THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 13 Issue 5

REVIEW ARTICLE

Connections between Multiple Chemical Sensitivity (MCS) and Mechanisms of Neurodegenerative Diseases – Hints and References from Scientific Literature

Hans-Ulrich Hill [1] and Wolfgang Huber [2]

[1] PhD in Biology, with focus on Immunology and toxicology, practicing as censor and textbook-author.
[2] Professor emeritus at University-Clinic Heidelberg/Mannheim, Germany, Nephrology, later on qualifying in Environmental Medicine and one of the founders of the German Professional Association of Clinical Environmental Medicine (dbu, Deutscher Berufsverband Klinischer Umweltmediziner e.V.).

OPEN ACCESS

PUBLISHED
31 May 2025

CITATION
Hans-Ulrich, H., and Wolfgang, H., 2025. Connections between Multiple Chemical Sensitivity (MCS) and Mechanisms of Neurodegenerative Diseases – Hints and References from Scientific Literature. Medical Research Archives, [online] 13(5). https://doi.org/10.18103/mra.v13i5.6463

DOI
https://doi.org/10.18103/mra.v13i5.6463

ISSN
2375-1924

ABSTRACT

This review focuses on pathologic mechanisms of neurodegenerative diseases and Multiple Chemical Sensitivity (MCS) in order to find out common properties that give hints to their common origin and mechanisms. Many epidemiologic studies already have proven that both, MCS and neurodegenerative diseases, especially Alzheimer's and Parkinson's Disease, are initiated by exposure to environmental chemicals. The mechanisms following these exposures show similar properties. They are initiated by binding to and activation of receptors located at cells of the brain immune system and at neurons, mainly the so called "transient receptor potential receptors" (TRP-receptors). As a consequence, the activation of N-methyl-D-aspartat-receptors (NMDA-receptors) in the Central Nervous System (CNS) plays a central role in the expression of neurotoxic mechanisms such as excitotoxicity, apoptose (programmed cell death) and chronic inflammation in the brain. The inflammation in brain is mainly performed by activated astrocytes and gliacells that are part of the inborn immune system. Under normal conditions these cells support the functions of neurons in the brain. Under pathologic conditions caused by different environmental chemicals these cells are activated and turn into a pathogenic state that supports inflammation. They then secrete cytokines as signal molecules that activate different inflammation mechanisms, leading to production of oxygen radicals ("oxidative stress") and peroxynitrite ("nitrosative stress"). These pathogenic mechanisms constitute self enhancing vicious cycles that cause a risk of proceeding neurodegeneration. There are hints that some of these mechanisms also have been proven for Multiple Chemical Sensitivity (MCS).

Introduction

Different epidemiological studies have focused on environmental factors that initiate processes in brain that lead to neurodegenerative processes in brain. Concerning Alzheimer's Disease about 95% of cases are of sporadic origin and depend not mainly on genetic factors.[1] For these cases external risk factors are responsible for the probability to become dementia. Important risk factors are preexisting diseases such as diabetes type II, adipositas and other diseases of the metabolic syndrome like hypertension, arteriosclerosis, chronic inflammations, autoimmune diseases, and disturbed fat-metabolism. Concerning this there rises the question of reasons and origins of chronic inflammation processes by environmental factors, including life style such as lack of exercise, quantity and kind of food, smoking, consumption of alcoholic drinks, former infectious diseases, but also exposition to environmental chemicals such as pesticides, organic solvents, air pollution by fine dust particles, ozone, nitric oxides, sulphur-dioxide and others. Long time use of medical drugs, especially antibiotics, may in combination with other medicines and chemicals support neurodegenerative processes.[2] Epidemiological studies have proven that elevated concentrations of fine dust PM 2,5 cause a clear risk of becoming Alzheimer`s Disease.[3,4]

It is evident that the onset of dementia by environmental factors corresponds to other diseases of environmental origin such an allergies, autoimmune diseases, toxic encephalopathy (TE) and Multiple Chemical Sensitivity (MCS). Regarding fundamental physiological and biochemical mechanisms of these diseases one can find similar and corresponding pathogenic processes in both diseases of dementia and of environmental origin.

Mechanisms of Neurodegeneration and Multiple Chemical Sensitivity (MCS) are corresponding

The urban outdoor air is contaminated with a complex mixture of numerous pollutants, such as airborne particulate matter (PM) and gases, including carbon monoxide, polyaromatic hydrocarbons, sulfur dioxide, nitrogen oxides, ozone and volatile organic compounds (VOCs).[5,6]

Chemicals of air pollution inside of building-rooms are organic solvent molecules, formaldehyde, acetic acid, trichloro-ethylene, tetrachloro-methane, pentachoro-phenol, polychlorinated biphenyls and dioxins and others. Most of these air polluants trigger pathophysiological mechanisms by binding to transient-receptor-potential-receptors of type V1 and A1 (TRPV1 and TRPA1) that are located at sensorial nerve-fibers of the peripheral nervous system. These receptors are upregulated by exposure to chemicals, leading to overstimulation of sensorial nerves and corresponding functional areas in the brain, followed by neurodegenerative processes and loss of brain-mass in these areas. There is likely damage to the olfactory system in neurodegeneration and trigeminal nerve hypersensitivity in MCS, with different effects on olfactory processing. This is accompanied by cognitive decline, chronic headache and loss of smell. Upregulated TRPV1 and TRPA1 were found in patients with neurodegeneration, chemical asthma, migraine, and MCS. Persons with chemical sensitivity have elevated sensitivity of these receptors and a lowered reaction threshold, causing a forced reaction towards exposition to environmental chemicals. The system of sensorial nerves for smell and the nerves of the Trigeminus show signs of neurodegeneration after chronic exposition to chemicals. These patients also mostly show unspecific hypersensitivity to air polluting chemicals typical for the MCS disease.[6]

A cohort-study of the staff of the New-York Fire-Department, that had been engaged in rescue-activities during the 9-11-Terror Attack, has shown long lasting toxic effects on cognitive brain functions. The firemen had been exposed to high and toxic dust-concentrations for many hours. The incidence of dementia of 5010 firemen, that had been investigated about 13 to 19 years after the terror-attack, was more than 10 times higher depending on time and intensity of exposition.[7].

Other studies were focused on neurotoxins in the dust and waste of the former World-Trade-Center (WTC) and had investigated immunological markers corresponding to cognitive decline with the rescue personal after the terror event. They found upregulated neuroimmunological reactions of macrophages and increased concentrations of phosphorylated Tau-protein that indicated neurodegenerative processes. Investigations by functional MRT-scans of brains of rescue crew members showed activated glia cells and signs of inflammation in the area of hippocampus especially with persons of high toxic exposition. Some recent studies of the years up to 2024 had shown increasing hints for the connection between neurodegenerative diseases and exposition to environmental chemicals and air-dust.[8] .

Epidemiologic studies have also found a context between the frequency of cases of **Parkinson's Disease** and the extent of pesticide contamination especially of farmers and personal working in agriculture, see review of Ascherio et al. (2006).[9] Another epidemiologic study found that a former long lasting exposure of farmers and inhabitants of the Central Valley in California, USA, to the fungicide Maneb and the herbicide Paraquat enhanced the risk to get Parkinson's Disease to about 75%.[10] Freire and Koifman (2012)[11] stated evidence of association of pesticide exposure and Parkinson's Disease (PD) in a review study. They observed a significant increase of the risk of PD in 13 of 23 case-control studies that considered overall exposures to pesticides and 10 of 12 studies using other research designs. Increased PD risk has been associated with insecticides, especially chlorpyriphos and organochlorines, and with the herbicide Paraquat and the fungicide Maneb. Thus, besides Paraquat, animal studies have suggested that pesticides with related properties such as rotenone, maneb, dieldrin, heptachlor and atrazine are causally linked to α-synuclein accumulation and to dopaminergic cell degeneration and apoptosis.[12, 13, 14, 15]

Effects of environmental chemicals enhance inflammation and neurodegenerative processes

The link between neurodegeneration and exposition to environmental chemicals has been reviewed for example by Cannon and Greenamyre (2011).[2] They stated: "Given that humans are exposed to numerous environmental toxicants in the course of a life span, identifying such a factor has proven to be very difficult, if not impossible. However, epidemiology and laboratory-based science have identified factors that influence risk and reproduced the key pathological features using animal models of the major neurodegenerative diseases." Here only few examples of the influence of environmental chemicals on neurodegeneration can be reviewed.

Chemicals enter the brain via the Blood-Brain-Barrier (BBB) because of their non-polar properties or because the BBB has been damaged by inflammatory mechanisms. Once arrived in the brain they interact with different cell types such as astrocytes, glia cells, oligodendrocytes and directly with neurons (fig. 1).[2]

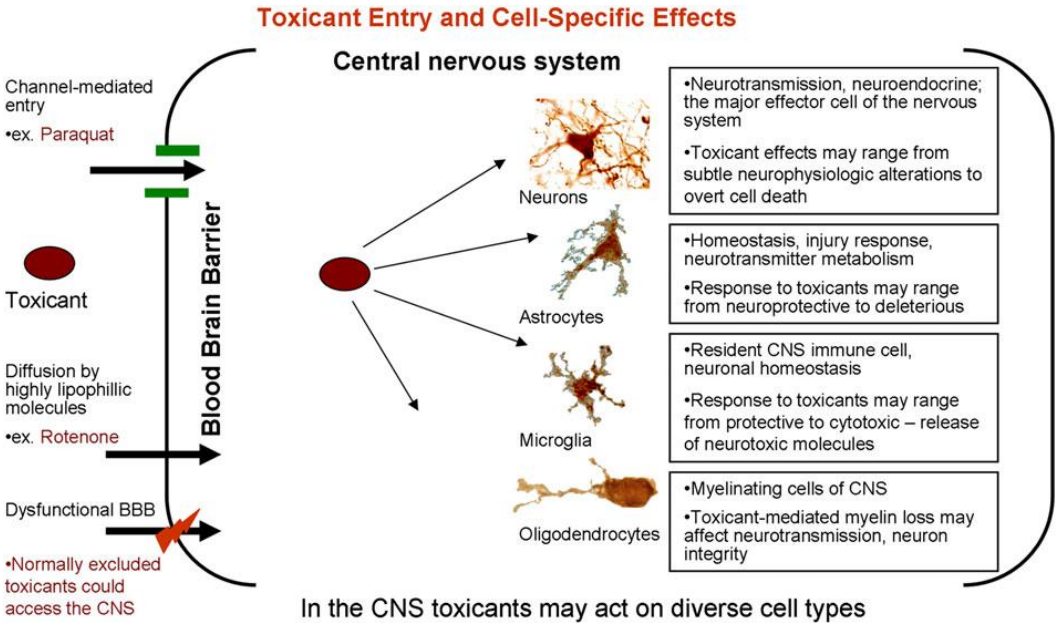


Fig. 1: Toxicant entry into the CNS and interactions with diverse cell types, adapted from Cannon and Greenamyre (2011).[2] The picture shows that environmental chemicals may enter the brain via the blood-brain-barrier (BBB) and then activate cells of the inborn brain immune system (astrocytes, microglia, oligodendrocytes) and neurons via special receptors such as TRP-receptors. The immune cells then turn into a pathogenic state supporting inflammation mechanisms and releasing toxic molecules such as cytokines, histamine, prostaglandines and oxygen radicals. According to Molot et al. (2022)[6] we suppose that these mechanisms also are important for the onset of Multiple Chemical Sensitivity (MCS).

TRP-Receptors play an important role in the activation of mechanisms leading to neuronal damage in the central nervous system. They have been investigated by studies concerning the causes of pain in the nervous system (Fig. 2).[16]

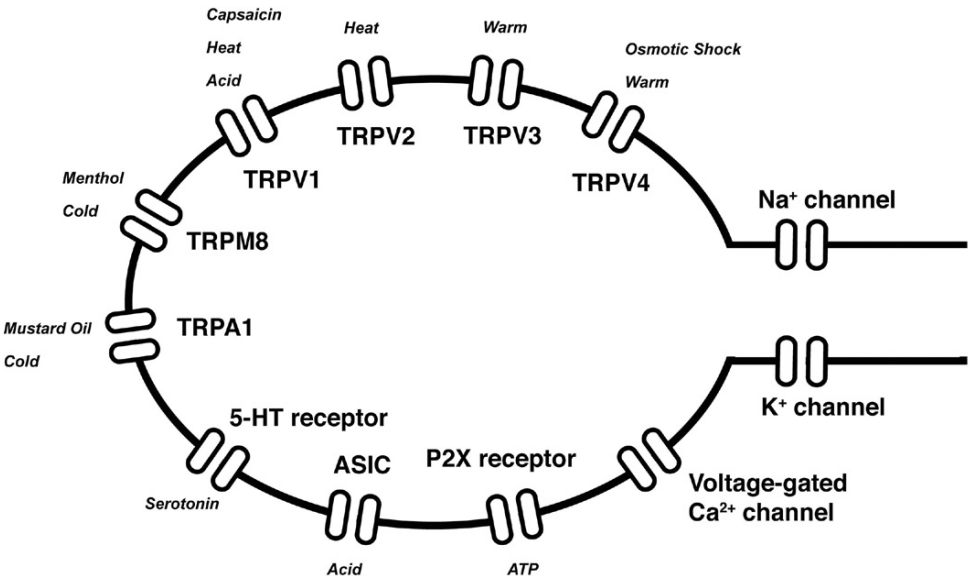


Fig. 2. Ion channels expressed in sensory neurons that presumably are implicated in nociception, adapted from Lee et al. (2005)[16]

The findings of neurodegeneration caused by TRP-receptor activation is supported by studies on the action of capsaicin by activating the TRPV1-receptor. Many studies have utilized pharmacological activation of TRPV1 receptors with capsaicin.[17] Capsaicin is an ingredient of chilli spice. Studies have shown that people suffer from cognitive decline if they often have consumed chilli spice. A study with 4852 participants of age 63, who consumed more than 50 g fresh or dried chilli shells per day, had a more than doubled risk of cognitive decline than the group of control persons without chilli consummation.[18] Massive activation of TRPV1-receptor by capsaicin results in enhanced secretion of glutamate by activated neurons. This leads to overstimulation of NMDA-receptors (*N*-Methyl-D-aspartate Receptor) by glutamate.[19, 20] The consequence is excitotoxicity and in extreme cases death, as has been documented by dozens of cases after the use of capsaicin-spray against drug-consumers by police officers. This has been reported by the German press organ "Spiegel", No. 53 (2009).[21] The death of these cases seems to be a result of combined action of capsaicin and active substances of the drugs.

Pesticide-action and neurodegeneration

There are still other mechanisms that lead to neurodegenerative processes in brain and the nervous system. Some pesticides such as organophosphate- and organic chlorinated insecticides enhance neurodegenerative process by direct action at synapses in brain.

Organophosphate compounds such as Paraoxone, Parathione (E 605), Chlorpyriphos and others inhibit the enzyme acetylcholine-esterase in the synaptic cleft at the end of cholinergic neurons, so that the neurotransmitter acetylcholine is not degraded and accumulated, leading to muscle spasms and to Organophosphate-induced delayed Neuropathy (OPIDN) in the central nervous system (CNS), as has been observed with farmers, who often had used insecticides.[22] Also crew members and passengers of aeroplanes had suffered from fume events caused by leaks of hydraulic oil lines of the jets. The toxic substance in the hydraulic oil is tricresyl-phosphate that acts similar as the organophosphate-insecticides, resulting in accumulation of glutamate and activation of NMDA-receptors in the brain. Crew members and passengers exposed to the hydraulic oil stream showed 1 to 3 weeks after exposition symptoms of organophosphate-induced delayed neuropathy (OPIDN) as ataxia, pain of muscles and joints, neuropathy of peripheral nerves, arrhythmias of the heart, cognitive decline, disturbances of memory and concentration, general poor performance, fatigue, depression, loose of emotional control . Patients showing the multiple symptoms of OPIDN often also express symptoms of an unspecific hypersensitivity to other xenobiotic chemicals as has been reported by medical doctors of neurology in Germany [23, 24], resembling the symptoms of Multiple Chemical sensitivity.[25]

Excess of acetylcholine in brain causes overactivation of muscarinic acetylcholine-receptors in brain, especially in forebrain, hippocampus and striatum, resulting in secretion of glutamate by these neurons. Glutamate then activates the NMDA-Receptor at neurons in different areas of the brain, activating different functions of these brain areas. A consequence of enhanced activation of NMDA-receptors by excess of glutamate is excitotoxicity, which means activation of signalling pathways leading to apoptose, the programmed cell death of neurons in brain areas where NMDA receptors are abundant. Glia cells in these brain areas respond to this event by elevated inflammation mechanisms producing additional oxidative and nitrosative stress and causing a vicious cycle that enhances neurodegeneration.[26, 27]

Organic chlorinated insecticides and biocides such as pentachlorophenol, DDT, Lindan, polychlorinated biphenyls, Endosulfan and dioxins bind and activate the so called Ah-Receptor (aryl-hydrocarbon-receptor) in astrocytes, glia cells an macrophages. In consequence transcription factors are activated, leading to production of cytokines of inflammation mechanisms such as IL-6, IL-1β, and of enzymes of the detoxification system such as Cytochrome-p450-Monooxygenase 1A1 (CYP 1A1). The result is chronic inflammation in the brain.[28, 29]

The effects of chlorinated organic substances such as those mentioned above have some common features of chronic and long time effects, as these are:

- Mitochondria show damaged structures resulting in dysfunction of the respiration-chain, lack of ATP (adenosine triphosphate), production of oxygen radicals, lowered amount of reduced glutathione, causing reduced detoxification mechanisms by glutathione-transferases.[30, 31, 32, 33]
- Insertion of chlorinated organic molecules into the structure of lipid membranes causing dysfunction of neurons and interfering with the function of natrium channels, leading to defects of the excitation conduction of nerves.
- Some chlorinated organic substances such as Lindane and Endosulfane inhibit GABA-receptors in the central nervous system, causing neuronal hyperexcitability in some brain regions that may support chemical hypersensitivity.[34, 35]

Taken together these effects result in a delayed appearance of chronic symptoms known as "neurogenic inflammation". This appears as "desynchronization", that means the initiating trigger by the chemicals may be followed by the symptoms of neurogenic inflammation even months or years after the trigger event.[30] This causes a problem in practical medicine, because medical doctors often do not see the connection between the trigger event by exposition to environmental chemicals and the delayed appearance of symptoms.

Environmental Chemicals, for example heavy metals, Nonylphenol, Di-(2-ethylhexyl)phthalat and Methoxychlor enhance processes of ageing by activating chronic inflammation mechanisms and especially inhibiting the production of protective molecules such as chaperones in the Endoplasmatic Reticulum of cells, that are responsible for the correct

folding of tertiary structure of proteins and enzymes. In consequence proteins with disturbed structures accumulate and cause inflammatory processes. Degradation of such proteins by proteasomes is inhibited.[36]

Heavy Metals: Mercury, Neurodegeneration and Multiple Chemical Sensitivity

Mercury hat been used as a component of Amalgam-fillings in dental medicine until 2025, when its use has been restricted by the European Union. But until now (2025) many people carry amalgam fillings and suffer from toxic effects of mercury-vapour that is emitted from the amalgam fillings at body temperature of 37°C.[37, 38] The mercury-vapour consists of mercury in elemental form (Hg^0) which is non polar, passes biological membranes including the Blood Brain Barrier (BBB) and accumulates in brain as Hg^{++} after being oxidized by the enzyme Catalase.[39] The mercury ions (Hg^{++}) show different toxic effects in human body:

- They bind to SH-groups of cysteine residues in proteins and of reduced glutathione (GSH) and therefore inhibit enzyme activities and the antioxidant capacity of the body. So in many organs including brain the energy-metabolism is inhibited. The respiratory chain in mitochondria is blocked, followed by accumulation of oxygen radicals, oxidative Stress and damage of mitochondria membranes.[40]
- Mercury ions (Hg^{++}) and also ions of other heavy metals induce the formation of oxygen radicals and oxidative stress in connection with the appearance of neurodegenerative diseases.[40, 38]
- Even low concentrations of Hg^{++} of about 0,1 mM (millimols) cause axon-degeneration and formation of neurofibrills in vitro.[41] Low dose exposure to mercury is connected with a higher risk of getting Alzheimer's disease.[40, 65]

Epidemiologic studies have found a connection between the number of amalgam fillings in teeth and the risk of getting a neurodegenerative diseases such as Alzheimer's Disease, Parkinson Disease, and Multiple Sclerosis.[39, 38] Other studies have proven the connection between exposure to mercury and the risk of getting Alzheimer's disease, see review by Mutter et al. (2007).[66] In my own observations as censor with patients showing typical symptoms of MCS, it was conspicuous that they had amalgam fillings in their teeth, and this without exception. These observations had been made by writing about 30 expert opinions for patients with MCS-diagnosis.

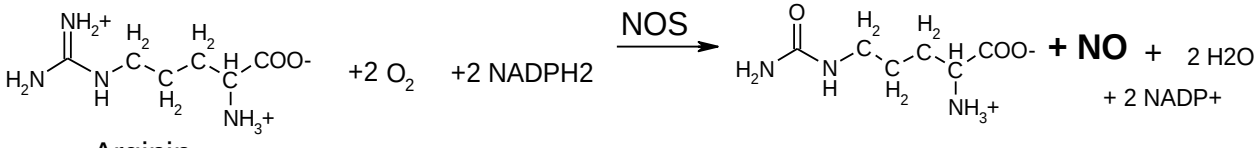
The following representations will show that mechanisms caused by mercury exposition in their end coincide with those following expositions to other neurotoxic chemicals.

Oxidative and Nitrosative Stress are key-mechanisms in neurodegeneration and MCS

The immune-system in the brain consists of specialized cells as there are glia cells and astrocytes that are part of the blood-brain-barrier and are associated to nerve-fibres in the brain. Astrocytes play an important role in brain-function. They comprise about 35% of cells in brain. Their protective function towards brain neurons concerns support of energy metabolism and anabolism of neurotransmitters. Astrocytes and neurons exchange signal molecules by special gap junctions. They form functional networks that support the function of synapses and the blood-brain-barrier.[42] Astrocytes regulate the extracellular glutamate concentration in brain and therefore inhibit damage of neurons by excitotoxicity caused by overstimulation of NMDA-receptors by elevated glutamate concentrations. This stimulation causes an activation of apoptose-signaling (programmed cell death) of neurons. Under normal conditions astrocytes regulate activities of immune cells of the adaptive and innate immune system to avoid inflammation in brain. They produce antioxidant substances such as reduced glutathione, thioredoxine and metallothioneines to prevent oxidative damage and apoptose by reactive oxygen radicals (ROS) and peroxynitrite that are formed by inflammation mechanisms.[43]

Under condition of chronic inflammation in brain astrocytes and glia cells change their function and become pathogenic, especially when chemicals activate Toll-like Receptors (TLR) at the membrane of astrocytes. Inflammatory cytokines are secreted by glia cells and activate pathogenic forms of astrocytes. These cells then degrade the gap junctions that are located between astrocytes, endothelial cells and neurons. The blood brain barrier is damaged, the extracellular glutamate concentration rises because of the lack of astrocyte- and glia cell- function.[44] This leads to the above mentioned overstimulation of NMDA-receptors in brain.

The NMDA-receptor is connected to a calcium-channel in the membrane of the neuron. Activation of the receptor causes influx of calcium-ions into the cell, causing further signalling cascades, for example leading to the activation of NO-synthases (eNOS, nNOS, iNOS).[45, 46] The NO-synthases degrade the amino-acid Arginine to Citrulline under oxidative conditions and the release of nitrogen-monoxide (NO):



Arginin Citrullin

Elevated calcium-concentrations also inhibit enzymes of the respiration chain in mitochondria, causing elevated production of hydrogen-superoxide (H_2O_2). Nitrogen-oxide (NO) and hydrogen-superoxide react to produce peroxynitrite ($ONOO^-$) which is highly reactive causing different pathogenic effects in the cell:

- Elevation of the activity of the NMDA-receptor and so forming a positive feedback-cycle that leads to enhancement of production of NO and peroxynitrite. This is because NMDA stimulation leads to increases of the iNOS-activity and overproduction of NO.[47]
- Peroxynitrite damages the blood-brain-barrier so that chemical substances and signalling molecules of inflammation processes can enter the brain.
- Peroxynitrite activates the induction-factor NF-kB, that induces genes to produce inflammatory cytokines such an interferone-gamma (Ifn-γ), tumornecrosis-factor-alpha (TNF-α) and interleukine-1-beta (IL-1β), and so activating inflammation-mechanisms by the innate immune-system.
- Peroxynitrite initiates damage of biological membranes of neurons and mitochondria by a process called lipid-peroxidation[63], followed by inhibition of the function of mitochondria to produce ATP. The organism thus suffers from a lack of energy, which is for example a characteristic feature of chronic fatigue syndrome/myalgic encephalopathy (CFS/ME), an illness often found by patients with Multiple Chemical Sensitivity (MCS).[45]
- An excess of NO also inhibits the activity of cytochrome-p450-monooxigenases, the enzymes of phase-I of the detoxification-mechanisms, causing accumulation of toxic substances in the body. Patients with MCS often suffer from genetic deficits in the detoxification-system[48], so that inflammation mechanisms with elevated concentrations of NO enhance the effects of genetic deficits of the detox-system.
- NO acts as a retrograde messenger, as it is released by the postsynaptic cell after activation of the NMDA-receptor.[45] It diffuses to the presynaptic neuron and activates the release of the neurotransmitter glutamate. This mechanism is normally supporting learning and memory by strengthening the activity of the synapses participating in the learning process, but under condition of brain inflammation it enhances the pathogenic action of glutamate leading to excitotoxicity. This is known as activation of apoptose signalling by excess of glutamate.[19]

Consequences of NO and peroxynitrite formation

Damage of membranes of neurons by peroxynitrite causes secretion of signalling molecules by the neurons that activate microglia, such as glutamate, ADP (adenosine-dophoaphate), and signalling proteins like HMGB1 (high-mobility group protein 1) und CCL-21 (Chemokin-Ligand 21). This leads to further activation of microglia and their secretion of cytokines of the inflammation-reaction such as IL-1β, TNFα, IL-6, IL-12, Ifnγ, Fas-Ligand and additional glutamate. So there is another feedback cycle that enhances the inflammation in the brain. The concentrations of reactive oxygen-radicals (ROS), Superoxid-Anions, NO, peroxynitrite und hydroxyl-radicals rise and inflammation proceeds.[49, 50]

Chronic inflammation in brain has consequences for the metabolism of neurotransmitters. The cytokines of inflammation mechanisms such as IL-6, IL-1β, TNF-α, Ifn-γ as inductors activate the gene for the enzyme Indolamine-2,3-dioxygenase (IDO), that converts tryptophane to kynurenine, that is then degraded to chinolinic acid. Chinolinic acid has neurotoxic properties and activates NMDA-receptor, enhancing its neurotoxic function leading to excitotoxicity.[51, 52]

Kynurenine also binds and activates the Ah-receptor similar to the action of polychlorinated dioxins and biphenyls and enhances their neurotoxic action.[53]

This is only a small part of all the mechanisms and signal-pathways that happen during inflammation as a consequence of neurodegeneration in brain, as it has been described for Alzheimer's Disease or Parkinson's Disease (comprehensive reviews see for example Lajtha, 2007, and Ahmad, 2012).[54, 55] As most of these mechanisms may also be initiated or supported by binding of chemicals to receptors of TRP-type, there is a connection to initiation of Multiple Chemical Sensitivity (MCS), which appears as another kind of multisystem inflammation illnesses.

Pathologic mechanisms in Multiple Chemical Sensitivity (MCS) are similar to those of neurodegeneration in neurodegenerative diseases

Multiple Chemical Sensitivity (MCS) is listed in the ICD-Code (International Statistical Classification of Diseases and Related Health Problems) as ICD-10 T78.4. Although it is not regarded as a disease by official institutions of health care in Germany. Hence there are many proofs and studies cited for example by Pall[45] that support the fact that MCS is a chronic inflammatory multisystem illness.

The initiation of the disease state of MCS is commonly self-reported as a single precipitating event of severely intoxicating overexposure, or as a chronic exposure to lower doses of an environmental pollutant, of a kind that may be totally unrelated to subsequent triggering molecules acting during the phase of established disease.[56]

MCS is one of the inflammatory multisystem illnesses, where the activation of NMDA-receptor plays a central role in the mechanism.[45] As described above the consequence of NMDA- and TRP-receptor activation is a chronic inflammation process that is initiated by activation of the transcription factor NF-kB and followed by production of cytokines of the inflammation reaction. Part of the central mechanism of MCS and other inflammatory multisystem illnesses such as ME/CFS (Myalgic Encephalopathy /Chronic Fatigue Syndrome) and Toxic Encephalopathy (TE) is the action of the activated induction factor NF-kB, that expresses a

feedback cycle with self enhancing activity and results in the production of hydrogen peroxide, nitric oxide (NO) and peroxynitrite, known as the NO/ONOO⁻cycle.[45] These pathogenic mechanisms are also known as important parts of neurodegeneration mechanisms in Alzheimer's and Parkinson's Disease as described above.[49, 50]

Evidence indicates that most of the cytotoxicity is attributed to peroxynitrite, which is produced from the diffusion-controlled reaction between NO and another free radical, the superoxide anion. Peroxynitrite interacts with lipids, DNA, and proteins via direct oxidative reactions or via indirect, radical-mediated mechanisms. These reactions trigger cellular responses ranging from subtle modulations of cell signaling to overwhelming oxidative injury, committing cells to necrosis or apoptosis. In vivo, peroxynitrite generation represents a crucial pathogenic mechanism in conditions such as stroke, myocardial infarction, chronic heart failure, diabetes, circulatory shock, chronic inflammatory diseases, cancer, neurodegenerative disorders and also inflammatory multisystem illnesses such as MCS and ME/CFS.[57, 45]

Pall[45] proposed a central mechanism for the exquisite sensitivity to organic solvents apparently induced by previous chemical exposures in MCS. This mechanism is centered on the activation of N-methyl-D-aspartate (NMDA) receptors as a consequence of activation TRP-receptors by environmental chemicals such as organic solvents and different pesticides, leading to production of elevated nitric oxide and peroxynitrite, leading in turn to increased stimulating of and hypersensitivity of NMDA receptors. In this way, organic chemical exposure may produce progressive sensitivity to these chemicals. Pesticides such as organophosphates and carbamates 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 aspects of MCS.[45]

A self-enhancing feedback-loop-cycle as a central mechanism of inflammatory multisystem illnesses has been supported by many different studies in scientific literature cited by Pall (2007).[45] Therefore it is evident that the mechanisms of neurodegeneration of Alzheimer's disease and other neurodegenerative diseases such as Parkinson's Disease correspond to the central biochemical mechanisms of chronic inflammatory multisystem illnesses such as MCS, ME/CFS (chronic fatigue syndrome) and some autoimmune diseases such as multiple sclerosis.

Diagnostic imaging by SPECT and PET had shown signs of neurodegeneration of patients with MCS-diagnosis.[58, 59] SPECT-analyses of brains of persons that had been exposed to neurotoxic chemicals (pesticides, organic solvents) have shown a diminished blood flow in different areas of the brain, indicating a lowered function of these brain areas as consequence of the exposition to neurotoxic chemicals.[60] Similar results have been reported by Mueller et al. (2008, 2000)[61, 62] with 200 patients after exposition to organic solvents, formaldehyde, pentachlor-phenol, organophosphate-pesticides, and mercury. A greater part of these patients suffered from toxic encephalopathy and MCS simultaneously. These findings suggest that SPECT examination of brain blood-flow indicates impaired cerebral function following exposition to neurotoxic chemicals. Patients with MCS therefore also may be involved to neurodegerative processes after exposition to neurotoxic chemicals.

Summary and Conclusion

There are similar pathogenic mechanisms in neurodegenerative diseases and Multiple Chemical Sensitivity (MCS) that are initiated by exposition to environmental chemicals resulting in the activation of receptors in the central nervous system (CNS) such as TRP- and NMDA-receptors. The activation of these receptors leads to accumulation of acetylcholine and glutamate in the CNS, initiating noxious signaling in neurons and probably ending in the mechanism of apoptose of neurons. These events are accompanied and supported by chronic inflammation mechanisms in brain under participation of glia cells, astocytes and macrophages. As a central part of these inflammation mechanisms there exists a vicious and self enhancing cycle initiated by peroxides, NO and peroxynitrite, called „NO-ONOO-Cycle".[45] Once initiated this cycle leads to irreversible damages in parts of the brain and enhances inflammation mechanisms. Membranes of neurons and mitochondria are damaged by perioxynitrite and oxygen-radicals in a process called radical-chain-reaction.[63] This leads to loss of function of neurons and mitochondria, causing further cycles of inflammation and neurodegeneration in brain. These mechanisms result in the lowering of the threshold of personal reaction to exposition to environmental chemicals, as it is a typical feature of MCS.

In our own experience as censors for patients that had been exposed to the wood preservative pentachlor-phenole, to insecticides of organophosphate-type, to vapours of chlorinated organic solvents, or mercury emitted by amalgam-fillings in teeth we recognized in all cases severe symptoms of MCS accompanied by chronic fatigue and cognitive decline.

On the other hand, it should be emphasised that MCS is not a neurodegenerative disease, because its course mostly does not lead to progressive degeneration of the brain. This can be explained by an inhibition of noxious vicious cycles after avoidance of further exposure to toxic chemicals. This is due to a regeneration of antioxidant capacities such as reduced glutathione (GSH) that neutralize peroxynitrite and oxygen radicals. As a successful therapy supplies of antioxidant GSH and vitamins such as vitamin C, alpha lipoic acid, and others are strongly recommended.[64] This kind of therapy seems not suitable for typical progressing neurodegenerative diseases such as Alzheimer's Disease or Parkinson.

The described mechanisms of both MCS and neurodegenerative diseases and their initiation by

environmental chemicals strongly demand prevention measures to avoid exposure to toxic environmental chemicals such as pesticides used in conventional agriculture, organic solvents, fine dust in the air, microplastic particles, biocides for wood conservation, preservatives and synthetic colours in food, scents in detergents, plasticizers in clothes and shoes, and many others, by the institutions of public health and environmental policy.

Conflicts of Interest Statement

No conflicts of interest are connected with this publication. There are no fundings by institutions from outside of the author's private engagements.

Acknowledgements

Thanks to Prof. Martin L. Pall and Dr. Kurt E. Müller for giving support to the statements in this publication and in the book "Umweltschadstoffe und Neurodegenerative Erkrankungen des Gehirns", published (in German) 2014 by Hans-Ulrich Hill. Special thanks to Dr. Volker von Baehr, Institute of Medical Diagnostic (IMD) at Berlin, who and his staff have developed many new methods of detection of pathologic mechanisms for diagnosis of chronic inflammatory multisystem illnesses such as MCS and chronic fatigue syndrome (ME/CFS).

References

1. Roßner S. Molekulare Mechanismen der Amyloidogenese. Lecture during the programme „Neurowissenschaften in der gymnasialen Oberstufe“ of the „Neurowissenschaftliche Gesellschaft e.V“, Paul-Flechsig-Institute for Brain Research, University of Leipzig, Germany, March 16, 2017.
2. Cannon JR, Greenamyre JT (2011): The Role of Environmental Exposures in Neurodegeneration and Neurodegenerative Diseases. *Toxicological Sciences*. 2011;124(2): 225–250, doi:10.1093/toxsci/kfr239
3. Calderón Garcidueñas L, Mukherjee PS, Waniek K, et al. (2018): Non-Phosphorylated Tau in Cerebrospinal Fluid is a Marker of Alzheimer's Disease Continuum in Young Urbanites Exposed to Air Pollution. *J Alzheimers Dis*. 2018;66(4):1437-1451, doi: 10.3233/JAD-180853
4. Wilker EH, Preis SR, Beiser AS, et al. Long-Term Exposure to fine particulate matter, residential proximity to major roads and measures of brain structure, *Stroke*. 2015;46(5): 1161-1166, doi: 10.1161/STROKEAHA.114.008348
5. WHO World Health Organization. Burden of disease from the joint effects of household and ambient air pollution for 2016.2018. Available from: https://www.who.int/airpollution/data/AP_joint_effect_BoD_results_May2018.pdf?ua=1 [Accessed 23 Oct 2020].
6. Molot, J., Sears, M., Marshall, L.M., et al. Neurological susceptibility to environmental exposures: pathophysiological mechanisms in neurodegeneration and multiple chemical sensitivity. *Reviews on Environmental Health*.2021, De Gruyter, September 16th, 2021, https://doi.org/10.1515/reveh-2021-0043
7. Clouston SAP, Mann FD, Meliker J et al. Incidence of dementia before age 65 years among World Trade Center attack responders. *JAMA Netw Open* 2024;7(6): e2416504; doi:10.1001/jamanetworkopen.2024.16504)
8. DGN, 2024: Deutsche Gesellschaft für Neurologie e.V. (DGN), report: www.dgn.org, in *Umwelt Medizin Gesellschaft* 2024;37(3):8
9. Asherio A, Honglei C, Weisskopf MG, et al. Pesticide exposure and risk for Parkinson's disease. *Ann Neurol* 2006;60(2):197-203
10. Wheeler, M. (2009): Pesticide exposure found to increase the risk of Parkinson's disease. 2009;UCLA (University of California, Los Angeles), press release 4 /20/2009
11. Freire, C., and Koifman, S. (2012): Pesticide exposure and Parkinson's Disease: Epidemiological evidence of association. *NeuroToxicology*. 2012;33(5):947-971
12. Betarbet R, Sherer TB, MacKenzie G, Garcia-Osuna M, Panov AV, Greenamyre JT. Chronic systemic pesticide exposure reproduces features of Parkinson's disease. 2012; *Nat Neurosci*. 2012;2000(3):1301–1306.
13. Moretto A, Colosio C. Biochemical and toxicological evidence of neurological effects of pesticides: the example of Parkinson's disease. *Neurotoxicology*. 2011;32:383–391.
14. Thiruchelvam M, Brockel BJ, Richfield EK, Baggs RB, Cory-Slechta DA. Potentiated and preferential effects of combined paraquat and maneb on nigrostriatal dopamine systems: environmental risk factors for Parkinson's disease? *Brain Res*. 2000;873:225–34.
15. Thiruchelvam M, Richfield EK, Baggs RB, Tank AW, Cory-Slechta DA. The nigrostriatal dopaminergic system as a preferential target of repeated exposures to combined paraquat and maneb: implications for Parkinson's disease. *J Neurosci*. 2000; 20(24):9207–9214.
16. Lee, Y., Chang-Hun Lee, C.H., and Oh, U. Painful Channels in Sensory Neurons. *Mol Cells*. 2005;20(3):315-324
17. Steenland HW, Shanelle W, Ko W, Wu LJ, Zhuo M. Hot receptors in the brain. *Molecular Pain*. 2006;2:34; doi:10.1186/1744-8069-2-34
18. Shi Z, El Obeid T, Riley M, et al. High chili intake and cognitive function among 4582 adults: An open cohort study over 15 years. Nutrients. 2019;11(5):1183,
    1. online: https://doi.org/10.3390/nu11051183
19. Neves D, Salazar I.L, Almeida RD, Silva RM. Molecular mechanisms of ischemia and glutamate excitotoxicity. *Life Sciences*. Textbook Elsevier 2023; p. 328, https://doi.org/10.1016/j.lfs.2023/121814
20. Thiel G, Backes TM, Rössler OG. Chili und der Capsaicinrezeptor TRPV1. *Biol Unserer Zeit*. 2020;50(4):246-252
21. Spiegel, German press organ, No. 53 (2009)
22. Hargreaves AJ. Neurodegeneration induced by organophosphorous compounds. In: Ahmad SI (Ed.): Neurodegenerative Diseases. Springer Science + Business Media, LLC/Landes Bioscience, New York, 2012: Series*: Advances in Experimental Medicine and Biology*. 2012;724:189-204
23. Binz P. Zerstörung von familiären und sozialen Strukturen als Folge von Hirnschäden. Lecture at: Studientagung „Gewissenhafte Forschung. Diagnose und Handlungsmöglichkeiten bei Vergiftungen in der Arbeitswelt. Katholische Akademie Trier, 15.-17.5.2009
24. Binz P. (2010): 10 Fallberichte (Kasuistiken) von Patienten mit Chemikalienbelastungen (Organophosphat-Pestizide, Reinigungsmittel mit Chlorgehalt) aus der neurologischen Praxis. 2010; Personal letter communication and summary of medical status-reports of his patients as practising neurological physician.
25. Eicher T, Avery E. Toxic Encephalopathies. *Neurol Clin*. 2005;23:353-376
26. Okun E, and Mattson MP. Neuronal vulnerability to oxidative damage in aging. In: Veasey, S.C. (Ed.): Oxidative Neural Injury. *Humana Press/ Springer*, Dordrecht, Heidelberg, London, New York, 2009, p. 83-95
27. Bak LK, Schousboe A, Waagepetersen HS. Glutamate and glutamin in brain disorders. In: Blass, J.P. (Ed.): Neurochemical mechanisms in disease. *Advances in Neurobiology* 2011;1:196-209, Springer Science + Business Media

28. Chen G, Bunce NJ. Interaction between halogenated aromatic compounds in the Ah receptor signal transduction pathway. *Environ Toxicol.* 2004;19(5):480-489.
29. Denison MS, Nagy SR (2003): Activation of the aryl hydrocarbon receptor by structurally diverse exogenous and endogenous chemicals. *Annu Rev Pharmacol Toxicol.* 2003;43:309-334. Epub 2002 Jan 10.
30. Straub RH. Lehrbuch der klinischen Pathophysiologie komplexer chronischer Erkrankungen. (In English: Textbook of clinical pathophysiology of complex chronic diseases). Vandenhoek & Ruprecht 2007, Vol. II, p.20-21
31. Straub RH. Drei Gedächtnisse für den Körper (Textbook). Springer-Verlag, New York, Heidelberg, 2020, p. 214-217
32. Straub RH. Frühe Traumata als Ursprung von chronischer Entzündung. Textbook, Springer Verlag, New York, Heidelberg, 2022, p.173
33. Huber W, Prull KJ, Kochen W. Zu den Spätfolgen des Einsatzes chlororganischer Holzschutzmittel. (Longtime consequences of exposure to chloroorganic wood preservatives.) *Umwelt, Medizin, Gesellschaft* 2024;37(3):14-17
34. Vale C, Fonfria E, Bujons J, et al. The organochlorine pesticides γ-hexachlorocyclohexane (lindane), α-endosulfan and dieldrin differentially interact with GABAa and glycine-gated chloride channels in primary cultures of cerebellar granule cells. *Neuroscience* 2003;117:397-403
35. Suñol C, Vale C, Rodríguez-Farré E, et al. Polychlorocycloalkane insecticide action on GABA- and glycine-dependent chloride flux. *Neurotoxicology* 1998;19(4-5):573-580
36. Taghavi A, Heine K, Kalberlah F. Synopse zu Wirkungsmechanismen von Spurenstoffen im Säugerorganismus als Grundlage der Bewertung des Wirkungspotenzials von Stoffsummen und der Erkennung „neuer" toxischer Endpunkte, Umweltbundesamt (UBA, Ed.), Brochure, 2014, p.88ff
37. Guzzi G, Grandi M, Cattaneo C, et al. Dental amalgam and mercury levels in autopsy tissues. Food for thought. *Am J For Med Path.* 2006;27:42-45
38. Mutter J, Naumann J, Sadaghiani C, et al. Alzheimer Disease: Mercury as pathogenic factor and apolipoprotein E as a moderator. *Neuroendocrinology Letters.* 2004;25(5):331-339
39. Jirau-Colon, H., Gonzalez-Parrilla, L., Martinez-Jimenez, J., Adam, W., Jimenez-Velez, B. Rethinking the dental amalgam dilemma: an integrated toxicological approach. *Int J Environ Res Public Health.* 2019;16(6):1036, online under: https://www.ncbi.nlm.nih.gov/pmcarticles/PMC6446133/)
40. Olivieri G, Novakovic M, Savaskan E, et al. (2002): The effects of ß-estradiol on SHSY5Y neuroblastoma cells during heavy metal induced oxidative stress, neurotoxicity and ß-amyloid secretion. *Neurosci.* 2002;113:849-855
41. Leong, C., Syed, N., Lorscheider, F., et al. (2001): Retrograde degeneration of neurite membrane structural integrity of nerve growth cones following in vitro exposure to mercury. *Neur Rep.* 2001;12:733-737
42. Takeuchi H. Glial communication via gap junction in neuroinflammation. In: Suzumura A., Ikenaka K.: Neuron-glia interaction in neuroinflammation. Springer, New York, Heidelberg, 2013, p.119-134
43. Farina C. Neuron-glia-interaction via neurotrophins. In: Suzumura A, Ikenaka K. Neuron-glia interaction in neuroinflammation. Springer, New York, Heidelberg, 2013, p.101-118
44. Reinisch VM, Krause DL, Müller N. Neuroinflammation in Alzheimer's Disease. In Peterson PK, Toborek M (Ed.): Neuroinflammation and Neurodegeneration. Springer, New York, 2014, p.161-177.
45. Pall, M.L. (2007): Explaining Unexplained Illnesses. Disease paradigm for Chronic Fatigue Syndrome, Multiple Chemical Sensitivity, Fibromyalgia, Post-Traumatic Stress Disorder, Gulf War Syndrome, and Others. Harrington Park Press, New York, London, 2007, doi: 10.1300/5139-a.
46. Pall, M.L. (2009): Multiple Chemical Sensitivity: Toxicological Questions and Mechanisms. In: Timothy C. Marrs, Tore Syversen (Eds.): General and Applied Toxicology. Chapter XX John Wiley & Sons, London, 2009
47. Acarin L, Peluffo H, Gonzalez B, Castellano B (2002): Expression of inducible nitric oxide synthase and cyclooxygenase-2 after excitotoxic damage to the immature rat brain. *J Neurosci Res.* 2002;68:745-754
48. Schnakenberg, E., Fabig, K.R., Stanulla, M., et al. (2007): A cross sectional study of self reported chemical-related sensitivity is associated with gene variants of drug metabolizing enzymes. *Environ. Health.* 2007;6(1):6 http://www.ehjournal.net/content/6/1/6
49. Suzumura A (2013): Interactions between neurons and microglia during neuroinflammation. In: Suzumura A., Ikenaka K. Neuron-glia interaction in neuroinflammation. Springer, New York, Heidelberg, 2013, p. 63-73.
50. Lee, SJ. Toll-like receptors and neuroinflammation. In: Suzumura A., Ikenaka K. Neuron-glia interaction in neuroinflammation. Springer, New York, Heidelberg, 2013, p. 135-156.
51. Godbout JP, Chen J, Abraham J, Richwine AF, Berg BM, Kelley KW, Johnson RW. Exaggerated neuroinflammation and sickness behaviour in aged mice following activation of the peripheral innate immune system. *FASEB J.* 2005;19:1329-1331
52. Chang, Q., Szegedi, S.S., O'Connor, J.C., Dantzer, R., Kelley, K.W. Cytokine induced sickness behavior and depression. In: Siegel, A., und Zalcman, S.S. (Ed.): The neuroimmunological basis of behaviour and mental disorders. Springer, New York, 2009, p. 145-181
53. Opitz CA, Litzenburger UM, Sahm F, et al. An endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor. *Nature.* 2011;478(7368):197-203
54. Lajtha, A. (Ed.): Handbook of Neurochemistry and Molecular Neurobiology: Degenerative Diseases of the Nervous System. Springer Science +Business Media, 2007

55. Ahmad SI (Ed.): Neurodegenerative Diseases. Springer Science +Business Media, Landes Bioscience, 2012
56. Genuis, S.J. Sensitivity-related illness: the escalating pandemic of allergy, food intolerance and chemical sensitivity. *Sci Total Environ*. 2010;408:6047-6061.
57. Pacher, P, Beckman, JS and Liaudet, L. Nitric oxide and peroxynitrite in health and disease. *Physiol Rev*. 2007;87:315-424.
58. Fabig KR. ZNS-Schäden durch Umweltgifte: SPECT. In: Daunderer: Handbuch der Umweltgifte, II-3.3.4: p. 4-24, Ecomed, Landsberg, 1990
59. Fabig KR. Six measurements of PCDD/PCDF and five measurements of brain function with with Single Photon Emission Computed Tomography (SPECT) in one individual. A case study. *Organohalogen Compounds* 1998;37:23-27
60. Heuser G, Mena I. Neurospect in Neurotoxic Chemicals Exposure. Demonstration of Longterm Functional Abnormalities. *Toxicology and Industrial Health*. 1998;14 (6):813-827
61. Müller KE. Toxisches Parkinson-Syndrom nach Pentachlorphenol-Exposition. *Zeitschrift für Umweltmedizin*. 2000;8(4):225-227
62. 62 Müller KE. personal communication, letter report, 2008
63. Younes M. Freie Radikale und reaktive Sauerstoffspezies. In: Marquardt H, Schäfer S (Ed.): Lehrbuch der Toxikologie (Textbook of Toxicology). Wissenschaftliche Verlagsgesellschaft Stuttgart, 2nd Edition, 2003, p. 125-127, Chapter 6.4.3.: Interaktion freier Radikale mit Lipiden. Die Lipidperoxidation.
64. Pall ML. Wie heilt man Erkrankungen mit Beteiligung des NO/ONOO-Zyklus? (How to treat illnesses based on the NO/ONOO-cycle.) Information-sheet DeltaStar Nutrients, http://www.martinpall.info , 2010
65. Zahir F, Rizwi SJ, Haq SK, and Khan RH. Low dose mercury toxicity and human health. *Environ Toxico. Pharmakol*. 2005;20(2):351-360
66. Mutter J, Naumann R, Schneider H, Walach H (2007): Quecksilber und Alzheimer-Erkrankung. *Fortschr Neurol Psychiatr*. 2007;75:528-538

