents were exposed to a complex mixture of airborne pollutants.
Methods: We review current knowledge of aerodigestive inhalation lung injuries resulting from this complex exposure and present new data on the persistence of nonspecific bronchial hyperreactivity (methacholine PC20 ≤8 mg/mL) in a representative sample of 179 Fire Department of the City of New York (FDNY) rescue workers stratified by exposure intensity (according to arrival time) who underwent challenge testing at 1, 3, 6, and 12 months post-collapse.
Results: Aerodigestive tract inflammatory injuries, such as declines in pulmonary function, reactive airways dysfunction syndrome (RADS), asthma, reactive upper airways dysfunction syndrome (RUDS), gastroesophageal reflux disease (GERD), and rare cases of inflammatory pulmonary parenchymal diseases, have been documented in WTC rescue/recovery workers and volunteers. In FDNY rescue workers, we found persistent hyperreactivity associated with exposure intensity, independent of airflow obstruction. One year post-collapse, 23% of highly exposed subjects were hyperreactive as compared with only 11% of moderately exposed and 4% of controls. At 1 yr, 16% met the criteria for RADS.
Conclusions: While it is too early to ascertain all of the long-term effects of WTC exposures, continued medical monitoring and treatment is needed to help those exposed and to improve our prevention, diagnosis, and treatment protocols for future disasters.

Kilburn K.H. 2003. Effects of hydrogen sulfide in neurobehavioral function. *Southern Medical Journal* 90(10): 997-1106.

In the 19th century, deaths from acute exposure to hydrogen sulfide (H2S) portended permanent brain injury from nonlethal doses. The neurobehavioral effects of H2S exposures lasting from moments to years were compared in 16 subjects, 2 years to 22 years afterward. METHODS: Neurophysiologic and psychologic tests were used to appraise mood status and frequencies of 35 symptoms. Functions and frequencies, described as percent predicted adjusted for age, sex, educational achievement, and other factors, were compared with those in an unexposed

population. RESULTS: Frequencies were elevated for 31 of 33 symptoms. Balance was impaired (246% predicted with eyes closed, 159% predicted with eyes open), and simple and choice reaction times were prolonged (151% and 130% predicted, respectively). Visual fields performance was decreased to 72% predicted (right) and 55% predicted (left), color discrimination was abnormal, and hearing was decreased. Psychologic domains showed cognitive disability, reduced perceptual motor speed, impaired verbal recall and remote memory, and abnormal mood status. CONCLUSIONS: Exposure to H2S must be avoided.

Kilburn K.H. 1999. Measuring the effects of chemicals in the brain. *Archives of Environmental Health* 54(3): 150.

(Editorial) Discusses issues on the effects of chemicals on the brain. Result of the comparison measurements of group of individuals who had been exposed to chemicals; Implication of the widespread use of chemicals and the repetitive patterns of exposure; Practical and safe strategy of preventing the effects of chemicals on the brain.

Koch F., Hughes J.M. 1998. Perioperative care of environmentally sensitive patients. *AORN Journal* 68(3): 375-82.

In today's complex environment, with an increasing number of chemicals and environmental contamination, some individuals have developed sensitivities to their surroundings. Surgical intervention for environmentally sensitive patients provides an opportunity to reach beyond the boundaries of the OR. These patients require highly individualized perioperative nursing assessments and care planning on a multidisciplinary level. Presbyterian Hospital of Dallas has developed a protocol to initiate collaborative planning for these patients and has had the opportunity to successfully care for these patients.

Lax M.B., Henneberger P.K. 1995. Patients with multiple chemical sensitivities in an occupational health clinic: presentation and follow-up. *Archives of Environmental Health* 50(6): 425-31.

Thirty-five people with work-related Multiple Chemical Sensitivities were studied to learn about the onset and progression of illness. The subjects were selected from patients at an occupational health clinic. Individuals were identified as subjects if they fulfilled a seven-point case definition for Multiple Chemical Sensitivities and if onset of symptoms was related to workplace exposures. Three occupational exposures to solvents, poor indoor-air quality, and remodeling were associated with onset of Multiple Chemical Sensitivities in 63% of the subjects. Symptoms indicative of a nervous-system disorder topped the list of the most frequently reported symptoms. Commonalities in exposures and symptoms suggest that Multiple Chemical Sensitivities represents a distinct diagnostic category. Even with an incomplete understanding of etiology, it may be possible to limit the onset of work-related Multiple Chemical Sensitivities.

Lieberman A.D., Craven M.R. 1998. Reactive Intestinal Dysfunction Syndrome (RIDS) caused by chemical exposures. *Archives of Environmental Health* 53(5): 354-58.

In this study, the authors describe a new "reactive syndrome," Reactive Intestinal Dysfunction Syndrome (RIDS), which has similarities to the previously described clinical syndromes Reactive Airway Dysfunction Syndrome (RADS) and Reactive Upper Airway Dysfunction Syndrome (RUDS). Given that at least 5 neuropeptides are common to both the respiratory tract and digestive tract, the authors propose that the abnormal secretion of these neuropeptides or the abnormal numbers of their receptors play a role in what is perceived clinically as RADS, RUDS, and RIDS. The relatively large surface areas of both the lungs and gut render them especially vulnerable to the environment to which they are exposed constantly.

LoVecchio F., Fulton S.E. 2001. Ventricular fibrillation following inhalation of Glade Air Freshener. *European Journal of Emergency Medicine* 8(2): 153-54.

Intentional hydrocarbon inhalation can be fatal. Death can be secondary to hydrocarbon's cardiopulmonary effects. We present a case of a patient who survived ventricular fibrillation after inhalation of Glade Air Freshener(TM), which contains short chain aliphatic hydrocarbons (butane and isobutane). Unlike our case, myocardial sensitization and hypoxia are more commonly described with aromatic, halogenated or longer chain hydrocarbons.

Mackness B., Durrington P.N., Mackness M.I. 2000. Low paraoxonase in Persian Gulf War Veterans self-reporting Gulf War Syndrome. *Biochemical and Biophysical Research Communications* 276(2): 729-33.

Exposure to organophosphate (OP's) insecticides and nerve gases during the Persian Gulf War has been implicated in the development of Gulf War Syndrome. Paraoxonase (PON1) present in human serum detoxifies OP's. We determined the levels of PON1 in the serum of Gulf War Veterans and compared these to those found in a control population. One hundred fifty-two Gulf War Veterans from the UK who self-reported the presence of Gulf War Syndrome via a questionnaire and 152 age and gender matched controls were studied. PON1 activity, concentration, and genotype were determined. In the Gulf War Veterans, paraoxon hydrolysis was less than 50% of that found in the controls (100.3 (14.8-233.8) vs 214.6 (50.3-516.2) nmol/min/ml, $P < 0.001$). This low activity was independent of the effect of PON1 genotype. The serum PON1 concentration was also lower in the Gulf War Veterans (75.7 (18.1-351.3) vs 88.2 (34.5-527.4) microg/ml, $P < 0.00025$), which was again independent of PON1 genotype. There was no difference in the rate of diazoxon hydrolysis between the groups (10. 2 +/- 4.1 micromol/min/ml vs 9.86 +/- 4.4, P = NS). A decreased capacity to detoxify OP insecticides resulting from low serum PON1 activity may have contributed to the development of Gulf War Syndrome.

MacPhail R.C. 2001. Animal models for chemical intolerance: role of central nervous system plasticity - episodic exposures to chemicals: what relevance to chemical intolerance? *Annals of the New York Academy of Sciences*. 933:103-11.

Episodic exposures refer to intermittent acute exposures to chemicals that ordinarily have a rapid onset and short duration of effect. There has been a long tradition in preclinical behavioral pharmacology of using episodic-exposure paradigms in order to establish dose-response functions in individual organisms. In these experiments, stable baselines of behavior are first established and then followed by administering varying doses of a drug intermittently, for example, once or twice a week. The power of this approach is well established; the within-subjects design reduces error variance, allows exploration of the entire range of effective doses, and can be used to identify individual differences in drug sensitivity. Of course, the approach is only applicable to reversibly acting compounds, and checks need to be included to insure effects of one dose are not influenced by prior exposure to another dose. We have used baseline approaches to evaluate the effects of pesticides and solvents on the behavior of adult male rats and mice. Moreover, a novel probabilistic dose-tolerance analysis applied to the data suggests substantial individual differences in chemical sensitivity, often spanning orders of magnitude. These results suggest that individual differences in chemical sensitivity may be much greater than previously acknowledged.

MacPhail R.C. 2001. Episodic exposures to chemicals: What relevance to chemical intolerance? *Annals of the New York Academy of Sciences* 933:103-11.

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McKeown-Eyssen G., Baines C., Cole D.E.C., Riley N., Tyndale R.F., Marshall L, Jazmaji V. 2004. Case-control study of genotypes in multiple chemical sensitivity: CYP2D6, NAT1, NAT2, PON1, PON2 and MTHFR. *International Journal of Epidemiology* 33(5): 971-78.

Background: Impaired metabolism of toxic chemicals is a postulated mechanism underlying multiple chemical sensitivity (MCS). Because genetic variation alters the rate of chemical metabolism, this study was designed to determine if MCS cases differed from controls for genetic polymorphisms in drug-metabolizing enzymes.

Methods: Female Caucasian participants (203 cases and 162 controls) were drawn from a larger case-control study based on a reproducible and validated case definition. Common polymorphisms for CYP2D6, NAT1, NAT2, PON1, and PON2 were genotyped.
Results: Comparing cases and controls, significant differences were found in genotype distributions for CYP2D6 ($P = 0.02$) and NAT2 ($P = 0.03$). Compared with the referent homozygous inactive (CYP2D6) or slow (NAT2) metabolizers, the odds for being CYP2D6 homozygous active (OR = 3.36, $P = 0.01$) and NAT2 rapid (OR = 4.14, $P = 0.01$) were significantly higher in cases than controls. The odds for being heterozygous for PON1-55 (OR = 2.05, $P = 0.04$) and PON1-192 (OR = 1.57, $P = 0.04$) were also significantly higher in cases.
Conclusions: A genetic predisposition for MCS may involve altered biotransformation of environmental chemicals. The CYP2D6 enzyme activates and inactivates toxins; the NAT2 enzyme bioactivates arylamines to protein-binding metabolites. A gene–gene interaction between CYP2D6 and NAT2 suggested that rapid metabolism for both enzymes may confer substantially elevated risk (OR = 18.7, $P = 0.002$). Our finding parallels others' observation of a link between PON1 heterozygosity and neurological symptoms in Gulf War syndrome. This first demonstration of genetic variation in drug-metabolizing enzymes in association with MCS requires replication. However, it suggests new research directions on genetically variable toxin pathways that might be important in MCS.

Mckeown-Eyssen G.E., Baines C.J., Marshall L.M., Jazmaji V., Sokoloff, E.R. 2001. Multiple chemical sensitivity: Discriminant validity of case definitions. *Archives of Environmental Health* 56(5): 406-12.

In this study, the authors used the University of Toronto's Health Survey self-administered questionnaire to determine discriminant validity of multiple chemical sensitivity definitions. The authors distributed a total of 4,126 questionnaires to adults who attended general, allergy, occupational, and environmental health practices. The authors then matched responses to features selected from existing case definitions posited by Thomson et al.; the National Research Council; Cullen; Ashford and Miller; Randolph; Nethercott et al.; and the 1999 Consensus (references 4–7, 2, 9, and 10, respectively, herein). The overall response rate was 61.7%. The prevalence of reported symptoms was lowest in general practices, was intermediate in occupational health and allergy practices, and was highest in environmental health practices. Features from the definitions presented by Nethercott et al. and the 1999 Consensus (references 9 and 10, respectively, herein) correctly identified more than 80% of environmental health practice patients and more than 70% of general practice patients. Combinations of 4 symptoms (i.e., having a stronger sense of smell than others, feeling dull/groggy, feeling “spacey,” and having difficulty concentrating) also discriminated successfully. In summary, features from 2 of 7 case definitions assessed by the University of Toronto Health Survey achieved good discrimination and identified patients with an increased likelihood of multiple chemical sensitivity.

Meggs W.J., Cleveland C.H. Jr. 1993. Rhinolaryngoscopic examination of patients with the multiple chemical sensitivity syndrome. *Archives of Environmental Health* 48(1): 14-18.

Ten patients who met the Cullen case definition for the multiple chemical sensitivity syndrome were evaluated; a history was taken, and physical examination and fiberoptic rhinolaryngoscopy were performed. All patients had an initial chemical exposure, which was followed by multiple

physical and mental complaints in response to subsequent exposure to a variety of odorous organic chemicals. Rhinitis was a prominent complaint in nine patients, but one patient denied any nasal symptoms. Rhinolaryngoscopic findings were abnormal in all patients; edema, excessive mucus, a cobblestone appearance of the posterior pharynx and base of the tongue, and mucosal injection were observed frequently. A particularly striking finding was focal areas of blanched mucosa that surrounded a prominent vessel. These results suggest that nasal pathology may be a prominent feature of this disorder.

Meggs W.J., Dunn K.A., Bloch R.M., Goodman P.E., Davidoff A.L. 1996. Prevalence and nature of allergy and chemical sensitivity in a general population. *Archives of Environmental Health* 51(4): 275-82.

The objectives of this study were (a) to determine the self-reported prevalence of allergy and chemical sensitivity in a rural population of eastern North Carolina, (b) to determine the type and frequency of symptoms for each condition, and (c) to determine the demographic groups affected. A random general telephone survey was conducted during the period May 14, 1993, to September 10, 1993, and questions about allergy and chemical sensitivity were asked. Of the 1 446 households contacted, 1 027 (71%) individuals agreed to participate. Allergies were reported by 365 (35%) individuals. Thirty percent of allergic individuals reported that symptoms occurred once or more each week, whereas 61% reported that symptoms occurred, at most, once each month. Allergic symptoms that occurred daily were reported by 5.3% of the total population. Chemical sensitivity was reported by 336 (33%) individuals. Thirty-five per cent of chemically sensitive individuals reported symptoms at least once each week, whereas 53% reported that symptoms occurred once (or less) each month. Symptoms of chemical sensitivity that occurred daily were reported by 3.9% of the total population. Both allergy and chemical sensitivity were distributed widely across age, income, race, and educational groups. Simultaneous allergy and chemical sensitivity were reported by 16.9% of the population, allergy without chemical sensitivity by 16.0%, chemical sensitivity without allergy by 18.2%, and neither condition by 48.9%. If the prevalence of sensitivity to chemical irritants is, in fact, equivalent to that of allergy, as was found in this study, then support for the scientific investigation of chemical sensitivity is justified.

Meggs W.J. 1993. Neurogenic inflammation and sensitivity to environmental chemicals. *Environmental Health Perspectives* 101(3): 234-38.

Neurogenic inflammation as a pathway distinct from antigen-driven, immune-mediated inflammation may play a pivotal role in understanding a broad class of environmental health problems resulting from chemical exposures. Recent progress in understanding the mediators, triggers, and regulation of neurogenic inflammation is reviewed. Evidence for and speculations about a role for neurogenic inflammation in established disorders such as asthma, rhinitis, contact dermatitis, migraine headache, and rheumatoid arthritis are presented. The sick building syndrome and multiple chemical sensitivity syndrome have been defined as clinical entities in which exposure to chemical inhalants gives rise to disease. Current data on the existence of chemical irritant receptors in the airway and skin are discussed; neurogenic inflammation arising from stimulation of chemical irritant receptors is a possible model to explain many of the aspects of chemical sensitivities.

Meggs W.J. 1995. Neurogenic switching: a hypothesis for a mechanism for shifting the site of inflammation in allergy and chemical sensitivity. *Environmental Health Perspectives* 103: 54-56.

Neurogenic switching is proposed as a hypothesis for a mechanism by which a stimulus at one site can lead to inflammation at a distant site. Neurogenic inflammation occurs when substance P and other neuropeptides released from sensory neurons produce an inflammatory response, whereas immunogenic inflammation results from the binding of antigen to antibody or leukocyte receptors. There is a crossover mechanism between these two forms of inflammation. Neurogenic switching is proposed to result when a sensory impulse from a site of activation is rerouted via the central nervous system to a distant location to produce neurogenic inflammation at the second location. Neurogenic switching is a possible explanation for systemic anaphylaxis, in which inoculation of the skin or gut with antigen produces systemic symptoms involving the respiratory and circulatory systems, and an experimental model of anaphylaxis is consistent with this hypothesis. Food-allergy-iducing asthma, urticaria, arthritis, and fibromyalgia are other possible examples of neurogenic switching. Neurogenic switching provides a mechanism to explain how allergens, infectious agents, irritants, and possibly emotional stress can exacerbate conditions such as migraine, asthma, and arthritis. Because neurogenic inflammation is known to be triggered by chemical exposures, it may play a role in the sick building syndrome and the multiple chemical sensitivity syndrome. Thus neurogenic switching would explain how the respiratory irritants lead to symptoms at other sites in these disorders.

Meggs W.J. 1999. Mechanisms of allergy and chemical sensitivity. *Toxicology and Industrial Health* 15(3): 331-38.

Allergy and chemical sensitivity are closely related disorders in which environmental exposures produce inflammatory reactions. For allergy, environmental proteins bind to IgE antibody on mast cells leading to the release of inflammatory mediators. In chemical sensitivity, low molecular weight chemicals bind to chemoreceptors on sensory nerve C-fibers leading to the release of inflammatory mediators. Clinical manifestations are similar in the two conditions. The overlap between the two conditions has a basis in mechanism, so the similarity of clinical manifestations and high percentage of individuals with both conditions may have a biological basis. Chronic exposures can lead to adaptation phenomena. Depression has been associated with both allergy and chemical sensitivity. Both the allergic and chemical irritant responses may be subjected to conditioning so that the response is triggered by other stimuli. Evidence for conditioning is strongest for allergy. Both allergy and chemical sensitivity can be acquired in association with irritant exposures.

Meggs, W.J. 1997. Hypothesis for induction and propagation of chemical sensitivity based on biopsy studies. *Environmental Health Perspectives* 105 (Suppl 2): 473-78.

The reactive airways dysfunction syndrome (RADS), the reactive upper airways dysfunction syndrome (RUDS), the sick building syndrome (SBS), and the multiple chemical sensitivity syndrome (MCS) are overlapping disorders in which there is an intolerance to environmental chemicals. The onset of these illnesses is often associated with an initial acute chemical exposure. To understand the pathophysiology of these conditions, a study of the nasal pathology of individuals experiencing these syndromes was undertaken. Preliminary data indicate that the

nasal pathology of these disorders is characterized by defects in tight junctions between cells, desquamation of the respiratory epithelium, glandular hyperplasia, lymphocytic infiltrates, and peripheral nerve fiber proliferation. These findings suggest a model for a relationship between the chronic inflammation seen in these conditions and an individual's sensitivity to chemicals. A positive feedback loop is set up: the inflammatory response to low levels of chemical irritants is enhanced due to the observed changes in the epithelium, and the epithelial changes are propagated by the inflammatory response to the chemicals. This model, combined with the concept of neurogenic switching, has the potential to explain many aspects of RADS, RUDS, SBS, and MCS in a unified way.

Meggs W.J. 1994. RADS and RUDS—the toxic induction of asthma and rhinitis. *Clinical Toxicology* 32(5): 487-501.

Inhalation exposures can produce asthma and rhinitis by several mechanisms. Sensitization with the production of IgE specific for a substance can lead to symptoms on reexposure via mast cell degranulation and the release of inflammatory mediators. Some substances, known as environmental adjuvants, enhance the immune response to concomitant exposures with the environmental adjuvant. Respiratory irritants can lead to asthma and rhinitis through interaction with chemical irritant receptors in the airway, leading to release of substance P from sensory nerves and neurogenic inflammation. The reactive airways dysfunction syndrome is a chronic asthma-like syndrome resulting from a single acute exposure to a respiratory irritant, while the reactive upper-airways dysfunction syndrome is chronic rhinitis stemming from an irritant exposure. The dysregulation of neurogenic inflammation by chemical exposures may be an important mechanism in the toxic induction of reactive airways dysfunction syndrome and reactive upper-airways dysfunction syndrome and may play a role in understanding the sick building syndrome and the multiple chemical sensitivity syndrome.

Meggs W.J. 1995. Multiple chemical sensitivities—chemical sensitivity as a symptom of airway inflammation. *Journal of Toxicology. Clinical Toxicology* 33(2): 107-10.

The term multiple chemical sensitivity confuses etiology with diagnosis. Chemical sensitivity is a symptom expressed by patients. The symptoms complex is also expressed by the majority of patients with asthma reactive airway dysfunction syndrome or rhinitis following a single acute exposure, called reactive upper airway dysfunction syndrome. The chemically sensitivity patient merits evaluation for upper airway and bronchial reactivity that may cause extra-airway symptomatology.

Miller C.S., Gammage R.B., Jankovic J.T. 1999. Exacerbation of chemical sensitivity: a case study. *Toxicology and Industrial Health* 15(3-4): 398-402.

We report exacerbation of symptoms and chemical intolerances in three of four self-described chemically sensitive women following relocation to a newly constructed office building. Levels of total volatile organic compounds (TVOCs) in this building prior to occupancy were approximately 200 $\mu g/m^3$ (toluene equivalent units) with a myriad of individual components present. By day 50 after occupancy, the concentration of TVOCs in the building dropped to approximately 50 $\mu g/m^3$. Nevertheless, three women reported significant worsening of their

symptoms with spreading of their sensitivities to previously tolerated chemical exposures. One woman relocated to another building, while the other two managed their symptoms by reducing time spent in the building or by using a room air cleaner. By day 600 following occupancy, although TVOCs had increased significantly (perhaps due to cleaning agents), there were fewer individual VOCs present in the air, and some of the women were able to tolerate the air in the building. We conclude that complex mixtures of VOCs at very low levels tolerated by the majority of building occupants may pose problems for persons who report pre-existing chemical sensitivities. TVOC measurements may not correlate with symptoms in these individuals. Reasonable accommodations by an employer can reduce problem exposures, making it possible for some affected individuals to continue productive employment.

Miller C., Ashford N., Doty R., Lamielle M. Otto D., Rahill A., Wallace L. 1997. Empirical approaches for the investigation of toxicant-induced loss of tolerance. *Environmental Health Perspectives* 102 (Suppl 2): 515-19.

It has been hypothesized that sensitivity to low-level chemical exposures develops in two steps: initiation by an acute or chronic chemical exposure, followed by triggering of symptoms by low levels of previously tolerated chemical inhalants, foods, or drugs. The Working Group on Toxicant-induced Loss of Tolerance has formulated a series of research questions to test this hypothesis: Do some individuals experience sensitivity to chemicals at levels of exposure unexplained by classical toxicological thresholds and dose-response relationships, and outside normally expected variation in the population? Do chemically sensitive subjects exhibit masking that may interfere with the reproducibility of their responses to chemical challenges? Does chemical sensitivity develop because of acute, intermittent, or continuous exposure to certain substances? If so, what substances are most likely to initiate this process? An experimental approach for testing directly the relationship between patients' reported symptoms and specific exposures was outlined in response to the first question, which was felt to be a key question. Double-blind, placebo-controlled challenges performed in an environmentally controlled hospital facility (environmental medical unit) coupled with rigorous documentation of both objective and subjective responses are necessary to answer this question and to help elucidate the nature and origins of chemical sensitivity.

Miller C.S. and Mitzel H.C. 1995. Chemical sensitivity attributed to pesticide exposure versus remodeling. *Archives of Environmental Health* 50(2): 119-29.

One hundred twelve individuals who reported onset of multiple chemical sensitivity following well-documented exposure to either (1) a cholinesterase-inhibiting organophosphate or carbamate pesticide or (2) remodeling of a building completed mail-out/mail-back questionnaires concerning their exposure, symptoms, sensitivity to ingestants and inhalants, utilization of health-care resources, and impact of their illness on lifestyle. It was hypothesized that if multiple chemical sensitivity resulted from neurotoxic exposure, then organophosphate-exposed respondents should report greater severity of illness resulting from the relatively greater neurotoxicity of this class of chemicals. Pesticide-exposed and remodeling-exposed multiple chemical sensitivity groups reported similar patterns of symptoms and identified similar inhalants and ingestants as triggers for their symptoms; these results suggested a common mechanism (biological and/or psychological) for their conditions. The pesticide-exposed group,

however, reported significantly greater symptom severity than did the remodeling-exposed group, especially for neuromuscular, affective, airway, gastrointestinal, and cardiac symptoms. These findings provide evidence for (1) a possible biological basis for multiple chemical sensitivity and (2) a distinct pathophysiology or final common pathway for the condition that, while as yet undefined, appears to be shared by these two groups. Although subjective multisystem health complaints characterize both multiple chemical sensitivity and somatoform disorder, features of this multiple chemical sensitivity sample were inconsistent with somatoform disorder, i.e., onset after 30 y of age in 83%, the predominance of severe cognitive symptoms, and attributions of environmental causation. No group differences were found with respect to lifestyle impact. Eighty-one percent of respondents said they had been working full-time at the time they were exposed, yet at the time of the survey (on average, 7.7 y post exposure) only 12.5% were working full-time. The majority said they had quit their jobs, changed jobs, or changed careers because of their illness. Approximately 40% reported that they had consulted 10 or more medical practitioners. The persistent, disabling neuropsychological symptoms reported by these multiple chemical sensitivity groups are strikingly similar to those reported among individuals exposed occupationally to pesticides and solvents. These parallel findings suggest that the types and levels of exposures associated with extermination and remodeling may not be inconsequential, at least for a subset of the population. Further studies from a variety of perspectives, including human challenge studies and the development of animal models, are needed to define the pathophysiological and psychological mechanisms underlying this costly condition.

Miller C.S. and Prihoda T.J. 1999. The Environmental Exposure and Sensitivity Inventory (EESI): a standardized approach for measuring chemical intolerances for research and clinical applications. *Toxicology and Industrial Health* 15(3/4): 370-85.

The lack of a generally accepted case definition for multiple chemical sensitivity (MCS) and the absence of a standardized approach for measuring salient aspects of chemical sensitivity that would permit cross-comparison of findings by different investigators have hindered progress in this area. Based upon findings from an earlier study of 112 persons with self-reported chemical sensitivity who attributed their chemical sensitivity to a well-defined exposure event, we developed an instrument with self-rating scales to assess Symptom Severity, Chemical (Inhalant) Intolerances, Other Intolerances (e.g., foods, medications, alcohol), Life Impact, and Masking (a measure of ongoing chemical exposures). When administered to four patient groups and controls, the scales showed good reliability and validity overall (n=421) and in each group. Used together, the scales provided sensitivity of 92% and specificity of 95% in differentiating chemically sensitive persons from controls. Our results support use of these scales individually or collectively for a variety of applications including the selection of chemically sensitive subjects and controls for research, assessment of chemical sensitivity in various study populations, cross-comparison of groups studied by different investigators, pre- and post-assessment of therapeutic interventions, clinical evaluation of complex patients who report intolerances, and teaching medical residents and students how to evaluate patients for chemical sensitivity and MCS.

Miller, C.S. 2001. The compelling anomaly of chemical intolerance. *Annals of the New York Academy of Sciences* 933:1-23.

In science, anomalies expose the limitations of existing paradigms and drive the search for new ones. In the late 1800s, physicians observed that certain illnesses spread from sick, feverish individuals to those contacting them, paving the way for the germ theory of disease. The germ theory served as a crude, but elegant formulation that explained dozens of seemingly unrelated illnesses affecting literally every organ system. Today, we are witnessing another medical anomaly—a unique pattern of illness involving chemically exposed groups in more than a dozen countries, who subsequently report multisystem symptoms and new-onset chemical, food, and drug intolerances. These intolerances may be the hallmark for a new disease process or paradigm, just as fever is a hallmark for infection. The fact that diverse demographic groups, sharing little in common except some initial chemical exposure event, develop these intolerances is a compelling anomaly pointing to a possible new theory of disease, one that has been referred to as "Toxicant-Induced Loss of Tolerance" ("TILT"). TILT has the potential to explain certain cases of asthma, migraine headaches, and depression, as well as chronic fatigue, fibromyalgia, and "Gulf War syndrome". It appears to evolve in two stages: (1) initiation, characterized by a profound breakdown in prior, natural tolerance resulting from either acute or chronic exposure to chemicals (pesticides, solvents, indoor air contaminants, etc.), followed by (2) triggering of symptoms by small quantities of previously tolerated chemicals (traffic exhaust, fragrances, gasoline), foods, drugs, and food/drug combinations (alcohol, caffeine). While the underlying dynamic remains an enigma, observations indicating that affected individuals respond to structurally unrelated drugs and experience cravings and withdrawal-like symptoms, paralleling drug addiction, suggest that multiple neurotransmitter pathways may be involved.

Miller C.S., Prihoda T.J. 1999. A controlled comparison of symptoms and chemical intolerances reported by Gulf War veterans, implant recipients, and persons with multiple chemical sensitivity. *Toxicology and Industrial Health* 15(3/4): 386-97.

Using the Environmental Exposure and Sensitivity Inventory (EESI), a standardized instrument for measuring chemical sensitivity, we obtained and compared ratings of symptoms, chemical (inhalant) intolerances, other intolerances (e.g., drugs, caffeine, alcohol, skin contactants), lifeimpact, and masking (ongoing exposures) in five populations: multiple chemical sensitivity (MCS) patients who did (n=96) or did not (n=90) attribute onset of their illness to a specific exposure event, patients with implanted devices (n=87), Gulf War veterans (n=72), and controls (n=76). For each patient group, mean scores on the first four scales were significantly greater than for controls. MCS patients reported avoiding more chemical exposures (were less masked) than the other groups. Across groups, for a given level of symptoms, as masking increased, mean scores on the Chemical Intolerance Scale decreased. In contrast, mean scores on the Other Intolerance Scale appeared to be less affected by masking. These findings suggest that some patients with antecedent chemical exposures, whether exogenous (chemical spill, pesticide application, indoor air contaminants) or endogenous (implant), develop new chemical, food, and drug intolerances. Reports of new caffeine, alcohol, medication, food, or other intolerances by patients may signal exposure-related illness. Masking may reduce individuals' awareness of chemical intolerances, and, to a lesser degree, other intolerances.

Miller C.S. 1999. Are we on the threshold of a new theory of disease? Toxicant-induced loss of tolerance and its relationship to addiction and abdiction. *Toxicology and Industrial Health* 15(3/4): 284-94.

`Toxicant-induced loss of tolerance' (or TILT) describes a two-step disease process in which (1) certain chemical exposures, e.g., indoor air contaminants, chemical spills, or pesticide applications, cause certain susceptible persons to lose their prior natural tolerance for common chemicals, foods, and drugs (initiation); (2) subsequently, previously tolerated exposures trigger symptoms. Responses may manifest as addictive or abdictive (avoidant) behaviors. In some affected individuals, overlapping responses to common chemical, food, and drug exposures, as well as habituation to recurrent exposures, may hide (mask) responses to particular triggers. Accumulating evidence suggests that this disease process might underlie a broad array of medical illnesses including chronic fatigue, fibromyalgia, migraine headaches, depression, asthma, the unexplained illnesses of Gulf War veterans, multiple chemical sensitivity, and attention deficit disorder.

Miller C.S. 1992. Possible models for multiple chemical sensitivity: conceptual issues and the role of the limbic system. *Toxicology and Industrial Health* 8(4): 181-90.

Conceivably, chemicals contacting olfactory nerve projections in the nose could either be transported into or relay electrical signals to the limbic region, leading to a vast array of symptoms. Likewise, thought processes and mood states may trigger or interrupt pre-existing limbic activity. At present, however, no evidence suggests that limbic activity triggered by environmental exposures can be entirely overcome by psychologic interventions. One important ramification of a limbic hypothesis, if true, is that no convenient biologic marker for multiple chemical sensitivity may exist at the present time. Ten years from now, we may finally confirm the existence of multiple chemical sensitivities (by careful, blinded challenges) but still have no single mechanism to explain it; that is, after all avenues of biochemical and immunologic inquiry have been exhausted, no single cause or marker for this disorder may be apparent. The theory that adaptation plays a role in MCS is based on the observed responses of patients in a deadapted state who have been housed in an environmental unit. Although adaptation is only an observation at this time, not a mechanism, biologic limits might regulate how much an organism can adapt. Such limits could be highly individual and vary by orders of magnitude. Certainly adaptation occurs at all levels of biologic systems, from enzyme systems to cells, tissues, organs, and even behavior (Fregly, 1969). Theoretically, a major insult or the accumulation of lower-level injuries within these systems could lead to a kind of "overload" or "saturation" effect with respect to adaptive capacity. This might cause an individual to have environmental responses, which, instead of being flexible and fluid, would become fragile and overly responsive. Many MCS patients report that years, and in some cases decades, after the onset of their problems, they have recovered only a portion of their former energies and tolerance for their environment. Their descriptions seem to suggest the loss of an intangible capacity to adapt, parts of which may be temporary and recoverable and other parts of which may not. Perhaps our patients have been telling us the diagnosis.

Miller, C.S. 1996. Chemical sensitivity: symptom, syndrome or mechanism for disease? *Toxicology* 111(1-3): 69-86.

Several different meanings have been attached to the term "chemical sensitivity" by those who use it. Feeling ill from odors is a *symptom* reported by approximately one-third of the population. The *syndrome* of chemical sensitivity, frequently called "Multiple Chemical Sensitivity" or "MCS" has been the subject of three federally sponsored workshops; at least five different case definitions for research on MCS have been proposed. In contrast, the hypothesis that chemical sensitivity may be a *mechanism for disease* posits that a broad spectrum of "recognized" chronic illnesses, ranging from asthma and migraine to depression and chronic fatigue, may be the consequence of environmental chemical exposures. According to this theory, a two-step process occurs: (1) an initial salient exposure event(s) (for example, a one-time, intermittent, or continuous exposure to pesticides, solvents, or air contaminants in a sick building) interacts with a susceptible individual, causing loss of tolerance for everyday, low level chemical inhalants (car exhaust, fragrances, cleaning agents), as well as for foods, drugs, alcohol, and caffeine; (2) thereafter, such common, formerly well-tolerated substances trigger symptoms, thus perpetuating illness. "Masking" (acclimatization, apposition, and addiction) may hide these exposure-symptom relationships, thus obfuscating the environmental etiology of the illness. Accumulating clinical observations lend credence to a view of chemical sensitivity as an emerging theory of disease causation and underscore the need for its testing in a rational, scientific manner. While chemical sensitivity may be the consequence of chemical exposure, the term "toxicant-induced loss of tolerance" more fully describes the two-step process under scrutiny.

Miller C.S. 1997. Toxicant-induced loss of tolerance—an emerging theory of disease? *Environmental Health Perspectives* 105 (Suppl 2): 445-53.

This paper attempts to clarify the nature of chemical sensitivity by proposing a theory of disease that unites the disparate clinical observations associated with the condition. Sensitivity to chemicals appears to be the consequence of a two-step process: loss of tolerance in susceptible persons following exposure to various toxicants, and subsequent triggering of symptoms by extremely small quantities of previously tolerated chemicals, drugs, foods, and food and drug combinations including caffeine and alcohol. Although chemical sensitivity may be the consequence of this process, a term that may more clearly describe the observed process is toxicant-induced loss of tolerance. Features of this yet-to-be-proven mechanism or theory of disease that affect the design of human exposure studies include the stimulatory and withdrawal-like nature (resembling addiction) of symptoms reported by patients and masking. Masking, which may blunt or eliminate responses to chemical challenges, appears to have several components: apposition, which is the overlapping of the effects of closely timed exposures, acclimatization or habituation, and addiction. A number of human challenge studies in this area have concluded that there is no physiological basis for chemical sensitivity. However, these studies have failed to address the role of masking. To ensure reliable and reproducible responses to challenges, future studies in which subjects are evaluated in an environmental medical unit, a hospital-based facility in which background chemical exposures are reduced to the lowest levels practicable, may be necessary. A set of postulates is offered to determine whether there is a causal relationship between low-level chemical exposures and symptoms using an environmental medical unit.

Miller C.S. 2001. Toxicant-induced loss of tolerance. *Addiction* 96(1): 115-39.

Drug *addiction* and multiple chemical intolerance (abdiction) appear to be polar opposites - the former characterized by craving and dependency, the latter by aversion. However, when the two are viewed in juxtaposition similarities emerge, revealing a common underlying dynamic, one which appears to be a new paradigm of disease. TILT, or toxicant-induced loss of tolerance, bridges the gap between *addiction* and abdiction and has the potential to explain a variety of illnesses, including certain cases of asthma, migraine headaches and depression, as well as chronic fatigue syndrome, fibromyalgia and "Gulf War syndrome". This paper argues that both *addiction* and chemical intolerance involve a fundamental breakdown in innate tolerance, resulting in an amplification of various biological effects, particularly withdrawal symptoms. While addicts seek further exposures so as to avoid unpleasant withdrawal symptoms, chemically intolerant individuals shun their problem exposures, but for the same reason - to avoid unpleasant withdrawal symptoms. These observations raise critical questions: do addictive drugs and environmental pollutants initiate an identical disease process? Once this process begins, can both addictants and pollutants trigger symptoms and cravings? TILT opens a new window between the fields of *addiction* and environmental medicine, one that has the potential to transform neighboring realms of medicine, psychology, psychiatry and toxicology.

Millqvist E., Bengtsson U., Lowhagen O. 1999. Provocations with perfume in the eyes induce airway symptom in patients with sensory hyperreactivity. *Allergy* 54(5): 495-99.

In earlier studies, we have shown that patients with a history of sensory hyperreactivity develop asthma-like symptoms when exposed to strong scents, even if they cannot smell any scent. METHODS: For study of possible pathophysiologic mechanisms behind sensory hyperreactivity, the patients' airways and eyes were separately exposed to a common inducing factor, perfume. Eleven patients with a history of hyperreactivity to chemical trigger factors, such as perfume, were provoked single-blindly in a placebo-controlled, randomized study. During airway exposure, the eyes were covered and, during the eye exposure, the patients inhaled fresh air. A special face mask or a nose clip was used to avoid any smell. RESULTS: During the 30-min exposure to perfume, there was a gradual increase in three main symptoms; i.e., eye irritation, cough, and dyspnea, after both the airway and eye exposures. The increases were significant compared with placebo. CONCLUSIONS: Asthma-like and other symptoms, such as irritation of the eyes, may be induced by exposure of both the airways and the eyes in patients with sensory hyperreactivity. This points to the importance of studying the sensory nervous system, not only in the airways, but also in other organs.

Millqvist E. 2005. Changes in levels of nerve growth factor in nasal secretions after capsaicin inhalation in patients with airway symptoms from scents and chemicals. *Environmental Health Perspectives* 113(7): 849-52.

Patients complaining of upper and lower airway symptoms caused by scents and chemicals have previously been shown to have increased cough sensitivity to inhaled capsaicin, but the precise mechanisms behind this reaction are unknown. Hypothesizing that a neurochemical alteration related to sensory hyperreactivity (SHR) of the airway mucosa occurs, we measured levels of nerve growth factor (NGF) in nasal lavage fluid (NAL) before and after capsaicin inhalation provocations and related the capsaicin cough sensitivity to the NGF levels. Thirteen patients with

SHR and 14 control subjects were provoked with capsaicin inhalation at three different doses. We measured NGF in NAL before and after provocation and recorded cough and capsaicin-induced symptoms. All subjects demonstrated a dose-dependent cough response to capsaicin inhalation, with a more pronounced effect in patients than in controls. Basal levels of NGF were significantly lower in the patient group than in the control subjects ($p < 0.01$). After capsaicin provocation, the patients showed a significant increase in NGF ($p < 0.01$), which was related to capsaicin cough sensitivity. The findings demonstrate that, in patients with airway symptoms induced by scents and chemicals, SHR is real and measurable, demonstrating a pathophysiology in the airways of these patients compared to healthy subjects.

Österberg K., Ørbæk P., Karlson B., Åkesson B., Bergendorf U. 2003. Annoyance and performance during the experimental chemical challenge of subjects with multiple chemical sensitivity. *Scandinavian Journal of Work, Environment and Health* 29(1): 40-50.

Objectives This study explored the subjective reactions and psychological test performance of smell-intolerant subjects during consecutive challenges to chemicals with contrasting neurotoxic properties.
Methods: Women with symptoms compatible with multiple chemical sensitivity (N=10) and healthy referents (N=20) were individually challenged in an exposure chamber. All the subjects attended two separate 2-hour sessions of exposure to n-butyl acetate and toluene, in counterbalanced sequence. After an initial phase without exposure, air concentrations were increased in steps ranging from 3.6 to 57 mg/m^3 for n-butyl acetate and from 11 to 180 mg/m^3 for toluene. The response measures comprised ratings of annoyance and smell intensity and also neurobehavioral test performance.
Results: Both groups showed an increase in annoyance ratings and a decrease in test performance in the initial unexposed chamber phase and also in the first phase of the chemical exposure, these results indicating slight immediate expectancy or "suggestion" effects. During the six chamber phases, the ratings of mucous membrane irritation and fatigue showed a steeper increase in the group with multiple chemical sensitivity than among the referents, while the ratings of smell intensity and smell annoyance were similar in the two groups. A reduction in test performance was observed during the chamber phases, particularly in the group with multiple chemical sensitivity. No relation was found between the ratings or performance and chemical substance.
Conclusions: Stronger immediate expectancy or "suggestion" reactions than normal did not characterize the group with multiple chemical sensitivity. This group showed a stronger than normal gradual build-up of fatigue, mucous membrane irritation, and reduced performance during chemical exposure. The results offer the most support to an irritative basis for multiple chemical sensitivity.

Overstreet D.H., Djuric V. 2001. A genetic rat model of cholinergic hypersensitivity: implications for chemical intolerance, chronic fatigue, and asthma. *Annals of the New York Academy of Sciences* 933:92-102.

The fact that only some individuals exposed to environmental chemicals develop chemical intolerance raises the possibility that genetic factors could be contributing factors. The present communication summarizes evidence from a genetic animal model of cholinergic supersensitivity that suggests that an abnormal cholinergic system could be one predisposing genetic factor. The Flinders Sensitive Line (FSL) rats were established by selective breeding for

increased responses to an organophosphate. It was subsequently found that these FSL rats were also more sensitive to direct-acting muscarinic agonists and had elevated muscarinic receptors compared to the selectively bred parallel group, the Flinders Resistant Line (FRL) rats, or randomly bred control rats. Increased sensitivity to cholinergic agents has also been observed in several human populations, including individuals suffering from chemical intolerance. Indeed, the FSL rats exhibit certain behavioral characteristics such as abnormal sleep, activity, and appetite that are similar to those reported in these human populations. In addition, the FSL rats have been reported to exhibit increased sensitivity to a variety of other chemical agents. Peripheral tissues, such as intestinal and airway smooth muscle, appear to be more sensitive to both cholinergic agonists and an antigen, ovalbumin. Hypothermia, a centrally mediated response, is more pronounced in the FSL rats after nicotine and alcohol, as well as agents that are selective for the dopaminergic and serotonergic systems. In some cases, the increased sensitivity has been detected in the absence of any changes in the receptors with which the drugs interact (dopamine receptors), while receptor changes have been seen in other cases (nicotine receptors). Therefore, there may be multiple mechanisms underlying the multiple chemical sensitivity-chemical intolerance of the FSL rats. An elucidation of these mechanisms may provide useful clues to those involved in chemical intolerance in humans.

Pall M.L. 2002. NMDA sensitization and stimulation by peroxynitrite, nitric oxide, and organic solvents as the mechanism of chemical sensitivity in MCS. *The FASEB Journal* 16(11): 1407-17.

Multiple chemical sensitivity (MCS) is a condition where previous exposure to hydrophobic organic solvents or pesticides appears to render people hypersensitive to a wide range of chemicals, including organic solvents. The hypersensitivity is often exquisite, with MCS individuals showing sensitivity that appears to be at least two orders of magnitude greater than that of normal individuals. This paper presents a plausible set of interacting mechanisms to explain such heightened sensitivity. It is based on two earlier theories of MCS: the elevated nitric oxide/peroxynitrite theory and the neural sensitization theory. It is also based on evidence implicating excessive NMDA activity in MCS. Four sensitization mechanisms are proposed to act synergistically, each based on known physiological mechanisms: Nitric oxide-mediated stimulation of neurotransmitter (glutamate) release; peroxynitrite-mediated ATP depletion and consequent hypersensitivity of NMDA receptors; peroxynitrite-mediated increased permeability of the blood–brain barrier, producing increased accessibility of organic chemicals to the central nervous system; and nitric oxide inhibition of cytochrome P450 metabolism. Evidence for each of these mechanisms, which may also be involved in Parkinson's disease, is reviewed. These interacting mechanisms provide explanations for diverse aspects of MCS and a framework for hypothesis-driven MCS research.—Pall, M. L. NMDA sensitization and stimulation by peroxynitrite, nitric oxide, and organic solvents as the mechanism of chemical sensitivity in multiple chemical sensitivity.

Pall M.L. 2003. Elevated nitric oxide/peroxynitrite theory of multiple chemical sensitivity: central role of N-methyl-D-aspartate receptors in the sensitivity mechanism. *Environmental Health Perspectives* 111(12): 1461-64.

The elevated nitric oxide/peroxynitrite and the neural sensitization theories of multiple chemical sensitivity (MCS) are extended here to propose a central mechanism for the exquisite sensitivity

to organic solvents apparently induced by previous chemical exposure in MCS. This mechanism is centered on the activation of *N*-methyl-d-aspartate (NMDA) receptors by organic solvents producing elevated nitric oxide and peroxynitrite, leading in turn to increased stimulating of and hypersensitivity of NMDA receptors. In this way, organic solvent exposure may produce progressive sensitivity to organic solvents. Pesticides such as organophosphates and carbamates may act via muscarinic stimulation to produce a similar biochemical and sensitivity response. Accessory mechanisms of sensitivity may involve both increased blood-brain barrier permeability, induced by peroxynitrite, and cytochrome P450 inhibition by nitric oxide. The NMDA hyperactivity/hypersensitivity and excessive nitric oxide/peroxynitrite view of MCS provides answers to many of the most puzzling aspects of MCS while building on previous studies and views of this condition.

Pall M.L., Anderson J.H. 2004. The vanilloid receptor as a putative target of diverse chemicals in multiple chemical sensitivity. *Archives of Environmental Health* 59(7): 363-75.

The article analyzes the role of the vanilloid receptor in Multiple Chemical Sensitivity (MCS). The vanilloid receptor, which appears to play a central role in the irritant response, is the putative major target for organic solvents and certain other compounds in MCS. Its widespread distribution in both the central and peripheral nervous systems, as well as in certain other tissues, suggests a possible important role for this receptor as the main target of diverse chemicals in both central and peripheral chemical sensitivity mechanisms. The vanilloid receptor is reportedly hyperresponsive in MCS and can increase nitric oxide levels and stimulate N-methyl-Daspartate. Vanilloid receptor activity is markedly altered by multiple mechanisms, possibly providing an explanation for the increased activity in MCS and symptom masking by previous chemical exposure. Activation of this receptor by certain mycotoxins may account for some cases of sick building syndrome, a frequent precursor of MCS. Twelve types of evidence implicate the vanilloid receptor as the major target of chemicals, including volatile organic solvents in MCS.

Pall M.L. 2007. Nitric oxide synthase partial uncoupling as a key switching mechanism for the NO/ONOO-cycle. *Medical Hypotheses* 69(4): 821-25.

Short-term stressors, capable of increasing nitric oxide levels, act to initiate cases of illnesses including chronic fatigue syndrome, multiple chemical sensitivity, fibromyalgia and posttraumatic stress disorder. These stressors, acting primarily through the nitric oxide product, peroxynitrite, are thought to initiate a complex vicious cycle mechanism, known as the NO/ONOO– cycle that is responsible for chronic illness. The complexity of the NO/ONOO– cycle raises the question as to whether the mechanism that switches on this cycle is this complex cycle itself or whether a simpler mechanism is the primary switch. It is proposed here that the switch involves a combination of two variable switches, the increase of nitric oxide synthase (NOS) activity and the partial uncoupling of the NOS activity, with uncoupling caused by a tetrahydrobiopterin (BH4) deficiency. NOS uncoupling causes the NOS enzymes to produce superoxide, the other precursor of peroxynitrite, in place of nitric oxide. Thus partial uncoupling will cause NOS proteins to act like peroxynitrite synthases, leading, in turn to increased NF-κB activity. Peroxynitrite is known to oxidize BH4, and consequently partial uncoupling may initiate a vicious cycle, propagating the partial uncoupling over time. The combination of high NOS activity and BH4 depletion will lead to a potential vicious cycle that may be expected to switch

on the larger NO/ONOO– cycle, thus producing the symptoms and signs of chronic illness. The role of peroxynitrite in the NO/ONOO– cycle also implies that such uncoupling is part of the chronic phase cycle mechanism such that agents that lower uncoupling will be useful in treatment.

Pall M.L. 2001. Common etiology of posttraumatic stress disorder, fibromyalgia, chronic fatigue syndrome and multiple chemical sensitivity via elevated nitric oxide/peroxynitrite. *Medical Hypotheses* 57(2): 139-45.

Three types of overlap occur among the disease states chronic fatigue syndrome (CFS), fibromyalgia (FM), multiple chemical sensitivity (MCS) and posttraumatic stress disorder (PTSD). They share common symptoms. Many patients meet the criteria for diagnosis for two or more of these disorders and each disorder appears to be often induced by a relatively short-term stress which is followed by a chronic pathology, suggesting that the stress may act by inducing a self-perpetuating vicious cycle. Such a vicious cycle mechanism has been proposed to explain the etiology of CFS and MCS, based on elevated levels of nitric oxide and its potent oxidant product, peroxynitrite. Six positive feedback loops were proposed to act such that when peroxynitrite levels are elevated, they may remain elevated. The biochemistry involved is not highly tissue-specific, so that variation in symptoms may be explained by a variation in nitric oxide/peroxynitrite tissue distribution. The evidence for the same biochemical mechanism in the etiology of PTSD and FM is discussed here, and while less extensive than in the case of CFS and MCS, it is nevertheless suggestive. Evidence supporting the role of elevated nitric oxide/peroxynitrite in these four disease states is summarized, including induction of nitric oxide by common apparent inducers of these disease states, markers of elevated nitric oxide/peroxynitrite in patients and evidence for an inductive role of elevated nitric oxide in animal models. This theory appears to be the first to provide a mechanistic explanation for the multiple overlaps of these disease states and it also explains the origin of many of their common symptoms and similarity to both Gulf War syndrome and chronic sequelae of carbon monoxide toxicity. This theory suggests multiple studies that should be performed to further test this proposed mechanism. If this mechanism proves central to the etiology of these four conditions, it may also be involved in other conditions of currently obscure etiology and criteria are suggested for identifying such conditions.

Pall M.L., Satterlee J.D. 2001. Elevated nitric oxide/peroxynitrite mechanism for the common etiology of multiple chemical sensitivity, chronic fatigue syndrome, and posttraumatic stress disorder. *Annals of the New York Academy of Sciences* 933:323-29.

Chronic fatigue syndrome (CFS), multiple chemical sensitivity (MCS), post-traumatic stress disorder (PTSD), and fibromyalgia (FM) show three distinct types of overlap: each is typically induced by a short-term stress leading to a chronic pathology; all four show a set of substantial overlapping symptoms; and many patients have been diagnosed as having several of these disorders. These and other similarities have led to the suggestion that all four of these may be essentially identical, sharing a common, yet previously undefined etiology. For example, Buchwald and Garrity[1] concluded a study of CFS, MCS, and FM patients by suggesting that, "Despite their different diagnostic labels, existing data, though limited, suggest that these illnesses may be similar if not identical conditions…." Miller suggested that CFS, MCS, PTSD,

FM, and several other disorders may share a common, if undefined etiology,2 asking whether these constitute "an emerging theory of disease". One of us (M. L. Pall) has proposed a novel theory for the cause of CFS, based on elevated levels of peroxynitrite and its precursors, nitric oxide and superoxide.3 Central to this theory are six positive feedback loops, which act such that elevated peroxynitrite increases the levels of both nitric oxide and superoxide, reacting to form more peroxynitrite.3 By this vicious cycle mechanism (Fig. 1A), once the cycle is established, elevated levels of peroxynitrite and other components of this mechanism, notably nitric oxide, superoxide, and inflammatory cytokines, may produce the symptoms of CFS. Because the biochemical mechanisms involved here are not highly tissue-specific, some variation in tissue distribution of elevated peroxynitrite may produce the differences in symptoms often seen between, for example, classic cases of CFS and MCS. In this paper, we focus on MCS, asking whether the proposed elevated nitric oxide/peroxynitrite mechanism may be central to the etiology of MCS. The evidence examined here includes each of the following: evidence that incitants of MCS act to induce increased levels of nitric oxide; evidence for induction of the inducible nitric oxide synthase in MCS; evidence for elevated levels of oxidative stress, as might be produced by peroxynitrite; evidence that incitants can induce inflammatory cytokines; and multiple types of evidence from animal models of MCS showing that increased nitric oxide has an essential role in producing the responses in these models. We also suggest that peroxynitrite may play an additional role in MCS by inducing breakdown of the blood-brain barrier.

Parkinson D.K., Bromet S., Cohen L.O., Dunn M.A., Dew C. 1990. Health effects of long-term solvent exposure among women in blue-collar occupations. *American Journal of Industrial Medicine* 17(6): 661-75.

The relationship of solvent exposure to self-reported neurologic and somatic symptoms as well as neuropsychological performance was examined in a sample of 567 female blue collar workers who were members of the International Brotherhood of Electrical Workers (IBEW). Structured interviews were conducted at IBEW offices. Five solvent exposure categories were derived--never exposed, exposed prior to but not during the past year, exposed during the past year but not currently, currently exposed less than 50% of the time, and currently exposed more than 50% of the time. No differences among the groups on neuropsychological performance were found. On the other hand, heightened exposure was significantly related to depression, severe headaches, light-headedness, room spinning, appetite difficulties, funny taste in mouth, weakness/fatigue, rashes, and abdominal pain after controlling for the effects of seven risk factors (age, smoking, moderate-heavy alcohol consumption, severe obesity, history of physician-diagnosed chronic illness, working in a clean room, and exposure to other chemicals). These findings are consistent with Scandinavian studies of solvent-exposed male workers and point to the need for careful prospective research.

Perhall K.E. 2003. Contact and chemical sensitivities in the hospital environment. *Otolaryngologic Clinics of North America* 36(5): 1021-34.

As surgeons, otolaryngologists tend to most be interested in operative procedures and leave the hospital environment to the care of administrators and the nursing staff. Given the dangers that are present, it would seem prudent to spend some time considering the agents that are used in patient care and in operating suites, to minimize the risk to patients and co-workers.

Rea W.J., Ross G.H. 1989. Food and chemicals as environmental incitants. *The Nurse Practitioner.* 14(9): 17.

Susceptibility to environmental incitants such as air, food and water components is becoming an increasingly recognized health problem. These sensitivities and reactions can induce a spectrum of symptoms affecting smooth muscle, mucous membranes and collagen in the respiratory, gastrointestinal, genitourinary and vascular systems. These reactions may be mistaken for hypochondriasis, but actually are due to reactions to foods and chemicals found in the patient's home and work environments. Careful clinical histories should alert the nurse and physician, who can confirm suspicions by eliminating and challenging the patient with potentially offending agents under controlled circumstances.

Rea W.J., Pan Y., Johnson A.R. 1991. Clearing of toxic volatile hydrocarbons from humans. *Boletín de la Asociación Médica de Puerto Rico* 83(7): 321-24.

In this study, different modes of therapy for the removal of toxic chemicals from the human body have been assessed and compared. This consisted of: 1) thirteen inpatients in an environmentally controlled area in a hospital, 2) forty-one outpatients with home environmental control and work area change, and 3) fifteen outpatients in a physical therapy/sauna program with a good environmental control. Attention to manipulation of food, food contaminants, water and air pollution as well as nutritional therapy was important in all groups. Each modality seemed efficacious in++ its own right; 100% inpatients, 80% sauna/physical therapy patients, and 70% outpatients improved their signs and symptoms. Inpatient therapy in a finally controlled environment was far superior to the other two modalities in clearing of symptoms, as well as in clearing of organic chemicals. Outpatient and sauna/physical therapy are efficacious for less ill patients.

Rea W.J., Ross G.H., Johnson A.R., Smiley R.E., Sprague D.E., Fenyves E.J., Samadi N. 1991. Confirmation of chemical sensitivity by means of double-blind inhalant challenge of toxic volatile chemicals. *Boletín de la Asociación Médica de Puerto Rico* 83(9): 389-93.

Fifty chemically sensitive patients with vascular, asthmatic and arthritic signs, ranging in age from 21 to 61, were exposed to double-blind challenges of ambient doses of inhaled toxic chemicals in a specially designed booth in an Environmental Control Unit (ECU). Primary signs and symptoms were recorded before and after challenge with five chemicals and three placebos. Inhaled challenges included phenol (less than .0025 ppm), petroleum-derived ethyl alcohol (less than .5 ppm), formaldehyde (less than .2 ppm), chlorine (less than .3 ppm), and pesticide (2, 3,-D at less than .0034 ppm). Placebos were water or saline. A set on testing criteria were evaluated for maximizing the likelihood of well-defined, reproducible information from these ambient-dose double-blind challenges. For best results, these testing criteria include: Before testing, the patient must be housed in a chemically less polluted environment. The individual must have been de-adapted to food, air, and water pollutants by means of a water fat for three to four days. At the time of the challenge, the patient must be on food and water previously determined to be safe. An enclosed non-pulluted challenge booth must be used for these chemical exposures. Sign and symptom scores appropriate for that patient must be recorded, before and after challenge. Appropriate doses of the chemical in question (determined by air concentration and length of

exposure) are necessary to investigate a particular problem. The conclusion of the study is that in these patients, chemical sensitivity clearly does exist (pulse rate differences between positive responses and placebo - p .001).(ABSTRACT TRUNCATED AT 250 WORDS).

Rogers W.R., Miller C.S., Bunegin L. 1999. A rat model of neurobehavioral sensitization to toluene. *Toxicology and Industrial Health* 15(3-4): 356-69.

Some individuals report that, following either a single high-level or repeated lower-level exposures to chemicals (initiation), subsequent exposure to very low concentrations of chemicals (triggering) produces a variety of adverse effects, including disruption of cognitive processes. Our objective was to model this two-step process in a laboratory animal. Two groups of 16 rats, eight male and eight female, received whole-body inhalation exposure to toluene, either at 80 ppm for 6 h/day for 4 weeks (Repeat group) or to 1600 ppm for 6 h/day on one day only (Acute group). Two other groups (Trigger group and Clean group) of 16 were sham-exposed. After 17 days without toluene exposure, the Acute, Repeat and Trigger groups began a series of daily toluene `trigger' exposures (10 ppm for 1 h) followed immediately by testing on an operant repeated-acquisitions task requiring learning within and across sessions. The Clean group was sham-exposed prior to operant testing. Trigger or sham exposures and operant testing continued 5 days/week for 17 sessions. Analysis of variance revealed a variety of statistically significant ($P<0.05$) differences between treatment groups. Furthermore, the patterns of differences between groups differed ($P<0.05$) for female and male rats. For example, male rats of the Trigger group made the most responses, and female rats of the Repeat group responded most slowly. The observation of important changes in the operant behavior of female and male rats previously exposed to toluene, at relatively low concentrations (80 or 1600 ppm) and then later re-exposed at very low concentrations (10 ppm), is consistent with the experiences of humans reporting cognitive difficulties following acute or chronic exposures to chemicals.

Ross G.H., Rea W.J., Johnson A.R., Hickey D.C., Simon T.R. 1999. Neurotoxicity in single photon emission computed tomography brain scans of patients reporting chemical sensitivities. *Toxicology and Industrial Health* 15(3-4): 415-20.

The subset of patients reporting chemical sensitivity with neurocognitive complaints usually exhibits specific abnormalities of brain metabolism consistent with neurotoxicity, on imaging with single photon emission computed tomography (SPECT). These recurrent neurotoxic patterns are characterized by a mismatch in tracer uptake between early-and late-phase imaging, multiple hot and cold foci throughout the cortex, temporal asymmetry and increased tracer uptake into the soft tissues and, sometimes, the basal ganglia. Previous studies confirm these neurotoxic findings in patients with neurotoxic chemical exposures and breast implants. Affective processes such as depression do not, alone, show this pattern. These abnormalities in SPECT images correlate with documented neurocognitive impairment. Controlled challenges to ambient chemicals can induce profound neurotoxic changes seen on SPECT imaging in chemically sensitive patients. Detoxification treatment techniques frequently produce significant improvement on brain SPECT brain imaging in these patients. Neurotoxicity appears to be characteristic in many cases of chemical sensitivity.

Ross G.H. 1997. Clinical characteristics of chemical sensitivity: an illustrative case history of asthma and MCS. *Environmental Health Perspectives* 105 (Suppl 2) 437-41.

A case history of the induction of asthma and chemical sensitivity in a 42-year-old registered nurse illustrates several of the characteristic features of multiple chemical sensitivity (MCS). This patient's problems started shortly after moving into a new home under construction, with associated chemical exposures. Other MCS patients report the onset of the condition with other chemical exposures such as those encountered at their places of work or use of pesticides at their residences. Patients often describe a spreading phenomenon of increasing intolerance to commonly encountered chemicals at concentrations well tolerated by other people. Symptoms usually wax and wane with exposures, and are more likely to occur in patients or families with preexisting histories of migraine or with classical allergies. Idiosyncratic medication reactions (especially to preservative chemicals) are common in MCS patients, as are dysautonomia symptoms (such as vascular instability) and poor temperature regulation. Myalgia and joint pains and food intolerance are common features as well. Contamination with xenobiotic chemicals is frequently found in these patients when they are tested. Reactive airways dysfunction syndrome is a recently identified condition that exhibits features of both asthma and chemical sensitivity. MCS patients frequently have patterns of neurotoxic brain metabolism that can be confirmed on single photo emission computed tomography imaging.

Rossi J. 3rd. 1996. Sensitization induced by kindling and kindling-related phenomena as a model for multiple chemical sensitivity. *Toxicology* 111(1-3): 87-100.

It has been suggested that the neurobehavioral dysfunction observed in persons presenting with symptoms of Multiple Chemical Sensitivity (MCS) syndrome involves sensitization of neural circuits. Two hypotheses for the route of exposure in induction of neural sensitization in MCS are: (a) direct chemical stimulation of olfactory processes, or (b) general systemic response to inhaled chemicals. In either case, the mechanism of action may involve chemical kindling or kindling-related phenomena. A neural sensitization mechanism based on kindling or kindling-related phenomena is attractive and has been previously demonstrated in both in vitro and in vivo animal models. Without a testable animal model for chemically mediated induction of MCS, however, any argument that MCS is mediated by kindling or kindling-related phenomena is reduced to the circular argument "the mechanism of sensitization is sensitization." The present survey provides an overview of the experimental paradigms that result in sensitization, differentiated on the basis of probable neurophysiological and neurochemical mechanisms. Neurophysiological potentiation, electrical kindling, chemical kindling and behavioral sensitization are evaluated and discussed in relationship to MCS.

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

The central nervous, immune, and endocrine systems communicate through multiple common messengers. Over evolutionary time, what may be termed integrated defense system(s) (IDS) have developed to coordinate these communications for specific contexts ; these include the stress response, acute-phase response, nonspecific immune response, immune response to antigen, kindling, tolerance, time-dependent sensitization, neurogenic switching, and traumatic dissociation (TD) . These IDSs are described and their overlap is examined. Three models of

disease production are generated: damage, in which IDSs function incorrectly ; inadequate/inappropriate, in which IDS response is outstripped by a changing context ; and evolving/learning, in which the IDS learned response to a context is deemed pathologic. Mechanisms of multiple chemical sensitivity (MCS) are developed from several IDS disease models. Model 1A is pesticide damage to the central nervous system, overlapping with body chemical burdens, TD, and chronic zinc deficiency ; model 1B is benzene disruption of interleukin-1, overlapping with childhood developmental windows and hapten-antigenic spreading ; and model 1C is autoimmunity to immunoglobulin-G (IgG) , overlapping with spreading to other IgG-inducers, sudden spreading of inciters, and food-contaminating chemicals. Model 2A is chemical and stress overload, including comparison with the susceptibility/sensitization/triggering/spreading model ; model 2B is genetic mercury allergy, overlapping with: heavy metals/zinc displacement and childhood/gestational mercury exposures ; and model 3 is MCS as evolution and learning. Remarks are offered on current MCS research. Problems with clinical measurement are suggested on the basis of IDS models. Large-sample patient self-report epidemiology is described as an alternative or addition to clinical biomarker and animal testing.

Schnakenberg E., Fabig K.-R., Stannula M., Stroble N., Lustig M., Fabig N., Schloot W. 2007. A cross-sectional study of self-reported chemical-related sensitivity is associated with gene variants of drug-metabolizing enzymes. *Environmental Health* 6:6-16.

BACKGROUND: N-acetyltransferases (NAT) and glutathione S-transferases (GST) are involved in the metabolism of several ubiquitous chemical substances leading to the activation and detoxification of carcinogenic heterocyclic and aromatic amines. Since polymorphisms within these genes are described to influence the metabolism of ubiquitous chemicals, we conducted the present study to determine if individuals with self-reported chemical-related sensitivity differed from controls without self-reported chemical-related sensitivity with regard to the distribution of genotype frequencies of NAT2, GSTM1, GSTT1, and GSTP1 polymorphisms. METHODS: Out of 800 subjects who answered a questionnaire of ten items with regard to their severity of chemical sensitivity 521 unrelated individuals agreed to participate in the study. Subsequently, genetic variants of the NAT2, GSTM1, GSTT1, and GSTP1 genes were analyzed. RESULTS: The results show significant differences between individuals with and without self-reported chemical-related sensitivity with regard to the distribution of NAT2, GSTM1, and GSTT1 gene variants. Cases with self-reported chemical-related sensitivity were significantly more frequently NAT2 slow acetylators (controlled OR = 1.81, 95% CI = 1.27-2.59, P = 0.001). GSTM1 and GSTT1 genes were significantly more often homozygously deleted in those individuals reporting sensitivity to chemicals compared to controls (GSTM1: controlled OR 2.08, 95% CI = 1.46-2.96, P = 0.0001; GSTT1: controlled OR = 2.80, 95% CI = 1.65-4.75, P = 0.0001). Effects for GSTP1 gene variants were observed in conjunction with GSTM1, GSTT1 and NAT2 gene. CONCLUSION: The results from our study population show that individuals being slow acetylators and/or harbouring a homozygous GSTM1 and/or GSTT1 deletion reported chemical-related hypersensitivity more frequently.

Sykes R. 2006. Somatoform disorders in DSM-IV: mental or physical disorders? *Journal of Psychosomatic Research* 60(4): 341-44.

Objective: To examine analytically the question of whether the characterization of somatoform disorders (SFDs) in Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) provides adequate grounds for classifying them as mental disorders rather than as physical disorders.
Methods: Analytical examination.
Results: There are prima facie grounds for classifying SFDs as physical disorders since they are characterized by physical symptoms. The characterization of SFDs in DSM-IV does not provide adequate grounds for classifying them as mental disorders.
Conclusion: The spectrum of SFDs is drawn too widely in DSM-IV. At least some of the conditions now listed as SFDs in DSM-IV should be either given a dual diagnosis or classified simply as physical disorders.

Ternesten-Hasseus E., Bende M., Millqvist E. 2002. CME: Increased capsaicin cough sensitivity in patients with multiple chemical sensitivity. *Journal of Occupational and Environmental Medicine* 44(11): 1012-17.

Multiple chemical sensitivity (MCS) is characterized by chemically induced symptoms from multiple organ systems. No consistent physical findings or laboratory abnormalities have been determined for the associated symptoms. Twelve patients with chemically induced airway symptoms, who satisfied Cullen's criteria for MCS, were provoked double-blind, randomized with saline and three increments of inhaled capsaicin. The recordings were compared with those of a control group of healthy individuals. The results found that the patients coughed more than the control subjects at each dose of capsaicin (P _ 0.05 for 0.4 _mol/L capsaicin and P _ 0.005 for 2 _mol/L and 10 _mol/L). The capsaicin provocation also induced significantly more symptoms in patients with MCS. We conclude that airway sensory reactivity is increased in patients with MCS, a finding which suggests that neurogenic factors may be of importance in this condition.

Thrasher J.D., Broughton A., Madison R. 1990. Immune activation and autoantibodies in humans with long-term inhalation exposure to formaldehyde. *Archives of Environmental Health* 45(4): 217-23.

Four groups of patients with long-term inhalation exposure to formaldehyde (HCHO) were compared with controls who had short-term periodic exposure to HCHO. The following were determined for all groups: total white cell, lymphocyte, and T cell counts; T helper/suppressor ratios; total Ta1+, IL2+, and B cell counts; antibodies to formaldehyde-human serum albumin (HCHO-HSA) conjugate and autoantibodies. When compared with the controls, the patients had significantly higher antibody titers to HCHO-HSA. In addition, significant increases in Ta1+, IL2+, and B cells and autoantibodies were observed. Immune activation, autoantibodies, and anti-HCHO-HSA antibodies are associated with long-term formaldehyde inhalation.

Yu I.T., Lee N.L., Zhang X.H., Chen W.Q., Lam Y.T., Wong T.W. 2004. Occupational exposure to mixtures of organic solvents increases the risk of neurological symptoms among printing workers in Hong Kong. *Journal of Occupational and Environmental Medicine* 46(4): 323-30.

The health effects of low-dose occupational exposure to organic solvents remains unclear. A cross-sectional survey was conducted among 762 male printing workers to assess the impacts of exposure to mixtures of n-hexane, toluene, isopropyl alcohol, and benzene on neurological and other symptoms. After controlling for age, smoking, alcohol drinking, past exposure history, working hours and shift work, current exposure to solvent mixtures was significantly associated with the total number of neurological symptoms and with the prevalence of specific symptoms of the nervous system and mucous membrane irritation. The adjusted odds ratio of neurovegetative lability (1.7–5.9), abnormal or reduced smell (1.6–4.1), memory loss (1.8), and mucous membrane irritation symptoms (1.5– 4.6) significantly increased in the exposed group, especially when the summation index of exposure exceeded one.

Zibrowski L.M., Robertson J.M. 2006. Olfactory sensitivity in medical laboratory workers occupationally exposed to organic solvent mixtures. *Occupational Medicine* 56(1): 51-54.

BACKGROUND: Published epidemiological information relating the effects of occupational exposure to organic solvents (OS) to olfaction is limited. AIMS: The objectives of this pilot study were to measure the chemosensory abilities of medical laboratory employees occupationally exposed to OS mixtures, to compare these with control workers employed within the same occupational setting and to correlate chemosensory performance with OS exposure history and with employees' hedonic (pleasantness) perceptions about workplace OS odors. METHODS: Twenty-four medical laboratory employees (OS-exposed technicians plus control workers minimally exposed to OS) completed a health-related questionnaire, a test of pyridine odor detection threshold, along with a gustatory detection threshold test involving aqueous quinine solutions. Estimates of cumulative hours of OS exposure (CSI) were calculated from self-reports. RESULTS: OS-exposed laboratory technicians detected weaker concentrations of pyridine odor. Positive correlations were detected between CSI estimates to both pyridine detection and the degree that participants reported that OS odors were present in the workplace. However, no association was detected between pyridine detection and how unpleasant workplace OS odors were perceived. The OS-exposed participants were able to detect weaker concentrations of quinine. Compared to controls, OS-exposed workers complained more of experiencing several symptoms while working, including headaches, nasal irritation and mild cognitive impairment. CONCLUSIONS: The results of this cross-sectional pilot study indicated that, compared to controls, medical laboratory technicians exposed to low-level OS mixtures displayed evidence of elevated olfactory sensitivity (hyperosmia) to pyridine odor. The relation of this study's results to chemical intolerance warrants further investigation.

Ziem G. 1999. Profile of patients with chemical injury and sensitivity, part II. *International Journal of Toxicology* 18(6):401-409.

Exposures which can induce multiple chemical sensitivity (MCS) involve symptomatic, usually repeated, exposures to pesticides, solvents, combustion products, remodeling, sick buildings, carbonless copy paper (occupational heavy use) and other irritants and petrochemicals.

Accompanying toxic injury often involves the immune, endocrine and nervous systems as well as impairments in detoxification, energy and neurotransmitter metabolism, protein, mineral, and other nutrient deficiencies and gastrointestinal changes such as candida, parasites, reduced chymotrypsin (marker enzyme for reduced pancreatic enzyme function), gluten intolerance, and reduced Secretory IgA. Chronic cortisol elevation leading to adrenal insufficiency if not corrected is common. Such elevation can lead to protein and mineral deficiencies with increased osteoporosis and reduced steroid precursors for normal estrogen and testosterone production. Detoxification changes often involve reduction in one or more Phase II pathways which causes excess free radical production. Impaired digestive enzymes can reduce breakdown of foods, with larger more antigenic molecules being absorbed and consequent food intolerances. Many of these conditions are treatable. There is extensive overlap of MCS with Chronic Fatigue Syndrome and Fibromyalgia which may be one condition in many cases. Current occupational exposure limits are not health based and thus may not prevent MCS and are totally inadequate to accommodate sensitive persons. Warning symptoms indicating increased risk for MCS onset include repeated headache, eye and respiratory irritation and fatigue. Eliminating exposures which cause repeated symptoms is a critical strategy for preventing sensitization and MCS. It also significantly reduces the degree of disability in persons with MCS, the single most important factor from the literature. Affected persons with disability can utilize the Americans With Disability Act to request reasonable accommodations for work, home (condo, apartment), and school.

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

Patients reporting sensitivity to multiple chemicals at levels usually tolerated by the healthy population were administered standardized questionnaires to evaluate their symptoms and the exposures that aggravated these symptoms. Many patients were referred for medical tests. It is thought that patients with chemical sensitivity have organ abnormalities involving the liver, nervous system (brain, including limbic, peripheral, autonomic), immune system, and porphyrin metabolism, probably reflecting chemical injury to these systems. Laboratory results are not consistent with a psychologic origin of chemical sensitivity. Substantial overlap between chemical sensitivity, fibromyalgia, and chronic fatigue syndrome exists: the latter two conditions often involve chemical sensitivity and may even be the same disorder. Other disorders commonly seen in chemical sensitivity patients include headache (often migraine), chronic fatigue, musculoskeletal aching, chronic respiratory inflammation (rhinitis, sinusitis, laryngitis, asthma), attention deficit, and hyperactivity (affected younger children). Less common disorders include tremor, seizures, and mitral valve prolapse. Patients with these overlapping disorders should be evaluated for chemical sensitivity and excluded from control groups in future research. Agents whose exposures are associated with symptoms and suspected of causing onset of chemical sensitivity with chronic illness include gasoline, kerosene, natural gas, pesticides (especially chlordane and chlorpyrifos), solvents, new carpet and other renovation materials, adhesives/glues, fiberglass, carbonless copy paper, fabric softener, formaldehyde and glutaraldehyde, carpet shampoos (lauryl sulfate) and other cleaning agents, isocyanates, combustion products (poorly vented gas heaters, overheated batteries), and medications (dinitrochlorobenzene for warts, intranasally packed neosynephrine, prolonged antibiotics, and general anesthesia with petrochemicals). Multiple mechanisms of chemical injury that magnify

response to exposures in chemically sensitive patients can include neurogenic inflammation (respiratory, gastrointestinal, genitourinary), kindling and time-dependent sensitization (neurologic), impaired porphyrin metabolism (multiple organs), and immune activation.

Appendix: Related Articles

Anderson R.C. and Anderson J.H. 1997. Toxic effects of air freshener emissions. *Archives of Environmental Health* 52(6): 433-41.

To evaluate whether emissions of a commercial air freshener produced acute toxic effects in a mammalian species, the authors allowed male Swiss-Webster mice to breathe the emissions of one commercial-brand solid air freshener for I h. Sensory irritation and pulmonary irritation were evaluated with the ASTM-E-981 test. A computerized version of this test measured the duration of the break at the end of inspiration and the duration of the pause at the end of expiration--two parameters subject to alteration via respiratory effects of airborne toxins. Measurements of expiratory flow velocity indicated changes in airflow limitation. The authors then subjected mice to a functional observational battery, the purpose of which was to probe for changes in nervous system function. Emissions of this air freshener at several concentrations (including concentrations to which many individuals are actually exposed) caused increases in sensory and pulmonary irritation, decreases in airflow velocity, and abnormalities of behavior measured by the functional observational battery score. The test atmosphere was subjected to gas chromatography/mass spectroscopy, and the authors noted the presence of chemicals with known irritant and neurotoxic properties. The Material Safety Data Sheet for the air freshener indicated that there was a potential for toxic effects in humans. The air freshener used in the study did not diminish the effect of other pollutants tested in combination. The results demonstrated that the air freshener may have actually exacerbated indoor air pollution via addition of toxic chemicals to the atmosphere.

Anderson R.C. and Anderson J.H. 1998. Acute toxic effects of fragrance products. *Archives of Environmental Health* 53(2): 138-46.

To evaluate whether fragrance products can produce acute toxic effects in mammals, we allowed groups of male Swiss-Webster mice to breathe the emissions of five commercial colognes or toilet water for 1 h. We used the ASTM-E-981 test method to evaluate sensory irritation and pulmonary irritation. We used a computerized version of this test to measure the duration of the break at the end of inspiration and the duration of the pause at the end of expiration. Decreases in expiratory flow velocity indicated airflow limitation. We subjected the mice to a functional observational battery to probe for changes in nervous system function. The emissions of these fragrance products caused various combinations of sensory irritation, pulmonary irritation, decreases in expiratory airflow velocity, as well as alterations of the functional observational battery indicative of neurotoxicity. Neurotoxicity was more severe after mice were repeatedly exposed to the fragrance products. Evaluation of one of the test atmospheres with gas chromatography/mass spectrometry revealed the presence of chemicals for which irritant and neurotoxic properties had been documented previously. n summary, some fragrance products emitted chemicals that caused a variety of acute toxicities in mice.

Anderson R.C. and Anderson J.H. 2000. Respiratory toxicity of fabric softener emissions. *Journal of Toxicology and Environmental Health Part A* 60(2): 121-36.

To determine whether there is any biological basis for complaints that fabric softener emissions can cause acute adverse effects in certain individuals, screening tests were performed in which groups of mice were exposed to the emissions of 5 commercial fabric softener products (antistatic pads used in laundry dryers) for 90 min. Pneumotachographs and a computerized version of ASTM test method E-981 were used to measure acute changes in several respiratory cycle parameters, especially the pause after inspiration, the pause after expiration, and the midexpiratory airflow velocity. From these changes, sensory irritation (SI), pulmonary irritation (PI), and airflow limitation (AFL) of differing intensities were measured with each of the five brands tested. At the peak effect, SI ranged from 21 to 58% of the breaths, PI ranged from 4 to 23% of the breaths, and AFL ranged from 6 to 32% of the breaths. After three exposures, histopathology revealed mild inflammation of interalveolar septae of the lungs. Gas chromatography/ mass spectroscopy (GC/MS) analysis of the emissions of one pad identified several known irritants (isopropylbenzene, styrene, trimethylbenzene, phenol, and thymol). Laundry that had been dryed with one the fabric softener pads emitted sufficient chemicals to elicit SI in 49% of breaths at the peak effect. Placing one fabric softener pad in a small room overnight resulted in an atmosphere that caused marked SI (61% of breaths). These results demonstrate that some commercial fabric softeners emit mixtures of chemicals that can cause SI, PI, and reduce midexpiratory airflow velocity in normal mice. The results provide a toxicological basis to explain some of the human complaints of adverse reactions to fabric softener emissions.

Anderson R.C. and Anderson J.H. 1999. Acute respiratory effects of diaper emissions. *Archives of Environmental Health* 54(5): 353-58.

Mice were monitored with pneumotachographs while they breathed emissions of three brands of disposable diapers (described herein as brands A, B, and C) and one brand of cloth diapers for 1 hr. The authors used a computerized version of the ASTM-E-981 test method to measure changes in the pattern and frequency of respiration. In response to two brands of disposable diapers, many mice exhibited reduced mid-expiratory airflow velocity, sensory irritation, and pulmonary irritation. During the peak effects, brand A caused sensory irritation in 47% of the breaths and reduced mid-expiratory airflow velocity in 17% of the breaths (n = 39 mice), whereas the respective percentages noted for brand B were 20% and 15% of the breaths (n = 28 mice). The effects were generally larger during repeat exposures to these emissions, with up to 89% of breaths showing sensory irritation in response to brand A and up to 35% of breaths showing reduced mid-expiratory airflow velocity with brand B. A third brand of disposable diapers caused increases in respiratory rate, tidal volume, and mid-expiratory airflow velocity. The emissions of cloth diapers produced only slight SI and slight PI. Chemical analysis of the emissions revealed several chemicals with documented respiratory toxicity. The results demonstrate that some types of disposable diapers emit mixtures of chemicals that are toxic to the respiratory tract. Disposable diapers should be considered as one of the factors that might cause or exacerbate asthmatic conditions.

Anderson R. and Anderson J. 2003. Acute toxicity of marking pen emissions. *Journal of Toxicity and Environmental Health Part A* 66(9): 829-45.

To evaluate complaints of adverse reactions to marking pen emissions, groups of mice were exposed for 1 h to the emissions of 8 brands of felt-tip markers or white-board cleaner. Pneumotachographs and a computerized version of ASTM E-981 test method were used to measure changes in respiration. Sensory irritation (SI), pulmonary irritation (PI), and/or air flow limitation (AFL) of differing intensities were documented with each of the eight brands tested. At the peak of the effects, the largest SI was observed with pen F (72% of the breaths); the largest PI occurred with pen D (13% of the breaths), and the largest AFL was seen with pen F (25% of the breaths). Pens G and H produced minimal SI, PI, or AFL. A functional observational battery was used to screen for signs of neurotoxicity. Emissions from all eight of the pens produced behavioral abnormalities such as altered posture and gait, tremors, falling, and hyperactivity. The exposure concentrations were similar to the total volatile organic compounds (TVOC) values near marking pens in actual use. Gas chromatography identified mixtures of alcohols, acetates, and/or ketones. Exposures to white-board cleaner solution resulted in similar toxicity (SI, PI, AFL, and neurotoxicity). These results document that some marking pens and white-board cleaner emit mixtures of chemicals that can produce acute respiratory toxicity and acute behavioral abnormalities in normal mice. These results provide a toxicological explanation for some of the human complaints concerning respiratory and neurological reactions to marking pen emissions.

Anderson R.C., Anderson J.H. 2000. Respiratory toxicity of mattress emissions in mice. *Archives of Environmental Health* 55(1): 38-43.

Groups of male Swiss-Webster mice breathed emissions of several brands of crib mattresses for two 1-hr periods. The authors used a computerized version of ASTM-E-981 test method to monitor respiratory frequency, pattern, and airflow velocity and to diagnose abnormalities when statistically significant changes appeared. The emissions of four mattresses caused various combinations of upper-airways irritation (i.e., sensory irritation), lower-airways irritation (pulmonary irritation), and decreases in mid-expiratory airflow velocity. At the peak effect, a traditional mattress (wire springs with fiber padding) caused sensory irritation in 57% of breaths, pulmonary irritation in 23% of breaths, and airflow decrease in 11% of breaths. All mattresses caused pulmonary irritation, as shown by 17-23% of breaths at peak. The largest airflow decrease (i.e., affecting 26% of the breaths) occurred with a polyurethane foam pad covered with vinyl. Sham exposures produced less than 6% sensory irritation, pulmonary irritation, or airflow limitation. Organic cotton padding caused very different effects, evidenced by increases in both respiratory rate and tidal volume. The authors used gas chromatography/mass spectrometry to identify respiratory irritants (e.g., styrene, isopropylbenzene, limonene) in the emissions of one of the polyurethane foam mattresses. Some mattresses emitted mixtures of volatile chemicals that had the potential to cause respiratory-tract irritation and decrease airflow velocity in mice.

Anderson R.C. and Anderson J.H. 1999. Respiratory toxicity in mice exposed to mattress covers. *Archives of Environmental Health* 54(3): 202-209.

To evaluate factors that might contribute to the rise in prevalence of childhood asthma, we allowed groups of male Swiss-Webster mice to breath the emissions of six brands of waterproof crib mattress covers for 1 h. We used a computerized version of ASTM-E-981 test method to monitor respiratory frequency, pattern, and airflow velocity. Single exposure to the emissions of these mattress covers caused various combinations of sensory irritation, pulmonary irritation, and decreases in mid-expiratory airflow velocity. At the peak effects of these emissions, sensory irritation ranged from 9% to 51% of the breaths, pulmonary irritation ranged from 4% to 16% of the breaths, and airflow limitation ranged from 9% to 38% of the breaths. Three brands caused airflow limitation that persisted for at least 24 h after a single 1-h exposure of naive mice to these emissions. Repeat exposures to the emissions of four brands caused more marked effects (i.e., up to 96% of the breaths showing sensory irritation, up to 44% of the breaths showing pulmonary irritation, and up to 75% of the breaths showing airflow limitation). Histological evaluation of the lungs revealed a mild inflammatory response, with focal collections of polymorphonuclear leukocytes and edema, but there were no eosinophils and no bronchial mucosa changes. We used gas chromatography/mass spectrometry to evaluate one of the test atmospheres, and there was evidence of chemicals for which toxic properties have been documented previously. The results of our study demonstrated that some mattress covers emit mixtures of chemicals that can cause a variety of acute toxic effects in mice, including asthma-like reactions.

Bridges B. 2002. Fragrance: emerging health and environmental concerns. *Flavour and Fragrance Journal* 17(5): 361-71.

Products containing scent are a part of daily life. The majority of cosmetics, toiletries, household and laundry products contain fragrance. In addition, there is exposure to fragrance from products that are used to scent the air, such as air fresheners and fragranced candles. In spite of this widespread use and exposure, there is little information available on the materials used in fragrance. Fragrance formulas are considered trade secrets and components that make up the fragrance portion of the product are not revealed on labels. Fragrance is increasingly cited as a trigger in health conditions such as asthma, allergies and migraine headaches. In addition, some fragrance materials have been found to accumulate in adipose tissue and are present in breast milk. Other materials are suspected of being hormone disruptors. The implications are not fully known, as there has been little evaluation of systemic effects. There are environmental concerns as well, as fragrances are volatile compounds, which add to both indoor and outdoor air pollution. Synthetic musk compounds are persistent in the environment and contaminate waterways and aquatic wildlife. At present there is little governmental regulation of fragrance. The fragrance industry has in place a system of self-regulation. However, the present system has failed to address many of the emerging concerns. Industry needs to responsibly address concerns and ensure that scented products are safe for users, those inadvertently exposed and the environment. It is essential that an industry that is, and wishes to continue to be, self-regulated should identify and address concerns in a forthright and responsible manner.

Brown A.E. 1999. Developing a pesticide policy for individuals with multiple chemical sensitivity: considerations for institutions. *Toxicology and Industrial Health* 15(3/4): 432-37.

Institutions are increasingly being asked to accommodate individuals with multiple chemical sensitivity (MCS). Most establishments have chosen to provide such accommodations on a case-by-case basis only. This paper investigates feasible actions that may be taken by institutions to reduce exposure of MCS individuals as well as the general institutional population to pesticides and other substances. Emphasis is placed on procedures that can be instituted on a regular basis and may be combined with case-by-case management for better resolution of problems.

Cooper S.D., Raymer J.H., Pellizzari E.D., Thomas K.W. 1995. The identification of polar organic compounds found in consumer products and their toxicological properties. *Journal of Exposure Analysis and Environmental Epidemiology* 5(1): 57-75.

Exposure to volatile organic compounds (VOCs) in the indoor environment has received substantial research attention in the past several years, with the goal of better understanding the impact of such exposures on human health and well-being. Many VOCs can arise from consumer products used within the indoor environment. The VOCs emitted from five representative consumer products were collected onto Tenax-GC and subjected to thermal desorption and analysis by gas chromatography, in combination with low-resolution mass spectrometry (MS), high-resolution MS, and matrix-isolation Fourier transform infrared spectroscopy for structural characterization. An emphasis was placed on the polar organic compounds often used to provide fragrance in these products. The structures of a number of these compounds were confirmed, and an electronic literature search was carried out on them to determine any known toxic properties. The search revealed that many of the VOCs possess toxic properties when studied at acute, relatively high-level exposures. In addition, toxic effects were reported for a few of the chemicals, such as benzaldehyde, alpha-terpineol, benzyl acetate, and ethanol, at relatively low dose levels of 9-14 mg/kg. In general, the data were unclear as to the effect of chronic, low-level exposures. The widespread use of such chemicals suggests that the health effects of chronic exposures need to be determined. Validated analytical methods for the quantitative characterization of polar organic compounds at low concentrations will be required to make such work possible.

Destaillats H., Lunden M.M., Singer B.C., Coleman B.K., Hodgson A.T., Weschler C.J., Nazaroff W.W. 2006. Indoor secondary pollutants from household product emissions in the presence of ozone: a bench-scale chamber study. *Environmental Science and Technology* 40(14): 4421-28.

Ozone-driven chemistry is a source of indoor secondary pollutants of potential health concern. This study investigates secondary air pollutants formed from reactions between constituents of household products and ozone. Gas-phase product emissions were introduced along with ozone at constant rates into a 198-L Teflon-lined reaction chamber. Gas-phase concentrations of reactive terpenoids and oxidation products were measured. Formaldehyde was a predominant oxidation byproduct for the three studied products, with yields for most conditions of 20-30% with respect to ozone consumed. Acetaldehyde, acetone, glycolaldehyde, formic acid, and acetic acid were each also detected for two or three of the products. Immediately upon mixing of

reactants, a scanning mobility particle sizer detected particle nucleation events that were followed by a significant degree of secondary particle growth. The production of secondary gaseous pollutants and particles depended primarily on the ozone level and was influenced by other parameters such as the air-exchange rate. Hydroxyl radical concentrations in the range 0.04-200 x 10(5) molecules cm(-3) were determined by an indirect method. OH concentrations were observed to vary strongly with residual ozone level in the chamber, which was in the range 1-25 ppb, as is consistent with expectations from a simplified kinetic model. In a separate chamber study, we exposed the dry residue of two products to ozone and observed the formation of gas-phase and particle-phase secondary oxidation products.

Duty S.M., Ackerman R.M., Calafat A.M., Hauser R. 2005. Personal care product use predicts urinary concentrations of some phthalate monoesters. *Environmental Health Perspectives* 113(11): 1530-35.

Phthalates are multifunctional chemicals used in a variety of applications, including personal care products. The present study explored the relationship between patterns of personal care product use and urinary levels of several phthalate metabolites. Subjects include 406 men who participated in an ongoing semen quality study at the Massachusetts General Hospital Andrology Laboratory between January 2000 and February 2003. A nurse-administered questionnaire was used to determine use of personal care products, including cologne, aftershave, lotions, hair products, and deodorants. Phthalate monoester concentrations were measured in a single spot urine sample by isotope dilution-high-performance liquid chromatography coupled to tandem mass spectrometry. Men who used cologne or aftershave within 48 hr before urine collection had higher median levels of monoethyl phthalate (MEP) (265 and 266 ng/mL, respectively) than those who did not use cologne or aftershave (108 and 133 ng/mL, respectively). For each additional type of product used, MEP increased 33% (95% confidence interval, 14-53%). The use of lotion was associated with lower urinary levels of monobutyl phthalate (MBP) (14.9 ng/mL), monobenzyl phthalate (MBzP) (6.1 ng/mL), and mono(2-ethylhexyl) phthalate (MEHP) (4.4 ng/mL) compared with men who did not use lotion (MBP, 16.8 ng/mL; MBzP, 8.6 ng/mL; MEHP, 7.2 ng/mL). The identification of personal care products as contributors to phthalate body burden is an important step in exposure characterization. Further work in this area is needed to identify other predictors of phthalate exposure.

Muir T. and Zegarac M. 2001. Societal costs of exposure to toxic substances: economic and health costs of four case studies that are candidates for environmental causation. *Environmental Health Perspectives* 109 (Suppl 6): 885-903.

Four outcomes that evidence suggests are candidates for "environmental causation" were chosen for analysis: diabetes, Parkinson's disease (PD), neurodevelopmental effects and hypothyroidism, and deficits in intelligence quotient (IQ). These are an enormous burden in the United States, Canada, and other industrial countries. We review findings on actual social and economic costs, construct estimates of some of the costs from pertinent sources, and provide several hypothetical examples consistent with published evidence. Many detailed costs are estimated, but these are fragmented and missing in coverage and jurisdiction. Nonetheless, the cumulative costs identified are very large, totaling $568 billion to $793 billion per year for Canada and the United States combined. Partial Canadian costs alone are $46 billion to $52 billion per year. Specifics

include diabetes (United States and Canada), $128 billion per year; PD in the United States, $13 billion to $28.5 billion per year; neurodevelopmental deficits and hypothryoidism are endemic and, including estimates of costs of childhood disorders that evidence suggests are linked, amount to $81.5 billion to $167 billion per year for the United States and $2 billion per year in Ontario; loss of 5 IQ points cost $30 billion per year in Canada and $275 billion to $326 billion per year in the United States; and hypothetical dynamic economic impacts cost another $19 billion to $92 billion per year for the United States and Canada combined. Reasoned arguments based on the weight of evidence can support the hypothesis that at least 10%, up to 50% of these costs are environmentally induced--between $57 billion and $397 billion per year.

Steinemann A.C. 2009. Fragranced consumer products and undisclosed ingredients. *Environmental Impact Assessment Review* 29(1): 32-38.

Fragranced consumer products—such as air fresheners, laundry supplies, personal care products, and cleaners—are widely used in homes, businesses, institutions, and public places. While prevalent, these products can contain chemicals that are not disclosed to the public through product labels or material safety data sheets (MSDSs). What are some of these chemicals and what limits their disclosure? This article investigates these questions, and brings new pieces of evidence to the science, health, and policy puzzle. Results from a regulatory analysis, coupled with a chemical analysis of six best-selling products (three air fresheners and three laundry supplies), provide several findings. First, no law in the U.S. requires disclosure of all chemical ingredients in consumer products or in fragrances. Second, in these six products, nearly 100 volatile organic compounds (VOCs) were identified, but none of the VOCs were listed on any product label, and one was listed on one MSDS. Third, of these identified VOCs, ten are regulated as toxic or hazardous under federal laws, with three (acetaldehyde, chloromethane, and 1,4-dioxane) classified as Hazardous Air Pollutants (HAPs). Results point to a need for improved understanding of product constituents and mechanisms between exposures and effects.

Steinemann A. 2004. Human exposure, health hazards, and environmental regulations. *Environmental Impact Assessment Review* 24(7/8): 695-710.

United States environmental regulations, intended to protect human health, generally fail to address major sources of pollutants that endanger human health. These sources are surprisingly close to us and within our control, such as consumer products and building materials that we use within our homes, workplaces, schools, and other indoor environments. Even though these indoor sources account for nearly 90% of our pollutant exposure, they are virtually unregulated by existing laws. Even pollutant levels found in typical homes, if found outdoors, would often violate federal environmental standards. This article examines the importance of human exposure as a way to understand and reduce effects of pollutants on human health. Results from exposure studies challenge traditional thinking about pollutant hazards, and reveal deficiencies in our patchwork of laws. And results from epidemiological studies, showing increases in exposure-related diseases, underscore the need for new protections. Because we cannot rely solely on regulations to protect us, and because health effects from exposures can develop insidiously, greater efforts are needed to reduce and prevent significant exposures before they occur. Recommendations include the development and use of safer alternatives to common products,

public education on ways to reduce exposure, systematic monitoring of human exposure to pollutants, and a precautionary approach in decision-making.

Weschler C.J. 2009. Changes in indoor pollutants since the 1950s. *Atmospheric Environment* 43(1): 153-69.

Over the past half-century there have been major changes in building materials and consumer products used indoors. Composite-wood, synthetic carpets, polymeric flooring, foam cushioning, plastic items and scented cleaning agents have become ubiquitous. The same is true for mechanical and electrical appliances such as washer/dryers, TVs and computers. These materials and products emit an array of chemicals including solvents, unreacted monomers, and additives. The consequent changes in emission profiles for indoor pollutants have been accompanied by modifications in building operations. Residences and non-residences are less ventilated than they were decades ago. Air-conditioned buildings are more numerous, especially in certain parts of the world. Most of these recirculate a high fraction of their air. The personal habits of building occupants, including the fraction who smoke indoors, have also changed. Taken together, these changes have altered the kind and concentrations of chemicals that occupants are exposed to in their homes, workplaces and schools. Since the 1950s, levels of certain indoor pollutants (e.g., formaldehyde, aromatic and chlorinated solvents, chlorinated pesticides, PCBs) have increased and then decreased. Levels of other indoor pollutants have increased and remain high (e.g., phthalate esters, brominated flame-retardants, nonionic surfactants and their degradation products). Many of the chemicals presently found in indoor environments, as well as in the blood and urine of occupants, were not present 50 years ago. Given the public's exposure to such species, there would be exceptional value in monitoring networks that provided cross-sectional and longitudinal information regarding pollutants found in representative buildings.

Ziem G. 2005. Pesticide spraying and health effects. *Environmental Health Perspectives* 113(3): A150. (Letter to the editor—no abstract available)

Ziem G. 1999. Understanding patients with multiple chemical sensitivity. *American Family Physician* 59(8): 2101. (Letter to the editor—no abstract available.)

Este documento ha sido elaborado como respuesta a la «Guía de actualización en la valoración de fibromialgia, síndrome de fatiga crónica, sensibilidad química múltiple y electrosensibilidad», publicada el día 18 de enero de 2019 por el Instituto Nacional de la Seguridad Social.

Dada la incorformidad del colectivo afectado, puesto que en ella se detallan criterios diagnósticos inapropiados y obsoletos para los afectados, este documento muestra la necesidad de su modificación y propone tratamientos realmente efectivos.

Subvencionado por:

GOBIERNO DE ESPAÑA
MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL

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CONFESQ

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