



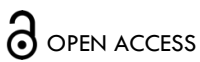
CASE REPORT

Description of a Case with Multiple Chemical Sensitivity in Combination with Neurotoxic Disease and Chronic Fatigue Syndrome

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ABSTRACT

Here we present a case of a lady, called Mrs. P., a shop assistant of a wholesale market for agricultural device and chemicals, who had been exposed to many different toxic chemicals during her professional work that caused severe symptoms of a disease like Multiple Chemical Sensitivity (MCS) combined with a disease that corresponded to a Toxic Encephalopathy and a Chronic Fatigue at the same time. This case had been examined by a detailed expert opinion for getting a compensation by the health insurance. But this did not succeed, as in Germany illnesses of environmental origin were not regarded as scientifically proved. The patient suffers up to now under continuing severe complaints without help or therapy by medical doctors and the health insurance.

The case presented here appears to be an example for the publication of Hill and Huber (2025)¹ that describes connections of the pathologic mechanisms between MCS and neurodegenerative diseases. The symptoms of the affected lady are consequences of mechanisms that appear during diseases such as MCS, Alzheimer's and Parkinson's Disease and Toxic Encephalopathy because of neurotoxic effects of the chemicals involved here. The multiple exposure to different highly toxic chemicals had been documented by the list of products that are sold by the wholesale market for agriculture, that was the workplace of the concerned lady in Germany.

The purpose of this publication is to strengthen our demand to the responsible institutions of health care and environmental policy in Germany to take action to verify precaution and to avoid exposures to toxic chemicals such as pesticides and other toxic organic chemicals at work places and in agricultural activities not only in Germany.

The information about the disease status of the concerned lady called "Mrs. P." has been collected from medical certificates and receipts, by a questionnaire and by personal reports of the patient. This investigation leads to the conclusion that Mrs. P. suffers from a severe disease since the beginning of her work at the wholesale market in the year 2000 up to her incapacity to work as consequence of her disease 12 Years later. The disease caused an inability to manage every day-tasks at work and even at home, with severe restrictions of her common life quality.

1. Situation of exposure to toxic chemicals at the workplace

During her professional work for 12 years Mrs. P. was exposed at her workplace, the wholesale market for products of agricultural enterprises, to a mixture of highly toxic chemical substances at about 12 hours per day. This exposure caused a severe chronic disease that appeared gradually increasing in the years after having started her work.

Because of regulations of data and personality protection the names of the concerned patient, her treating medical doctors and clinics and that of her workplace cannot be published here, they are known by the authors.

The affected patient started her job at the wholesale

market in the year 2000 as responsible market leader and stayed there for 12 years until in 2012 her inability to work because of a chronic disease had been certified. Up to this time she had been exposed daily to different highly toxic chemicals, that are used to be sold at wholesale markets for agricultural products, such as different pesticides (insecticides, herbicides, fungicides, rodenticides), biocides against pest-organisms, fertilizers, feedings mostly combined with antibiotics and pesticides, disinfectants, paints, building materials, organic solvents, and special work clothes mostly imported from overseas countries. A survey of the products offered at the wholesale market is given in table 1. The table indicates only a selected part of all the offered chemicals as there are pesticides, biocides, organic solvents and fuels.

Table 1: Pesticides offered at the concerning wholesale market for agricultural supplies

(Some of the product names are given in German as original product designations.)

Pesticides and biocides	Active substance	Scope
Roundup	Glyphosat	Herbicide
Vorox Unkrautvertilgung	Glyphosat, Glyphosat-Trimesium Diuron	Herbicide
Blattanex spezial	2% Propocur, Dichlorvos	Insekticide
Metasystox	Oxydemeton-methyl	Insekticide against aphids
Bayer Lizetan	Wirthiacloprid	Insekticide for interior plants
Calypso ungezieferfrei	Thiacloprid	Insekticide
Decis	Deltamethrin	Insekticide
Intermitox Powder	Cypermethrin, Glutaral	Insekticide for animal barns
Hexa Vetyl- Powder	Pyrethrum Extrakt, Piperonylbutoxid	Insekticide for animal barns
Trixi Universal Spray	Permethrin (9,8g/kg) Cypermethrin (0,9g/kg)	Insekticide against vermins
Etisso Wespex Quick	Permethrin, Esbiothrint, Piperonylbutoxid	Insekticide
Universal Pilzfrei M	Myclobutanil	Fungicide
Neudorf Rattengift	Brodifacoum	Rodenticide, rat poison
Rattengift	Cumarin	Rodenticide
Rattengift Bayer	Difethialon	Rodenticide
Brumelin Ultra F	Brodifacoum	Rodenticide

In addition, Mrs. P. was exposed to dust that was awirled during cleaning activities in the store-room. This was performed every two weeks. It is presumed that highly volatile toxic organic substances, that are emitted out of containers for pesticides and biocides, are attached to fine particles of the dust, and together with these they were incorporated by the respiratory tract into the lung. The containers of rat poison sometimes had been damaged, so that Mrs. P. had to clean the ground of the store room by sweeping and wiping.

Mrs. P. also reported special exposures by toxic substances, as she cleaned the shelves of different toxic products. Following these actions, she got severe acute symptoms such as tachycardia, nausea, headache, vertigo, tremor, and others.

Sometimes there happened accidents such as damaged packagings and special exposures by returned parcels that had been damaged during transports. Mrs. P. was responsible for the disposal of these materials. Because of lacking time protective measures such as hand gloves and respiratory protection often were not possible. Therefore she had contact to toxic chemicals by her skin and respiratory air.

LONGTIME EXPOSURE

Fertilizers and pesticides are used to be sold during spring time season from March to May and also during autumn in September and October. Therefore, the exposure to these chemicals was restricted to these seasons. On the other hand biocides against pest-organisms, fertilizers, feedings, antibiotics, disinfectants,

paints, building materials, fuels, organic solvents and workwear were sold all the time during the year. Mrs. P. had at least two times per week skin-contact to these products, often to rat poison, because sometimes damaged cardboard boxes had to be disposed.

In addition, sometimes there happened extremely high short time exposures to toxic insecticides such as pyrethroids and dichlorvos because of measures for pest control in the store room of the wholesale market. These caused acute toxic symptoms to the concerned patient. After the year 2008 Mrs. P. suffered from severe symptoms of chronic diseases, after the business premises had been fumigated with pyrethroids such as Cyphenothrin and Cypermethrin against mites. In August 2011 there happened an infestation of fertilizers by mites and moths in the store room, that had been fumigated by an expert enterprise again by pyrethroids. Prescribed active ingredient concentrations in the air had been exceeded several times, as later calculations had verified. Even 9 months after the performance of these measures the blood of Mrs. P. contained elevated concentrations of pyrethroids, corresponding to the investigation by the professional association. Mrs.P. was ordered to go on with her work in the salesroom short time after the measures had ended, and this without sufficient ventilation of the room.

ADDITIONAL EXPOSURE TO THE INSECTICIDE DICHLORVOS

In every room of the wholesale market regularly different insecticides had to be disseminated by fumigation according to legal requirements in order to remove moths that contaminate the fertilizers and seeds. Every 3 months insecticides of the label "Moth Guard" containing the insecticide Dichlorvos in small paperbags had been fixed under the shelves containing fertilizers and seeds. The insecticide therefore evaporates during all the time out of these bags and contaminated the indoor room air.

2. Symptoms of the disease

Several reports of findings and opinions from different medical doctors have been evaluated to get a survey of a lot of symptoms of the patient. Mrs. P. also had visited the author of this publication two times and had reported details of her disease and her restrictions in managing her every day life. She appeared to suffer from a severe fatigue and from desperation because of her ongoing complaints. The following list of symptoms was evaluated from questionnaires, written and oral reports of Mrs. P. as well as different written opinions and reports of the treating doctors, it characterizes the severe syndrome of the concerning patient.

SYMPTOMS OF THE NERVOUS SYSTEM

- Fatigue in a severe form, exhaustion, general weakness, incapability to do every day work, strongly diminished working efficiency,
- Sleep disorder in a severe form, including a period of three months without any sleeping,
- Often pronounced memory disturbance, especially from 2009 ongoing and increasing with time, especially concerning the short time memory,

- Drive malfunction, depression,
- Concentration disorder,
- Often severe headache, moving from the neck to the head,
- Often pronounced tinnitus,
- Visual impairment, especially disturbed accommodation, concerning the close and distance adjustment.
- Cardiac arrhythmias and tachycardia, sometimes and always at special situations during professional operations such as cleaning the shelves containing chemicals,
- Enhanced perspiring during the night,
- Numbness of the skin (paraesthesia) sometimes enhanced, specially at the left feet,
- Tingling at the legs often enhanced,
- Sometimes unusual clumsiness during work performance, increasing with the years.

DIGESTIVE SYSTEM

- Digestion of food mostly is incomplete. "It comes out as it has been ingested."
- Nausea, mostly in a reinforced manner,
- Food intolerance, mostly combined with spasmodic stomach ache during and after the meal, followed by flatulence and diarrhoea,
- The spasmodic stomach ache also appears independently of the meals several times per week,
- The flatulence appears often in a heavy manner.

MUSCULOSKELETAL SYSTEM

- Alternating pain at joints and bones, often appearing with elevated intensity,
- Pain, cramps and convulsions in the musculature often with elevated intensity,
- Mostly rapid exhaustion of musculature during physical activities.

SYMPTOMS OF THE IMMUNE SYSTEM, INFLAMMATION AND HYPERSENSITIVITY

- Enhanced hypersensitive reactivity to scents and gaseous extraneous chemicals manifesting since some years,
- Intolerance to medication, therefore local anaesthesia during dentist-treatment is not tolerated,
- Rashes are severe and extensive and look like erythemas.
- Enhanced bleeding tendency in mucous tissues of mouth and the respiratory system and in the skin, visible capillary bleedings.
- Severe signs of inflammation in the mucous tissues of the mouth, the nose and the bladder, frequently with associated with strong pain,
- Swelling of the sebaceous glands of the skin, that had been removed by operations.
- Swelling of lymph glands at the neck,
- Swelling of the eye lids with severe appearance, eyestrain, appearing often and strongly.
- Black discoloration of the toe nails.

3. Toxic effects and their influence to the disease of the patient

Mrs. P. had been exposed to lots of highly toxic

chemical substances during her 12 years of professional work at the wholesale market for agricultural products. The toxic effects of most of these substances are commonly well known, see table 2. Legal regulations

and limits up to now only concern effects of single substances and do not regard possible effects of combinations of different toxic substances to an organism.

Table 2: Pesticides offered at the concerned wholesale market and their known toxic effects

Pesticide	Active substance	Toxic effects known up to now (from Wikipedia, und Solecki and Pfeil, 2013) ²
Roundup	Glyphosat admixture: POE-Tallowamines	Effective as hormones (sexual hormone, Pseudoestrogens), causes fetal deformities, initiates Apoptose of cells by activating signaling pathways, toxic to waterorganisms, The admixture enhances toxic effects by opening barriers in the body.
Vorox, weed killer	Glyphosat, Glyphosat-Trimesium Diuron	Diuron: irritating to skin, neurotoxic: inhibition of brain functions at higher concentrations, causes changes to the spleen, bone marrow, blood, anemia, makes Met-Hemoglobin by the metabolite 3,4-DCA, Glyphosat: see Roundup
Calypso verminfree	Thiacloprid	The effective substance is a Neonicotinoide, these exert teratogenic effects to embryos and mutagenic effects to vertebrates including humans, especially neurotoxic effects to bees, to humans in higher concentrations.
Universal Fungicide M	Myclobutanil	Low general virulence, but as it is fat-soluble and as a organochlorous compound neurotoxic effects are probable .
Metasystox	Oxydemeton-methyl	Neurotoxic organophosphorous
		Insekticide, toxic effects see Dichlorvos as described below
Neudorf Rattengift	Brodifacoum	Highly toxic derivate of Hydroxycoumarine, inhibits enzymes of blood coagulation, damages blood vessels, causes bleedings of skin and mucous membranes also in humans (see symptoms of Mrs. P.), LD50 <0,3 mg/kg body weight
Rattengift	Coumarin	Wie Brodifacoum: Gerinnungshemmer
Rattengift Bayer (ratpoison)	Difethialon	Thiocoumarine-Derivative, inhibitor of bood coagulation, highly toxic for humans, effects see Brodifacoum.
Blattanex spezial	2% Propoxur, and Dichlorvos	Propoxur: neurotoxic also for humans, causes neurologic symptoms at high doses, enhances effects of Dichlorvos
Decis	Deltamethrin	Pyrethroid, neurotoxic effects like the other Pyrethroids (see above)

Combination effects of different chemicals may be additive, synergistic or antagonistic in an organism.³ Additive and synergistic effects cause an enhancement of the concerning single substance, and in the case of a synergistic effect the enhancement may be exponential. For the determination of legal limits this has not been taken into account.

Because most of the active substances to which Mrs. P. had been exposed have neurotoxic effects, and because these substances exert their effects at different places of action in the nervous system, one has to consider at least additive and most probably synergistic effects. So, the effective substances of phosphorous acid-esters like Dichlorvos may damage nerve fibers even stronger, if they had been pre-damaged by Pyrethroid-insecticides. The multiple disease symptoms of Mrs. P. indicate that double damage of her nerve system.

PATHOMECHANISMS OF TOXIC EFFECTS SUPPOSED FOR MRS. P.

The high exposure to the insecticide Dichlorvos is of special interest for the explanation of the disease of Mrs. P. This insecticide had been emitted intentionally as vapours in the premises of the market in order to remove the contamination of fertilizers and seeds by moths. Therefore Mrs. P. had incorporated the insecticide by the respiratory air, so that the poison had avoided the passage through the liver where it would have been decomposed by the detoxification system. The poison had been affiliated in a short way by mucous membranes of the nose and then by olfactory nerve fibers directly into the brain (bulbus olfactorius) and also from the respiration air into the lung tissues and then into brain by the blood of the pulmonary arteries. So, the poison acted toxic in the brain before a possible passage through the liver as the organ of detoxification.

The high toxicity of insecticides of the type of organic phosphoric acid-esters such as Dichlorvos concerns not only insects but also humans. It acts by the irreversible inhibition of the enzyme Acetylcholine-esterase, so that the neurotransmitter Acetylcholine accumulates in the brain.² The excessive Acetylcholine now binds to lots of muscarinic receptors in the brain and then caused enhanced nerve excitations of cholinergic neurons, that are situated in abundance in the brain and even in the peripheric nerve system. Concerned are brain areals functioning for learning and memory such as the Hippocampus.

The elevated excitation of cholinergic nerves causes enhanced secretion of glutamic acid in brain resulting in the activation of NMDA-receptors (NMDA: N-Methyl-D-Aspartate), that is responsible for disease mechanisms of chronic neurologic diseases such as Multiple Chemical Sensitivity (MCS) and CFS/ME (Chronic Fatigue Syndrome / Myalgic Encephalitis).⁴ As consequence of an extensive activation of glutamergic nerves by the NMDA-Receptor pathogenic pathways are activated that may end by triggering the apoptosis, the programmed cell death especially in the Hippocampus and other brain areas. This damaging mechanism is

known under the concept of the so called "excitotoxicity", which is triggered by binding of glutamate to the NMDA-receptor.^{5,6,7,8, 40}

The **Hippocampus** is a part of the evolutionary old human cerebral cortex and also of the **Limbic System**, which contains among other parts the Amygdala, the Gyrus cinguli and the Nucleus interpeduncularis in the midbrain. This system combines memory-contents with emotional feelings. The Limbic System and the Hypothalamus are functionally linked and therefore cause a connection between emotions and the hormone system. Thereby the Limbic System links memory contents to emotions. Excitations formed in the Limbic System cause the secretion of neurohormones in the Hypothalamus, that get into the blood after passage through the Pituitary Gland.³⁵

The Hippocampus also regulates the short-term-memory and the export of memory-contents to the long-term-memory. The Hippocampus is the most sensitive part of the brain towards environmental influences such as stress and pollutants, which is damaged first by the above described NMDA-glutamate-mechanism. By the NMDA-activation complex regulatory mechanisms and signalling pathways are initiated which may activate inflammation and cell-death (apoptosis) in the brain. This leads to a disturbance of the neuroendocrine functions of the Hypothalamus and the Pituitary Gland, followed by symptoms such as cognitive decline, drive malfunction, vigilance, chronic fatigue, depression and lack of energy, which are typical for chronic inflammation of the brain and for a Chronic Fatigue Syndrome, due to a dysfunction of the mitochondria, which had been described as "mitochondriopathy". The concerning biochemical mechanisms up to now had been largely clarified.^{4, 9,32}

EFFECTS TO THE VEGETATIVE NERVE-SYSTEM

The accumulation of the neurotransmitter acetylcholine in the brain also causes excitation of the parasympathetic nervous system, which leads to enhanced salivation, elevated mucous secretion in bronchia and to bronchial spasms, indigestions by enhanced gastric and intestinal secretion, combined with increased peristalsis, and impaired vision, blood pressure lowering, and sweat gland stimulation. The excessive acetylcholine causes muscle stiffness and twitches, tonic spasms, speech disorders, disturbances of consciousness and paraesthesia of the skin by binding to acetylcholine-receptors at sympathetic and parasympathetic ganglions of the vegetative nervous system as well as at motor end-plates in the muscle tissue.²

These symptoms are characteristic for the action of organophosphate insecticides which had been observed in and reported by Mrs. P., especially the reported enhanced secretion of sweat during the nights and the gastric indigestions. This gives a hint to the assumption, that the disease of Mrs. P. had been caused by the insecticide Dichlorvos.

THE INSECTICIDES OF PYRETHROID TYPE

Mrs. P. had been exposed to a mixture of different insecticides besides some other chemicals as described

in chapter 1. These exposures are of special importance for the syndrome of Mrs. P. that had been triggered by the combination of Pyrethroids and organophosphates such as Dichlorvos.

Pyrethroids are insecticides that have been developed from the plant based active ingredient Pyrethrum, of which later on the effectiveness and persistence had been increased by chemical modifications. Their toxicity not only concerns insects, as had been supposed in former times, but also affects humans by neurotoxic effects.

Affected people have reported that exposure to Pyrethroids causes the following symptoms: headache and throat sore, fatigue, tachycardia, nausea, skin rash, hair loss and cognitive impairment. Often a pronounced polyneuropathy has been observed.¹⁰ About 30000 veterans of the 1st Gulf War also complained general neurological symptoms. Their uniforms had been impregnated by Pyrethroids.¹¹

Pyrethroid-insecticides such as Permethrin exert a pronounced neurotoxicity in humans. They selectively bind to sodium-channels in nervous membranes which then are opened, so that an action potential is triggered. This causes a permanent opening of these potential-dependent sodium channels remain, so that sodium ions penetrate into the cell for a longer time, followed by an increased excitation of the nerve, resulting in shorter intervals of nervous impulses. The nerve cells become overexcitable, followed by spasms of muscles and tremor ("tremor-syndrome") and salivation ("TS-Syndrome").¹² The nerve cells become overexcitable, followed by spasms of muscles and tremor ("tremor-syndrome") and salivation ("TS-Syndrome").¹² In the brain an increased secretion of different neurotransmitters such as acetylcholine, noradrenalin, dopamine, and gamma-amino-butyric-acid (GABA) is triggered.¹³ By these effects attributed to pyrethroids mechanisms of the initiation of the disease "Multiple Chemical Sensitivity" (MCS) by a combination of different pesticide substances may be enhanced synergistically (see the chapter to MCS below). Pyrethroid-insecticides have a pronounced potential to contribute to chronic diseases.⁴

It is evident that the spasms of muscles at the neck and the gastrointestinal area, the head ache caused by these complaints, the tremor and the salivation reported from Mrs. P. coincide with the typical effects of Pyrethroids. In addition, the essential symptoms seen at Mrs. P. such as the chronic sleep disturbance, cardiac arrhythmias, tachycardia, the numbness of the skin (paraesthesia) sometimes enhanced, specially at the left feet, the often enhanced tingling at the legs, which she felt after she had cleaned the shelves, indicate effects of the Pyrethroids (see chapter 1).

COMBINATION EFFECTS OF PYRETHROIDS WITH NEUROLEPTIC MEDICINES

Neuroleptic medicines usually are given to patients with psychotic diseases in order to lower the symptoms without impairing consciousness and intellectual abilities.

They reduce psychomotor arousal and affective tensions.¹⁴ Mrs. P. had been treated by these medicaments because of the wrong assumption of medical doctors, that she would have a psychiatric disorder, with fatal consequences which had been seen later on.

Pronounced combination effects of Pyrethroids and neuroleptic medicines are well known. For example Haloperidol and Diazepam influence the density of receptors and their regulation at the membranes of neurons and therefore also their sensitivity concerning the excitation conduction.¹⁵

If both groups of substances, the Pyrethroids and the Neuroleptics, make impacts at the same time, fatal combination effects may take place which cause a pronounced increase of the sensitivity of the excitation of the neurons. This is of importance for the wrong conclusion of treating medical doctors, that the origin of diseases following an exposure to toxic chemicals would be psychiatric.

As described above this was the case with Mrs. P., who suffered from a collapse with uncontrolled movements and cramps after injection of Neuroleptics by a treating doctor in the year 2009. This incident is suitable to interpret, that the cause of the disease symptoms of Mrs. P. has to be attributed to the high exposition to Pyrethroids as a consequence of the fumigation of the storeroom of the wholesale market. Therefore the Pyrethroid-exposure proves to be one of the main causes of the disease of Mrs. P., because the symptomatology coincides with the effective mechanisms of Pyrethroids and the well known combination effects with neuroleptics.

Additional toxic effects had been caused by the exposure to rat poisons of Coumarin-derivates, because Mrs. P. often showed sudden bleedings of mucous membranes in the mouth, the nose and the bladder.¹⁶ Also in the year 2013 there were capillary bleedings seen at many areas of the skin of the face and the arms, which occasionally appeared and disappeared, as has been discovered by the author of this report himself during a meeting with Mrs. P.

4. Diseases of Mrs. P.

In consequence of the exposure to the chemicals described above Mrs. P. suffers even 13 years after beginning of the exposure from different chronic neurologic diseases as there are:

- A neurologic disease similar to a Toxic Encephalopathy corresponding to the German list of occupational diseases ("BK 1307"),
- Multiple Chemical Sensitivity (MCS), listed under ICD 10, T78.4 of the WHO classification of diseases,
- Chronic Fatigue Syndrome, combined with a mitochondrial dysfunction (ICD 10, G 93.3)³²

4.1. A NEUROLOGIC DISEASE SIMILAR TO A TOXIC ENCEPHALOPATHY (TE)

In an information-pamphlet concerning the occupational disease "Toxic Encephalopathy" (BK 1307) of the

German professional association for chemical industries, the symptoms of this disease are named as follows: spasmodic stomach ache, nausea, vomiting, headache, arousal, cramps, confusion, hallucinations, anxiety.¹⁷ Mrs. P. showed all the symptoms that are named in the information-pamphlets BK 1317 and BK 1307, although the information pamphlets for Toxic Encephalopathy mention only volatile organic compounds and solvents as causing agents, and not pesticides and specially insecticides, which are responsible for the disease of Mrs. P. These specially named symptoms are spasmodic stomach ache, continuing nausea, cramps of muscles, concentration- and memory-disorder, and head ache. Therefore the diagnosis of a "Toxic Encephalopathy" following the combined exposure to different neurotoxic substances is justified for the disease of Mrs. P.

Because of the list of neurologic symptoms of Mrs. P. described in chapter 2 the grade of the disease has to be classified as grade IIa with tendency to grade IIb, according according to the description of a Toxic Encephalopathy (TE) in the information pamphlet for "BK 1317" and also "BK 1307", "disease caused by organic phosphate-esters".^{17, 18}

Grade IIa means pronounced and permanent personality changes, increasing lack of memory and concentration, mood swings with depressive impact, affect lability, proven psychological performance reduction. **Grade IIb** comprises additionally to grade IIa-symptoms tremor, ataxia and other mild neurological symptoms. **Grade III** at last indicates the transition of the disease to dementia, which has to be proven by tests of intelligence and cognitive decline as well as brain atrophy by brain imaging such as MRT and CT.¹⁸

The neurologic disease of Mrs. P. complies to a Toxic Encephalopathy with symptoms described in the concerning above mentioned manual for this kind of diseases.¹⁸ This disease is the long-term consequence of effects of the active substances of the insecticides such as Pyrethroids and organic phosphoric acid esters that damage nervous cells in the brain. Both kinds of insecticide active substances cause an over-irritation of different brain areas, especially the Hippocampus, the brain center for working memory and connection to emotions. This over-irritation of nervous cells may lead to the mechanism of the so called "excitotoxicity", which is connected to the programmed cell death (apoptosis) of nervous cells in the Hippocampus and other brain areas.^{19, 6} The organic phosphoric acid esters act in a delayed neurotoxic mechanism causing an "organophosphate-induced delayed neuropathy" (OPIDN)²⁰.

The symptoms observed with Mrs. P. such as concentration- and memory-disorder as well as the altogether appearing depressive mood agree with a TE of grade IIa and correspond to a loss of function of the Hippocampus. As these mechanisms proceed slowly and irreversibly, the severe symptoms seen with Mrs. P. last at least one year after having finished her job at the wholesale market, although there are small signs of recovery.

The effects of neurotoxic substances in the Central Nervous System (CNS) depend on the dose and the duration of their influence. Neurologic symptoms caused by neurotoxic substances such as memory-decline, chronic fatigue, enhanced irritability, and mood fluctuations, are reversible during initial stage, but become irreversible, if the exposure lasts over a longer time with a higher dose.²¹ If there is a chronic exposure of low concentrations the symptoms may be unrecognized for a long time. Even after the chronic stress has ended, the mechanisms of action continue to develop in a hidden way and only some time later lead to the onset of symptoms.²² This effect is known as "desynchronization"^{22, 33, 34}. Therefore the connection between cause and effect of exposure to pollutants are not recognized at first sight. So the symptoms such as chronic fatigue, memory and cognitive decline will only gradually be obvious. Depending on the type of poison, duration and concentration of exposure damages may increase with time, but also, they may stay the same or even decrease.²²

The effects of the active substances of the pesticides in the brain are connected with inflammation processes, by which the effects of the pesticides are even further increased. These effects had been described by the concept of "Neurogenic Inflammation", by which oxygen radicals and peroxynitrite are produced by the cells of the inborn immune system in the brain, which cause damage of mitochondria membranes followed by ATP-decline and energy deficits in the brain and other harmful consequences. These mechanisms are considered as characteristic for a special kind of diseases, the so called "chronic inflammatory multisystem diseases".^{36, 4, 33}

4.2. MULTIPLE CHEMICAL SENSITIVITY (MCS)

The symptoms established with Mrs. P. indicate an unspecific hypersensitivity towards extraneous chemicals according to the typical characteristics of a Multiple Chemical Sensitivity besides the above described Toxic Encephalopathy. According to the specialist literature many statistical, epidemiological, and pathophysiological studies have confirmed that the disease called MCS is caused by environmental factors mainly by extraneous chemicals, but also other environmental factors operating at the same time such as traumatic stress-events, severe virus-infections or even high frequency electromagnetic and radar radiation. These environmental impacts only lead to the unspecific disease of a chemical hypersensitivity after a long lasting internal biochemical process, which at the end may resemble the features of a typical MCS. After the initiating event, may be an exposure to chemicals, the affected patients show reactions of hypersensitivity towards lowest concentrations of foreign and pollutant chemicals of many kinds in the air, which act in concentrations up to 1000 times lower than those concentrations that cause reactions with healthy people (literature is reviewed by Pall, 2007, and Molot et al., 2021).^{4, 23} The affected patients have acquired an unspecific hypersensitivity towards extraneous chemicals. The specification of chemicals initiating the disease of MCS is totally different from that causing the acute symptoms of hypersensitivity. This property of the

disease MCS is known under the concept of “desynchronization”, for further explanation see below.^{33, 34}

The Multiple Chemical Sensitivity (MCS) has been classified by the WHO in its international code of diseases **ICD 10, Nr. T78.4**. The case definition of *American Consensus* (MCS Consensus Conference, 1999) is used for the diagnosis of the disease MCS as described below:²⁴

DEFINITION OF MULTIPLE CHEMICAL-SENSITIVITY (MCS) – AMERICAN CONSENSUS

1. The symptoms are reproducible (after repeated exposure).
2. The condition is chronic.
3. Minimal exposures (even lower as formerly or generally tolerated) result in manifestation of the symptoms.
4. The symptoms improve or disappear when the trigger is removed.
5. Reactions are caused by multiple chemical substances.
6. The symptoms affect several organ systems.

According to Pall⁴ a cognitive decline is also characteristic for the disease MCS. Asthma, allergies, migraine, chronic fatigue syndrome, and fibromyalgia so not mean an exclusion diagnosis for MCS, they are often concomitant syndromes.

PATHOMECHANISM OF MCS: DESYNCHRONISATION

As explained in detail in chapter 3 the active substances of Organophosphate- and Pyrethroid-insecticides may trigger a complex damage mechanism in brain, which also are made responsible for the initiation of the disease MCS. This mechanism comprises the NMDA- and Muscarinic receptors in brain, which are activated either directly by special extraneous substances or indirectly by chronic inflammation processes. As explained in chapter 3 an excess of the neurotransmitter glutamate is secreted by neurons in the brain, which then activates the NMDA-receptor, followed by the mechanism of “excitotoxicity”, which causes complex self-reinforcing damage processes in the cells of the brain (nerve- and glia-cells). By these self-reinforcing damage processes nitrogen monoxide and peroxynitrite are produced, which act as signals for further damaging mechanisms such as activation of genes of the inflammation reaction by the induction factor NF- κ B (NF-kappaB). These mechanisms have been described or explained by Pall (2007)⁴, Mattson (2003)²⁵, Mattson and Liu (2002)²⁶, Acarin et al. (2002)²⁷. These are positive feedback mechanisms, which cause a lowering of the sensitivity threshold for chemicals, which is typical for the disease MCS.

During this mechanism a process of **desynchronization** takes place, which means, that the triggering chemicals such as the mentioned pesticides cause the complex mechanism of action during a longer period of time, during which the physiological supersystems are decoupled, so that the chronic symptoms of inflammatory diseases such as MCS, Chronic Fatigue

Syndrome or a Toxic Encephalopathy appear at a later time after the triggering of the disease.^{33,34}

Concerning the disease MCS it is striking, that the specificity of chemicals that initiate the disease of MCS is completely different from that of the chemicals triggering the acute hypersensitivity symptoms. So, for example it is common for MCS-patients, that gaseous chemicals such as scents, exhaust fumes from cars or fumes of solvents trigger the acute symptoms of hypersensitivity, after the disease of these patients had been initiated by the exposure to neurotoxic acting substances of pesticides such as Pyrethroids, Organophosphate compounds, exposure to heavy metals as mercury or to high concentrations of fine dust.

In conclusion the above mentioned criteria of the case definition for MCS have to be applied for the symptomatology and the clinical picture of Mrs. P. without any restriction. Especially it is conspicuous that some of the symptoms of Mrs. P. had decreased during a longer stay at a clinic, while symptoms of a toxic encephalopathy such as memory decline, chronic fatigue, and muscle cramps are continuing up to now.

PRECEDENT CASE: MCS AFTER EXPOSURE TO INSECTICIDES

The case of Mrs. P. is not exclusive. Only one of some more cases will be mentioned here: In the year 2000 there was reported a case of a saleswoman who had worked in a shop, which had been sprayed between the years 1997 – 1999 every 2-3 months with a mixture of insecticides containing Chlorpyrifos.²⁸ This insecticide is related to dichlorophos and has similar toxic properties. Ongoing from 1998 the woman showed increasing health problems such as enhanced sensitivity of the skin to light, skin redness, cough, irritation of eyes, seizure-like breathing difficulties and choking attacks, especially in the evening, and also dizziness, paralysis of legs and arms, rheumatic pain in the musculature, inhibited growth of finger- and toenails, tremor, numbness in the legs, feelings of fear.

Some time after this intoxication there appeared a hypersensitivity to other chemicals such as disinfectants, perfumes, nail polish and solvents. According to reports of the BGVV (the German Federal Institute for consumer protection and veterinary medicine) there are about 75 reports of accidents caused by Chlorpyrifos, including a fumigation of an open-plan-office, by which 42 persons had been damaged.²⁹

This precedent case shows striking features to the disease of Mrs. P., namely the features of MCS, concerning the initiating chemicals such as the insecticide dichlorophos as well as the acute symptoms of the disease caused by volatile substances. Here the employer’s liability insurance association had acknowledged a course of disease caused by an exposure to insecticides similar to that of Mrs. P. In the case of Mrs. P. there were different neurotoxic insecticides as active substances, which had caused a similar disease, but her insurance association did not accept the disease as consequence of an exposure to

neurotoxic substances such as insecticides. In contrast it is officially acknowledged that the disease MCS can be initiated by exposure to insecticides. Therefore, it is officially acknowledged that the disease MCS can be initiated by exposure to insecticides.

4.3. CHRONIC FATIGUE SYNDROME (CFS/ME), MITOCHONDRIAL DYSFUNCTION (“MITOCHONDRIOPATHIA”)

The symptoms reported from Mrs. P., which are characterized by a severe general exhaustion and physical weakness, correspond to another clinical picture, namely a Chronic Fatigue Syndrome and Myalgic Encephalopathy (CFS/ME).³² CFS/ME has been listed since many years under the code ICD10, G. 93.3.³⁰ This means that CFS/ME is not a syndrome of psychogenic origin, but it is based on well known biochemical mechanisms of a chronic inflammatory multisystemic disease, by which chemicals or other environmental factors such as viruses like corona or herpes like human cytomegalovirus (HCMV), or retroviruses initiate complex mechanisms of inflammation. Once activated the cells of the inborn immune system secrete cytokines as messengers of inflammation in the brain, and as a result, they cause the symptoms of the general exhaustion. These mechanisms of inflammation may also be triggered by the metabolism of foreign substances. They are connected to the production of oxygen- and nitrogen-radicals, which inhibit the oxidative respiratory chain in the mitochondria.^{4, 25}

This mechanism leads to an energy deficiency syndrome, which is based on a deficiency of the mitochondria to produce Adenosine-triphosphate (ATP), the energy exchanger substance of the cell metabolism. Because of the lack of ATP in the whole body the action of muscles and the brain functions are diminished. So energy deficiency syndromes like that had been named as “Mitochondriopathy”.³¹

The syndrome of CFS/ME is characterized by a list of symptoms as it has been published by Carruthers et al. (2003).³² These symptoms mainly concern the physical and mental state of exhaustion, which lead to a fundamental decrease of the general life activity of the concerning persons. The physical and mental load capacity is unusually diminished, cognitive decline is often observed. Pain of muscles, joints, head, and the nervous system are frequently seen, also sleep disorder, deficits of concentration and memory, confusion, disorientation, problems of information processing, a difficulty of finding words, sensory perception disorders, hypersensitivity towards light and noise. The functions of the autonomic nervous system such as control of blood pressure, heart-rhythm, the intestine functions, the kidney and its urine production are disturbed or diminished.

As the inflammation mechanisms occur primarily in the brain, they resemble those that are above mentioned as “Neurogenic Inflammation”, which is also characteristic for diseases like toxic encephalopathy. Therefore, the addition “ME” to the designation of the disease “CFS/ME” means “Myalgic Encephalomyelitis” and

concerns mechanisms that occur also during diseases like “Toxic Encephalopathy”.

According to the guidelines of the disease its symptoms should persist for at least six months and has to start at a defined time. Most of the symptoms mentioned by Carruthers et al. (2011)³² and the other guidelines were seen with Mrs. P. and persist for at least 13 years unabated up to now.

CONFIRMATION BY LABORATORY RESULTS

In the case of Mrs. P. an elevated level of lactate has been detected by laboratory testings. This is due to the lack of ATP following inflammation mechanisms which are characteristic for CFS/ME, and which is caused by a change of the oxidative metabolism to a kind of anaerobic lactic acid fermentation. The laboratory values of Mrs. P. showed decreased concentrations of pyruvate and an increased lactate-pyruvate-ratio. This finding may be explained by an increased activity of the enzyme Pyruvate-Kinase. Because the activity of the respiratory chain in the mitochondria is inhibited due to a accumulation of oxygen radicals, the energy-metabolism is regulated into the direction of an anaerobic lactic acid fermentation. Therefore, pyruvate is no longer metabolized, instead it is reduced to lactic acid by NADH (reduced hydrogen bound to Nicotinamide-Adenin-Dinucleotide, NAD). Therefore, the concentration of lactic acid rises and causes an acidification of the blood, which then triggers further pathologic effects in the brain.

Also Increased values for LDH-4 and -5, increased citrullin, lowered 5-Hydroxy-Vitamin-D, increased 1,25-Dihydroxy-Vitamin D, significantly increased Superoxide-Dismutase (SOD) in blood confirm the diagnosis of a multisystem inflammatory disease. Therefore, an essential pathomechanism of CFS/ME has been proved by laboratory methods in the case of Mrs. P., so that CFS/ME has to be accepted as a disease besides the other diseases MCS and another neurological disease like Toxic Encephalopathy.

THE PATHOMECHANISMS SHOW REFERENCES TO NEURODEGENERATIVE DISEASES

In recent times there are increasing hints in medical sciences for connections between mechanisms of neurodegenerative diseases such as Alzheimer’s and Parkinson’s disease and the Multiple Chemical Sensitivity (MCS). These neurodegenerative diseases had been proved to be initiated by environmental pollutants such as fine dust, micro-plastics, pesticides, volatile organic carbon-compounds (VOCs), that interact with TRP- and NMDA-receptors in the brain.^{23, 1, 40.} The disease MCS has been characterized as one of the chronic inflammatory multisystem diseases, by which the activation of the NMDA-receptor at nervous and glia cells in the brain plays a central role in the pathophysiologic process.^{4, 1, 23} Accordingly the activation of NMDA- and TRP-receptors causes a chronic inflammation-mechanism in the brain,²³ which initiates the induction of the synthesis of the induction-factor NF- κ B followed by the activation of the synthesis and secretion of cytokines of the inflammatory reaction. The

activated factor NF- κ B plays a central role for MCS and also for other chronic inflammatory multisystem diseases such as CFS/ME (Chronic Fatigue Syndrome), Toxic Polyneuropathy and Encephalopathy and Fibromyalgia.⁴ It causes a positive feedback cycle that is connected to a self-enhancing effect, which finally leads to the production of oxygen-radicals, hydrogen-peroxide (H₂O₂), nitrogen-monoxide (NO), and peroxynitrite (ONOO), which are known as components of the so called NO/ONOO-cycle as defined by Pall (2007).⁴ This mechanism is also a significant part of neurodegenerative processes of Alzheimer's and Parkinson's Disease.^{38, 39}

The case of Mrs. P. is characterized by a multiple exposure to highly neurotoxic substances during her 12 years of professional activity, which caused a complex clinical picture of chronic diseases such as MCS, a neurological disease corresponding to a Toxic Encephalopathy, and CFS/ME. As a result of the combined action of different neurotoxic substances pathomechanisms are initiated that are also known from research to Alzheimer's and Parkinson's Disease.^{1, 23} It should be emphasised that the disease of Mrs. P. is not clearly proven as neurodegenerative. But this case stands for an example for many other cases of diseases, which had been treated with unsuitable methods of diagnostics and therapy by doctors and medical institutions, either out of ignorance or of economic interests.

5. Conclusion

The aim of this publication was to show that an exposure of a combination of highly toxic chemicals such as pesticides and biocides may result in getting a complex and severe clinical picture, that strongly affects the quality of life of the affected patients. In our practice as experts for environmental diseases we made the experience with some hundreds of affected patients, who suffered from exposure to pesticides used in agriculture or wood preservatives such as pentachlorophenol, aldrin, polychlorinated biphenyls and others, that they showed similar clinical pictures of diseases.

The consequences of such kind of exposures resulting in complex environmental diseases are mostly not recognized by the institutions of the health care system as of environmental origin, but instead as diseases that have to be regarded as psychiatric because of symptoms that seem to indicate a mental defect of the affected patients. Therefore the patient seems to be responsible for origin of the disease by him- or herself, that means by his/her individual mental defect.

As an example, the severe clinical picture of the disease of Mrs. P. has not been recognized by the responsible institutions in Germany, such as the pension fund and the professional association, as a disease caused by chemicals. The application for a reduced earning capacity pension had been refused, and its justification should be rejected for technical reasons. The reply letter of the German pension insurance (DRV, Deutsche Rentenversicherung) to the application points out, that

the results of its medical investigations give only references to "mild bronchitis" and "temporarily elevated blood pressure". This interpretation was based on several reports of findings from attending physicians, which in their tendency are concentrated on the psychiatric symptoms of Mrs. P. Most of the opinions of the physicians who were involved in the case did not consider the severe symptoms of Mrs. P., as well as the exposure to toxic acting substances or the complex symptomatology and mechanisms of the disease, or the kind of diseases, which are results of toxic effects. The attending physicians made only a limited number of examinations with negative findings, and interpreted them by the argument, that environmental factors for the disease such as chemicals were not detected, and that therefore an environmental based disease could not be diagnosed. Instead, the institutions of the health care system classified the patient's illness as psychiatric.

This gives rise to the suspicion that the opinions of the attending physicians have been formulated in the economic interests of the insurance companies involved in order to distract from the obvious disease factors at the work place of the wholesale market. Therefore, the reply letter of the pension insurance and the refusal of the reduced earning capacity pension should be rejected as factually unfounded.

Also the psychiatric diagnosis for Mrs. P. and the resulting therapy with neuroleptics should be regarded as factually unfounded. In consequence Mrs. P. was ordered to start an inpatient treatment in a psychiatric clinic, where the anamnesis refused to consider the exposure to chemicals at her workplace. The injection of neuroleptics was done in consequence of the bias, which was justified by the wrong assumption of a psychiatric disorder. The interaction of neuroleptics with Pyrethroid-insecticides are well known since many years, which caused the convulsive collapse of Mrs. P. This event was clearly due to a medical malpractice. At the same time, it proves that neuroleptics were ineffective for the treatment of her disease, and that therefore the disease of Mrs. P. could not be diagnosed as of psychiatric origin. In addition, this incident proves that Mrs. P. had been exposed to Pyrethroids, because these insecticides are known to interact with neuroleptics to cause convulsive collapses.

This incidence has to be considered as a violence of paragraph 2.2 of the basic law of the Federal Republic of Germany, which concerns the fundamental right of physical integrity. In addition, the labour laws were violated, which concern the duty of the employer, in this case the owner of the wholesale market for agronomic products, to a health-care for his/her employees by avoiding any exposure to toxic substances at the workplace.

6. Summary

This publication gives an overview of the status of exposure, disease and disease-causes of the case Mrs. P. She had been exposed to different highly toxic biocide substances as components of insecticides and other pesticides, which were sold by the concerning

wholesale market, such as the neurotoxic active substances of organophosphate derivatives and Pyrethroids. Their properties are characterized as acute as well as chronic toxicity and may cause long time damages in the central and peripheral nervous system. In addition, the affected patient had contacts to rat poisons containing coumarin derivatives, which caused frequent and seizure-like bleedings of mucous tissues in mouth, nose and bladder and the visible capillary bleedings in the skin (see list of symptoms in chapter 2). These coumarin-derivatives are considered as highly toxic especially for humans, they cause long-lasting bleeding disorders already in trace amounts.

There is a striking correspondence of the identified disease symptoms with the specific spectra of action of the toxic acting substances, which had harmed the affected lady. These symptoms concern the severe muscle spasms associated with the exposure to Pyrethroids, the systemic neurological symptoms followed by the exposure to organophosphate insecticides, and an increased bleeding tendency of mucous tissues caused by the exposure to Coumarin-derivatives. The intensification of muscle spasms after injection of neuroleptics in June 2009, which was based on a synergistic action of Pyrethroids and neuroleptics¹⁵, should be interpreted as an additional indication of chronic poisoning of Mrs. P. by Pyrethroids (see Chapter 3).

The severe symptoms of food intolerance in Mrs. P., which caused her severe weight loss, have to be interpreted in connection to the exposure to organophosphate insecticides such as Dichlorphos. This kind of insecticides causes an accumulation of the neurotransmitter acetylcholine also in the vegetative nervous system, which leads to a dysregulation of the digestion by enzymes from the pancreas and the intestine.

As explained in detail in chapters 3 and 4 the toxic active substances cause complex pathophysiologic action mechanisms in the peripheral and central nervous system, which not only lead to acute symptoms, but also cause a chronic course of disease of the type of a Toxic Encephalopathy of the grade IIa with tendency to grade IIb. Because the disease of Mrs. P. had been triggered by the organophosphate insecticide

Dichlorphos, this disease in Germany commonly is listed under the designation of an occupational disease as “BK 1307”, “diseases caused by organic phosphorous compounds”.³⁷ The organic esters of phosphoric acid act in a delayed neurotoxic mechanism and cause an “**Organophosphate-Induced Delayed Neuropathy**” (OPIDN)⁹, which often appears with a time delay after exposure. This corresponds to the concept of a desynchronization of the effects of neurotoxic active substances as explained in chapter 4.2.

In addition Mrs. P. suffers from a **Multiple Chemical Sensitivity** (MCS) and at the same time a **Chronic Fatigue Syndrome** (CFS/ME). Both diseases have been listed according to the international WHO-classification-code **ICD10, T78.4 and G93.3** respectively. These diseases are present at Mrs. P.

The precedent case cited above in chapter 4.2. concerning another woman with MCS exposed to pesticides shows striking features correspondingly to the pollutant load and the clinical picture of Mrs. P. This case had been acknowledged by the German “Federal Institute of Consumer Protection and Veterinary Medicine” as a chronic hypersensitivity-syndrome of the type MCS caused by the organophosphate insecticide Chlorpyrifos. But this institution up to now did not acknowledge the disease of Mrs. P. as caused by environmental or chemical factors. In conclusion all three diseases of Mrs. P. appeared as a result of additive and synergistic combination effects of a variety of neurotoxic compounds,⁴¹ of which she had been exposed during the 12 years of her professional activity (see tab. 1). Also the laboratory values collected by several doctors confirm the diagnosis of a chronic inflammatory multisystem disease.

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.

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