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Multiple chemical sensitivity: an alarm bell for chemical pollution?

S. Rossi

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ISTITUTO SUPERIORE DI SANITÀ

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Dipartimento Ambiente e Salute

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Rapporti ISTISAN 22/11

Istituto Superiore di Sanità
Multiple chemical sensitivity: an alarm bell for chemical pollution?
Sabrina Rossi
2022, 46 p. Rapporti ISTISAN 22/11

Multiple Chemical Sensitivity (MCS) is a multisystem syndrome whose implications are still poorly defined. Given the hypothesized correlation with multiple exposures to low doses (below legal limits) or a single exposure to high doses (above the Threshold Limit Value) of hazardous chemicals or mixtures, this syndrome could in the future rise to a leading role in the identification of genetically and/or epigenetically vulnerable subjects, and in the identification of classes of substances and/or mixtures that are particularly dangerous and require a more thorough evaluation in the regulatory field of primary prevention. The Istituto Superiore di Sanità (ISS, the National Institute of Health in Italy) has had in the last 20 years a partial role in the analysis of the problem. It is considered appropriate instead a timely and multidisciplinary assessment of individual suspected cases currently existing, a greater clarity in the determination and collection of epidemiological case histories with related multidisciplinary research of possible markers of exposure, early biological effect and disease. To this end, in order to model analysis a precise description has been submitted as a follow-up (updated to 31 January 2022) of a suspect possible MCS case, discussing some of the critical points found.
Key words: Multiple chemical sensitivity; Chemical intolerance; Occupational health and safety; Environmental and health

Istituto Superiore di Sanità
Sensibilità chimica multipla: un campanello di allarme da inquinamento chimico?
Sabrina Rossi
2022, 46 p. Rapporti ISTISAN 22/11 (in inglese)

La sensibilità chimica multipla è una sindrome multisistemica dai risvolti ancora poco definiti. Data la correlazione ipotizzata con l'esposizione a basse dosi (sotto i limiti di legge) o a singola dose elevata sopra il limite a sostanze chimiche pericolose e/o a miscele delle stesse, questa sindrome potrebbe in futuro assurgere a ruolo guida sia nell'identificazione di soggetti geneticamente e/o epigeneticamente vulnerabili, sia nell'identificazione di classi di sostanze e miscele particolarmente pericolose e che richiedono una valutazione più approfondita in ambito regolatorio di prevenzione primaria. L'Istituto Superiore di Sanità (ISS) ha avuto negli ultimi 20 anni un ruolo parziale nell'analisi della problematica. Si ritiene invece opportuna una valutazione puntuale e multidisciplinare dei singoli casi sospetti attualmente esistenti, una maggiore chiarezza nella determinazione e raccolta della casistica epidemiologica con relativa ricerca multidisciplinare dei possibili marcatori di esposizione, effetto biologico precoce e di malattia. A tal fine si sottopone a modello di analisi una descrizione puntuale in follow-up (aggiornato al 31 gennaio 2022) di un possibile caso, discutendo alcuni i punti critici rilevati.
Parole chiave: Sensibilità chimica multipla; Intolleranza chimica; Salute e sicurezza sul lavoro; Ambiente e salute

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INTRODUCTION

The twentieth century has brought great transformations in all spheres of human existence, as the technical/scientific progress that has characterized the industrialized countries has been the engine that has allowed the net improvement of general living conditions, both in terms of quantitative life expectancy, and in terms of quality.

The industrial revolution has on the one hand allowed large-scale access to resources and products essential to life, but on the other hand has led to both a high exploitation of environmental resources and the production, consumption and disposal of synthetic substances.

We have gradually moved from an economy of essential goods to an economy in which the superfluous has become indispensable and waste its faithful companion, what in one term is called "consumerism".

Ignorance of the environment and health risks associated with this type of production, and in general with development models rarely committed to sustainability, have sometimes directed our actions and several disasters, both human and environmental, can be counted within this evolutionary path.

The multiple sources of pollution (chemical, electromagnetic, acoustic, etc.) are undermining the well-being achieved so far, contributing to an increased risk from diseases that recognize an environmental aetiology such as cardiovascular diseases, cancers, respiratory diseases, allergies and the onset of other less known health disorders that for this reason are called with the acronym MUPS (Medically Unexplained Physical Symptoms) (1).

Among these syndromes whose aetiology is still the subject of scientific debate, there is the Multiple Chemical Sensitivity (MCS) also known by several other terms (e.g., chemical sensitivity, chemical intolerance, idiopathic environmental intolerance, etc.) that is the subject of this report, as it could be an alarm bell for the detection of environmental pollution and a possible initial indicator of exposure/risk for single substances and/or mixtures that potentially escaped the appropriate regulation (2).

One of the main objectives of this century is to re-channel socio-economic development into a virtuous path, capable of protecting Health and the Environment as the essential binomial of Progress.

The latest UN report on sustainable development states in point 3.9: "By 2030, substantially reduce the number of deaths and illnesses from hazardous chemicals and from contamination and pollution of air, water and soil" (3).

The Istituto Superiore di Sanità (ISS, the National Institute of Health in Italy), as the technical and scientific body of the Italian Ministry of Health, collaborates with other national and international Institutions in the analysis and assessment of all the determinants of human and environmental health.

The main objectives of the ISS Department of Environment and Health are to:

1) identify, characterise and assess the risk factors related to chemical environmental pollution into air, water, soil and the trophic chain;
2) identify whether and through which mechanisms, the exposure to these pollutants may lead to the onset of morbid and pathological states in the human population;
3) provide decision-makers with adequate scientific evidence to define a correct control and prevention policy.

The assessment process is rather complex because people are constantly exposed to various chemical substances, even in the form of mixtures, for which they often have inadequate

information about the dangers. On the other hand, everyone is unique in terms of genetics, physiology, age, gender, pathology, lifestyle and habits, etc. The combination of these factors, therefore, contributes to a certain variability in response at both individual level and within the population living in a given, variously polluted, area.

As the scientific research succeeds in characterising both the individual and his/her environment, the weight of individual factors in determining the onset of a health problem must be studied and understood.

For a better definition of the MCS syndrome in the Italian context, the ISS believes it would be useful to set up and coordinate a multidisciplinary working group with the participation of public and private structures, all involved in the detection and assessment of possible patients, in order to:

1. establish a web-based platform for experts to share medical records of confirmed or suspected MCS cases, in order to outline their health status and agree on case definition;
2. set up health surveillance follow-up and, possibly, establish a national register of confirmed cases;
3. implement scientific researches, directed for example at:
    a) carrying out epidemiological studies (e.g., both on cohorts of workers exposed to chemical risk and on populations exposed as living in polluted sites),
    b) assessing the systemic (symptomatic and physiological) response to exposure to defined chemicals, following a defined testing protocol,
    c) evaluating various risk factors (polymorphisms, hormonal problems, early effect markers, and so on);
4. set up MCS training courses for health workers, within the framework of the Italian Network on Environment and Health (RIAS).

The body of multidisciplinary knowledge acquired in such an organic and coordinated strategy, should gradually lead us to an increasingly adequate activity of control and primary prevention, as well as a greater diagnostic certainty and precision for all morbid processes (for which an environmental aetiology is hypothesised) and, at last, a therapy that is as personalised as possible, limiting undesirable effects.

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WHAT IS MULTIPLE CHEMICAL SENSITIVITY?

Description of the syndrome

MSC is defined by clinical ecologists as a multi-system syndrome that in some individuals, probably more vulnerable due to genetic predisposition, innate or acquired, manifests itself with a multifaceted symptomatology following exposure to low doses, sometimes several orders of magnitude lower than the existing legal limits, to various environmental pollutants (Volatile Organic Compounds-VOCs, pesticides, metals) normally present in detergents, cleaners, drugs, cigarette smoke, etc., as well as in different environmental compartments including the food chain (1).

In some cases, people affected by MCS have intolerance to electromagnetic fields and this feature further complicates the evaluation framework related to exposure to chemical agents. Limiting the discussion to chemical intolerance, according to the etiological theory of toxicological type, also known with acronym TILT (Toxicant Induced Lost of Tolerance), following chronic chemical exposure to low doses or following even a single event at doses above the TLV (Threshold limit value), the individual would lose the ability to tolerate various chemicals even structurally different from each other (1, 2).

The symptomatology would concern the central nervous system, which represents in several pollution-related diseases one of the initial targets, with involvement of the olfactory apparatus and the limbic centre, and at least one other organ, apparatus, system (cardiovascular, dermal, gastroenteric, etc.) (3). Several mechanisms have been hypothesized (4) and according to the toxicological theory MCS would develop temporally according to an ingravescent stage path from stage 0 of psychophysical well-being to the final stage of disease.

The principal etiological hypotheses and malaise on MCS are:

- *Toxicological excursus,* with the following stages
  - 0-tollerance: individual is suitable for the environment
  - 1-sensitization: ocular, dermal and respiratory irritation, irritability, concentration and memory problems, tachycardia, dizziness, immunological disorders etc.
  - 2-inflammation: dermatitis, vasculitis, metabolic endocrine, immune diseases allergies etc.
  - 3-deterioration: autoimmunity, heart attack, cancer, haemorrhage, neurological and psychiatric syndromes;
- *Psychiatric/psychosomatic*: endogenous psychic origin not due to exposure-chemophobia;
- *Viral origins.*

The feature that makes this syndrome difficult to diagnose, at least in its early stages, is the difficulty in finding specific markers to perform an adequate differential diagnosis with respect to other diseases presenting similar symptoms (5).

Since the Central Nervous System is one of the first targets, the detectable symptoms (irritability, agitation, difficulty in concentrating and memorizing, tachycardia, difficulty in breathing) are substantially similar to those of an attack of anxiety, panic and other psychiatric syndromes. In addition, some patients in order to avoid contact with chemicals end up drastically altering their lifestyle (work, leisure, diet, place and house of residence) sometimes to the point of isolation, with serious socio-economic and ethical significance (6).

For these reasons among the various etiological hypotheses has emerged the psychiatric-psychosomatic theory that has led, sometimes, to rename the syndrome as "chemophobia", thus assuming the autogenous origin of the problem. For a long time, the psychiatric-psychosomatic hypothesis was highly regarded, openly opposing the toxicological hypothesis. Currently, the scientific attitude is cautious, also in view of the difficulty in assessing with certainty the aetiology of psychiatric diseases combined, conversely, to the certainty that some chemicals are neuro- and cardiotoxic (e.g., psycho syndromes and solvent encephalopathies), while several substances and mixtures have not yet known toxic potential. There are also hints to other etiological hypotheses, including a possible viral origin for the presence of flu-like symptoms.

MCS has not yet been identified with a specific code according to the International statistical classification of diseases and related health problems manual, but some nonspecific codes have been proposed in some States (Japan, Germany, Austria, Finland, etc.) for example:

– J68.9
  unspecified respiratory conditions due to inhalation of chemical fumes, gases, and vapours;
– T78.4
  unspecified allergies (allergic reactions Nitric oxide cycle (NOS)-hypersensitivity NOS-hydiosyncrasy NOS).

The numerous descriptive and analytical epidemiological studies conducted internationally have shown a variable prevalence of the syndrome (≤1- 15% and more) in the population samples analysed. The main source of bias is the more or less stringent criteria used to delineate the inclusion or exclusion of the subject in the case series (3, 7).

In general, however, it has been found that the female gender is more affected with a prevalence about twice that of the male gender. It is believed that women are in fact probably more vulnerable due to their physical constitution: height, different proportion between lean and fat mass with greater possibility of bioaccumulating hazardous agents and/or their metabolites following exposure to chemicals, hormonal and metabolic changes especially in the fertile period, and, according to some lines of thought, for sociocultural reasons that lead them to have less hesitation in revealing their health problems. Additional predisposing factors are socioeconomic level and high average education.

The first reports of this syndrome date back to the early 1950s and the first case histories included mainly workers exposed to chemicals (8, 9).

The categories considered most at risk are: workers exposed to chemicals, people living in polluted areas, but also those who live in "sick buildings", thus considering indoor pollution as a further potential risk factor (10).

Italian research and Associations of patients on MCS

In Italy, as well as worldwide, scientific research on the MCS subject is making progress with some difficulties, to find reproducible evidence that will allow the syndrome to be nosologically recognized as a specific pathology, with a defined ICD-10 (International Classification of Diseases, 10th revision) code and, if appropriate, with different degrees of disability.

Various strands of analysis have been activated in the epidemiological, physio pathological-cellular-molecular field. Some Italian researchers are working at various levels to detect any genetic, epigenetic and metabolic differences in the mechanisms involved both in the detoxification of xenobiotics and in inflammatory processes, as well as neuroimaging analysis to assess the different involvement of various brain structures before and after exposure and their

relationship with the olfactory system (11-15). At the same time, both evaluations of individual case reports (16), and epidemiological research aimed at characterizing the main symptoms of the cases detected and the correlation between symptoms of anxiety and depression with the presence in cases of MCS of some polymorphisms, such as, for example, paroxonase-1 (PON1), that it is involved in the processes of lipid peroxidation and in metabolism of organophosphates are proceeding (17, 18).

At the Centre of Personalized Medicine at "Sant'Andrea" University Hospital, Rome, a descriptive epidemiological study was conducted on 129 patients diagnosed with MCS. Inclusion criteria followed the indications of Cullen and Lacour, while subjects with serious diseases and pregnant patients were excluded. The suggestive hypothesis emerging from this double-published study (17, 18) is that among the symptoms and comorbidities detected in the analysed subjects, the presence of psychiatric symptoms could be related to an alteration of detoxification mechanisms that would determine oxidative stress and brain neuroinflammation. As reported by the authors, this study, although the results are supported by different literature, has some important limitations (small sample, absence of a control population, lack of a quantitative analysis of the level of anxiety and depression, etc.). Analysis of breath composition in terms of VOCs profile is also considered a potential gold standard for highlighting cases of hypoxia related to MCS (19).

It should be borne in mind that it is therefore necessary to address the problem at a multidisciplinary level (20-22) by analysing both any individual biophysiological differences and the correlations between them and the symptoms detectable as a result of exposure to single substances or, more often, mixtures, of which there is often inadequate information about potential synergistic effects, cumulative, etc. The different chemicals represent a varied class of hazards (irritants, toxic, harmful, carcinogenic) and are able to act simultaneously on different target systems (respiratory, cardiovascular, nervous, endocrine, immunological, etc.) unbalancing the delicate mechanisms of internal regulation essential for survival.

Personalized medicine, gender medicine and psychoneuroimmunology (PNEI) integrating an increasingly precise analysis of the genetic and metabolic makeup, to the holistic vision, are gradually establishing themselves in the international scientific landscape thanks to the information coming from genomics, metabolomics and transcriptomics (23, 24).

In this context, toxicology represents a crucial node for a better definition of the problem, through the increasingly accurate analysis of the risk arising from various sources and types of exposure and on the other hand through the establishment of appropriate primary prevention measures. It should be emphasized that some of the Italian specialists who have dealt with the problem in various capacities have found a point of agreement by drawing up the consensus document entirely available on PubMed (21).

On the other hand, however, it must be highlighted that other Italian experts did not subscribe to the same consensus and that some points of debate emerged that should be more analysed in order to move forward on a common agreement at the national level.

It is therefore necessary to set up a common protocol and adequate clinical trials to verify the efficacy of specific therapies, some of which are innovative (24), in order to protect the individual from inadequate treatments in favour of the most effective ones, in the perspective of evidence-based personalized medicine.

In this overview it is important to highlight the role played by various Associations and Committees such as AMICA (*Associazione Malattie da Intossicazione Cronica e Ambientale* – Association of Chronic and Environmental Intoxication Diseases, https:/www.infoamica.it) MARA (*Malattie Mentali Reciproco Aiuto* – Mental Illness Mutual Help, https://associazionemara.org), OltreLaMcs (https://www.oltrelamcs.org) that on the one hand provide a cognitive and moral support to patients and, on the other, act as a driving force for

research representing a contact point between researchers, patients and the political world. The politics in a transversal way with respect to the different ideologies, has dealt with the issue by presenting various bills (25, 26).

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WHAT ABOUT ITALIAN INSTITUTIONS AND MCS?

Role of the INAIL, the national institute for insurance against accidents at works in Italy

For the important relationship and repercussions that MCS can have in the working environment, it has been a subject of interest by the INAIL (*Istituto Nazionale per l'Assicurazione contro gli Infortuni sul Lavoro*, the National for Insurance against Accidents at Works in Italy) in its role of research and prevention of accidents and occupational diseases.

INAIL researchers in a review published in 2013 (1) on the needs for an occupational health surveillance protocol for MCS at the workplace highlight that in chemical risk both the dose, duration and chemical characterization of exposure, and the individual susceptibility, genetic or acquired, of the exposed individual are important. The concept of potential gradual loss of tolerance following prolonged exposures is emphasized by introducing the concept of a harmful effect in the absence of a directly dose-dependent relationship. In addition, the authors reported that the higher percentage of women who are affected by MCS compared to men could be due to physical structural and hormonal differences that make women more susceptible to bioaccumulation phenomena due to the higher percentage of fat mass compared to men, and due to hormonal changes related to the fertile period when they could be more sensitive to the action of endocrine disruptors.

Moreover, it was reported that the task of the competent doctor is also to detect in the worker particular psycho-physical conditions that make him more vulnerable to exposure, and therefore require more specific precautionary measures. In the event that the prodromes of the syndrome are hypothesized, the worker should be temporarily excluded from exposure but, if the physical condition improves, it would be appropriate to try a reintegration in the same task.

A proposal of guidelines for diagnosis and treatment of MCS mentions a possible protocol of analysis at different levels of investigation (2): first level of screening the questionnaire QEESI (Quick Environment Exposure Sensitivity Inventory questionnaire), EESI, etc. (3, 4), and then laboratory tests for liver function, kidney, haematocrit, dosage of thyroid hormones, psychological and neurological tests up to the analysis of genetic polymorphisms (PON1-Cyp 2D6-NAT2-GSTM1-CAT, etc.), profile of inflammatory cytokines, environmental and human monitoring.

Although the syndrome is not yet identified by a specific code, and therefore is not listed among the diseases of occupational origin, INAIL is continuing to follow the excursus through its magazine *SuperAbile*, freely downloadable from the website (www.inail.it).

INAIL could help in detecting also suspected possible cases of MCS both through a more specific analysis of incidents attributable to exposure to chemicals that are the subject of complaints, and in collaboration with other research institutions, through epidemiological studies of cohorts of exposed workers for whom occupational health surveillance is provided. This would mean setting up a network with a registry of all abnormal situations that occur and result in, for example, job changes and chemical hazard suitability cases whose reasons have not been adequately investigated (5).

Role of the ISS in the Italian context

The National Centre for Rare Diseases of the ISS has been interested in this topic since 2004, so much so that in the Institute's newsletter (*Notiziario dell'Istiuto Superiore di Sanità*) (6) there are two interviews with Domenica Taruscio, head of the Centre, in which she emphasizes the need to set up a task force at national level to work on protocols for diagnosis and treatment.

Dr Taruscio was then appointed by the Ministry of Health to establish and coordinate a technical table for the analysis and evaluation of the syndrome. In December 2005 the first meeting of the working group on Environmental Idiopathic Intolerance to Chemical Agents (*Intolleranza Idiopatica Ambientale ad Agenti Chimici*, IIAAC) (7), was held at the Ministry. Several institutional figures – including occupational physicians, researchers and managers of health departments – were involved and a protocol of diagnosis and treatment was drawn up which, after more than 15 years, appears to be substantially shared by some researchers both nationally and internationally, although there are some critical points, some procedural differences as well as some difficulties in implementation due to lack of economic resources and coordinated interventions (7-10). The diagnostic pathway of the document produced by the experts identified by the ISS, included in the first instance, if possible, the characterization of the chemical risk, clinical instrumental and laboratory examinations and finally the description of the subject and the results obtained. Diagnostic examinations can be more or less in-depth and are also useful to highlight any other pathologies that could either be the main cause of the symptoms detected or contribute to their onset (7). According to what is reported in the document, symptoms tend to reduce with the avoidance, as far as possible, of exposure. The treatment also includes symptom control according to Best Practice and Evidence Based Medicine. The conclusions of the working group were twofold: 1) to follow the diagnostic and therapeutic protocol and 2) to proceed with research also through controlled clinical trials.

In the following International Conference of the Network of Public Health Institutions on Rare Diseases (NEPHIRD), whose report has been published in a document published in the series *Rapporto ISTISAN* edited by the ISS (11), the intervention of Marco de Santis as a representative of the Association for Chronic and/or Environmental Intoxication Diseases is reported. At that time, he highlighted the need to promote research and to encourage the opening of specialized centres on the whole national territory.

As reported by Mura and Palagiano in the Report of the XII Permanent Commission (Social Affairs) XVI Legislature, Annex 2, 5-00542, the opinion expressed by the Consiglio Superiore di Sanità (the National Health Council in Italy) in 2008 was that MCS could not be considered a rare disease and they considered adequate the Italian essential levels of care. Thus, in fact, the actions to be promoted in relation to their own sources of funding were left to the regional autonomy of the Italian National Health System. In a few Regions, reference centres were opened in important hospitals, such as the following: University Hospital Sant'Orsola-Malpighi of Bologna, the Policlinic Umberto 1 of Rome in connection with the University Hospital Sant'Andrea of Rome, United Hospital of Brescia, the Hospital of Careggi, recognizing to potential sufferers a partially subsidized diagnostic pathway. Despite the importance given to this syndrome by Prof. Giuseppe Genovesi, immunologist, endocrinologist and psychiatrist, head of the reference centre in Rome, the same centre encountered many problems until its closure in 2016. The same fate happened to some other regional realities. The national context still appears variable and difficult to analyse due to the absence of unitary coordination at the national level and the still poor knowledge of the subject in the health care field.

Although the ISS has not been directly involved in the analysis of clinical data and research, in recent years it has been repeatedly called upon by the Ministry of Health to answer parliamentary questions on the subject. In the last two questions received between 2017 and 2019

(12, 13), the Institution in the figures of the National Centre for Rare Disease and Department of Environment and Health, responded in a coordinated manner, highlighting the critical points related to the difficulties of harmonizing both nationally and internationally the case definition criteria and the related diagnostic pathways to make the results of individual studies comparable. Then the opportunity has been reiterated both to carry out clinical studies – following the guidelines previously outlined in the report of the working group mentioned above –, and epidemiological studies on populations living in polluted sites and exposed workers, aimed at detecting groups of potential patients. As preventive and therapeutic measures, in addition to the avoidance and treatment of symptoms has also been proposed, where possible, the application of smart working and telecommuting that are important measures for the containment of personal exposure to pollutants and in general in the reduction of vehicular pollution.

This containment measure was also widely used during the current pandemic to reduce the chances of infection by SARS-CoV-2 and is therefore cited as an important structural change in living and working habits in the report on long-term Italian strategy on the reduction of greenhouse gas emissions (14).

In October 2018, the ISS in order to facilitate an initial exploratory exchange of information and debate among a relatively limited group of Italian experts, held a workshop on the definition, estimation of MCS frequency and correlations with environmental exposures. On that occasion, the Board proposed to set up a health and epidemiological surveillance system by implementing a systematic collection of case histories at the national level (15, 16). The working hypothesis promoted by the ISS consists in coordinating at national level a computerized collection of medical records of suspected cases according to predefined standards with the aim of both facilitating the discussion among experts and keeping a register in follow up of patients. Despite the interest shown by the parties at the time, it has not yet been possible to set up a coordinated program.

However, it is important to note that the topic has recently been included as a fact sheet (17) among the topics covered by the Italian Environment and Health Network (*Rete Italiana Ambiente e Salute*, RIAS) whose important work of integration and training of the assessment of the impact of environmental pollution on health can be consulted on the website: https://rias.epiprev.it/. This network was established in November 2017 and aims, among other objectives, to fill the training gaps of health professionals by creating a common cognitive humus at the interdisciplinary level. As an example, in the following chapter of this report it was considered potentially useful to describe and discuss the full medical record of a possible case. Critical points are being discussed.

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A POSSIBLE MCS CASE

Introduction

The Directive 89/391/EEC on safety at work and subsequent amendments and implementations to further protect the worker also of individual member states, foresees that all risks must be evaluated: physical, chemical, biological, radioactive as well as those related to work related stress. The goal is to reach not only the absence of illness but the psycho-physical well-being of the worker during the course of his activity.

The onset of work-related illnesses, including psychological syndromes resulting from inadequate work management, may increase the possibility of accidents and absenteeism with decreased productivity. A careful analysis of all the variables could make it possible to distinguish the real problems related to the work activity from incongruous behavioural codes of the worker, increasing personal satisfaction.

In this context we can study the MCS which is a multi-system syndrome, that manifests itself following exposure to various chemical substances such as volatile organic compounds and metals at lower concentrations to the limits established by the law.

The aetiology of this pathology is currently controversial (1) and could also have a working origin especially if the first evidences occur after exposure in this context and then manifest themselves in the daily environment as a result of chronicity and aggravation, whether it depends on purely pathophysiological causes or due to psychological conditioning (2-4).

In order to carry out a correct epidemiological study on the MCS it is necessary that there is already agreement on:

a) the existence of the syndrome with a known exposure aetiology;
b) the diagnostic criteria;
c) that it is possible to distinguish without reasonable doubts, those who can be included in the sample and those who have to be excluded.

The onset of unspecified symptomatology can lead to gradual exclusion from the work and social spheres, producing the healthy worker effect. This occurrence increases the possibility of a selection bias, with an underestimation of morbidity and mortality due to incongruous occupational chemical exposures, and an overestimation of these indices in the general population (5).

An example of a descriptive epidemiological follow-up study of a single possible clinical MCS case is reported below.

Description of the case

A fifty-two-year-old Italian female researcher, no-smoker and not addicted to alcohol or drugs, has carried out uninterrupted experimental activity for about 10 years (November 1993-February 2003) with semi-controlled exposure to different kinds of chemicals. Starting from March 2003, the experimental activity has been carried out intermittently.

In Tables 1-3 the substances used in these different periods of experimental activity are listed.

Table 1. Substances used by the study case for the experimental thesis (1993-1995)

Substance	CAS number	Final concentration/pH
Ammonium acetate	631-61-8	2 M
Aniline	62-53-3	200 mM
$CHCl_3$ (99%) chloroform	67-66-3	5 mM
Distilled acetylacetone	123-54-6	0,02 M
DTNB,5,5'-Dithiobis-(2-Nitrobenzoic Acid) (Ellman's reagent)	69-78-3	n.a.
EDTA bisodic salt	6381-92-6	1-2 mM
EDTA ethylene diamin tetracetic acid	60-00-4	1-2 mM
Erythromycin 98%	114-07-8	2 mM
Folin Ciocalteu reagent	mixture	1:2 dilution
Formaldehyde	50-00-0	3,3 mM
Glacial acetic acid	64-19-7	0.05 M
GSH	70-18-8	0.5 mM
HCl 37%	7647-01-0	pH 7.4
KCl potassium chloride	7447-40-7	0,15 M
KH_2PO_4/K_2HPO_4		1 mM
KOH potassium hydroxide	1310-58-3	pH 7.4
MeOH methanol	67-56-1	1 mL
NADPH	53-59-8	50 mM
NaOH sodium hydroxide	1310-73-2	0.1 mM
Para aminophenol	123-30-8	2 mM
Phenol	108-95-2	2%
Resorufin 98%	635-78-9	n.a.
TCA trichloroacetic acid	76-03-9	25-10%
TRIS Tris(Hydroxymethyl)aminomethane	77-86-1	50mM

n.a. not available

Table 2. Substances used by the study case for post-graduate experimental activity (1996-2003)

Substance	CAS number	Final concentration/ph
DMSO	67-68-5	10%
EDTA	60-00-4	10 mM
EDTA bisodic salt	6381-92-6	10 mM
Ethidium bromide	1239-45-8	few µL
EtOH 95% or absolute	64-17-5	95% absolute
Fluorescein diacetate	518-47-8	few µL
HCl 37%	7647-01-0	60 mL
MeOH 95% or absolute	67-56-1	95%absolute
NaOH	1310-73-2	5 N
Sodium hypochlorite	7681-52-9	50 mL
Tripan blue	72-57-1	few µL
Tris	77-86-1	10 mM
Triton X	9002-93-1	1%

Table 3. Substances used by the study case for a few months before definitive unfitness (2011-2012)

Substance	CAS number	Final concentration
Giemsa Stain	51811-82-6	5%
MeOh absolute	67-56-1	70 mL
Poly(butyl methacrylate-*co*-methyl methacrylate) (Eukitt mounting solution)	25608-33-7	few µL
Xylene	1330-20-7	70 mL

According to the subject's report in the early nineties, in the lab there were both common environmental and personal protection devices: fume and biological hoods, lab-coat, gloves and glasses but some instruments and furniture were outdated and chemicals were not store in dedicated ventilated cabinets. Moreover, due to experimental reasons, the substances were not always used under the protected environment of the fume hood. For example, in the thermostatic chamber (4°C-Celsius) where part of the experiment was carried out, the smell of various substances, such as dimethyl sulfoxide (DMSO) and Triton X-100, stagnated. For about 10 years she had never had problems due to exposure to chemicals, but in late 2002, after given birth to her first child, she gradually began to have recurrent cold syndromes with nasal and throat irritation and fatigue. At the same time, she also noticed the appearance of red spots on her face after using shampoo and conditioner that she had always used without any problem.

Before 2003, no diagnosis of chronic disease, no surgery and no access to the Emergency Room (ER) are reported. The subject continued her experimental activity until February 2003, when asthenia, palpitations and dizziness lead her to the ER twice. In that occasion, she reported her medical history (Appendix A1.1-A1.2) and the two diagnoses were: rhinitis and dizzy syndrome.

On the advice of the ER doctors, she reported the incident to the Health Surveillance Service of her employer. The judgment of suitability for the chemical risk was suspended without any other note. Hepatic and renal function were in the range as well as Erythrocytes Sedimentation Rate (ESR) with a slight anaemia. In addition to the checks proposed by Health Surveillance Service, she decided to go to hospital to perform other tests. The diagnosis was: Hashimoto's thyroiditis, since then treated with 75-100 µg of levothyroxine sodium in addition to a mild right Romberg.

For several years, the judgement of suitability for chemical risk remained pending and she was no longer directly exposed, despite the fact that her workstation was in continuity with the lab and in the direct vicinity of the fume hood.

In 2007, after more than 4 years of institutional activity, the subject obtained permission to be reintegrated into experimental activity. In about 7 months of work between July 2007 and February 2008, she performed several essays. Occasionally during the trial, she detected sporadic mild discomfort: breathing difficulties, as well as muscle weakness, fatigue and dizziness. No environmental or bio toxicological monitoring was carried out. Instead, she has been subjected to health surveillance on an annual basis. The blood tests verified a slightly altered ESR (1 h, 60; normal value <25) and hypochromic anaemia (21 µg/dL). The blockage of the experimental activity was defined unilaterally by the health surveillance system following an ambiguous episode of bronchus constriction detected after a short inhalation of "smells" coming from a not ventilated refrigerator in which bottles of various substances, including mutagens, were stored in both solid and liquid form.

Between 2009 and 2010 other three ER accesses, one probably due to spillage of acid products in the condominium drains that caused redness to her nose and eyes, and the other two ER accesses due to abundant menstrual flows that led to the diagnosis of a diffusely fibromatous uterus. Sometimes, when needed, she took a few vials of anti-haemorrhagic drug, but she did not take the contraceptive. On medical advice, she cyclically took vitamins and minerals.

In 2011, in the absence of specific analysis confirming sensitization to chemical substances, she resumed her experimental activity, using a different protocol and also exposing to other types of substances (*see* Table 3). The latter can therefore be considered a third direct re-exposure.

Again, after a few months of work, in April 2012 there was another episode following a spill of a few millilitres of xylene from a canister placed under the fume hood. She was working alone and anosmia prevented her from realizing that the xylene had pervaded the room. Her colleagues noticed the problem only later and ventilated the room. The anosmia was followed by general

malaise, tachycardia, a sense of fainting and anxiety. In the week from 16 to 22 April 2012 she went in and out from the ER of various hospitals (Appendix A1.3-A1.6), sometimes complaining of tremors, strong agitation interspersed with drowsiness and sporadic acute pain at the level of the hypochondrial organs. The ER diagnoses of the various accesses for this week were: malaise, anxious reaction, malaise with hypokalaemia. The prescribed therapies were: anxiolytics when needed, plus vitamins and minerals. Potassium and iron in particular due to some imbalances detected by blood tests. Following the long episode described above, she abstained from drinking both coffee and alcohol for several days, even though these drinks were always consumed in moderation. This decision was motivated by her perception that her cardiovascular and pressure situation was abnormal at that time, with episodes of sudden tachycardia, easy fatigue, muscle pain and wheezing for minimal efforts.

Following the incident with xylene on April 2012, the health surveillance service drew up, as a precautionary measure, the judgment of permanent unsuitability for chemical risk, not corroborated by any specific diagnosis. It should be noted that the toxicological analyses to evaluate the presence of xylene and metabolites were carried out about a month after the acute event (methyl-hippuric acid 38.00 mg/g; reference value <1300 mg/g creatinine).

These toxicological tests should have been performed in the acute period of the symptomatology, even if it is not always possible to find a link between absorbed dose and symptoms, especially when the quantities are probably low. She underwent tests for pollen and animal hair allergies too; the results, although moderately positives, were not directly linked to the event. The spirometry test gave the standard result. The researcher did not oppose this judgment because before the legal deadline for opposition (only thirty days in 2012, in Italy) she had not yet recovered from the incident either mentally and physically. Her workstation was definitively transferred to another building without laboratories. Despite these precautions and those she herself took, including carrying a gas mask along with a ready-to-use pressure/heart rate meter and anxiolytics, she sometimes failed to stop "panic-like symptoms". She had started to experience discomfort and tachycardia whenever there was a smell of solvent. Even the simple semi-permanent marker annoyed her.

Between September 2012 and August 2014 there were several other admissions to the emergency with similar prognoses to the previous ones. Medical records are not presented in this report. For a time, in addition to hypermenorrhoea, she was also diagnosed with xeroderma and seborrheic dermatitis.

In 2013, she decided to contact the Diagnosis and Treatment Centre of a famous polyclinic of her city, where an Italian MCS expert was present. In addition to the QEESI and an objective examination, the doctor performed a blood test and the genotyping of some isoenzymatic families (Appendix B). The patient did not perform any other investigations proposed by the team: lymphocyte transformation tests and DNA adduct tests. In the meantime, she sued the employer, making explicit request for a medical assessment. The Judge did not decide to call any MCS expert and the Appointed Technical Consultant did not carry out any specific investigations.

It is also noted that in April 2014, the patient spontaneously contacted the Department of Occupational Medicine of another important polyclinic. The conclusions based on the exams carried out were as follows:

> "[...] in the absence of an unambiguous nosological definition and of specific and validated diagnostic tests for the identification of multiple sensitization to chemical agents, at the present state the possibility of defining with a sufficient degree of probability a possible correlation between the symptoms described by the worker and exposure to specific work risk agents is not clear. Please refer to the occupational doctor of your employer for appropriate assessments and we recommend annual monitoring with your doctor, performing blood chemistry tests: complete blood count with formula, blood sugar, azotaemia, aspartate

aminotransferase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), total and fractional bilirubin, total cholesterol and fractionated, protein electrophoresis, total immunoglobulin E (IGE) and respiratory function test ". [The original is in Italian language].

This experience has numerous points of contact with the problem linked to solvent exposures (3, 6).

Between 2015 and 2017, she underwent treatment with a progestinic drug for about one year to reduce hypermenorrhoea. The outcome was positive and since June 2017 she has no longer taken any progestin. Even though sporadic imbalances continue to be detected, more than 10 years have passed since the onset of the first problem. In 2015 she had a new admittance to ER due to a strong urinary tract infection with blood in the urine, after having undertaken unsuccessful home therapies. The antibiotic therapy, established after this access was effective, although she was forced to suspend it 2 days early because of the side effects, fatigue, breathlessness and tachycardia, that occurred after the first intakes. The patient reports that she has begun to have occasional problem varying in degree following controlled drug intake: an event of epistaxis (nasal bleeding) after applying for about 2 hours of diclofenac patch placed on the lumbo-sacral region for slight sciatica. From that day on, she opted for equally effective thermal plasters and oral ibuprofen, without anomalous "coincidence" effects.

In September 2017, the patient turned to the ER to get out of a few days of insomnia, due to an acute episode of work-related stress, as can be partially seen from the summary in clinical records. The situation that led her to the ER was triggered by two factors:

1. her inability to face an ambiguous computer related work problem that slowed her down when she had to cope with a strict deadline.
2. the difficulty of quickly obtaining appropriate therapies for her insomnia.

This problem protracted for about 4 days even taking the prescribed anxiolytic-hypnoinducer drugs by oral administration, and quickly led to debilitating conditions, with extreme exhaustion, nausea, dizziness, anxiety and restlessness. Symptoms simultaneously present in a self-perpetuating vicious circle. The evaluation of how much is due to the psyche of the person and how much is to be attributed to the adverse effects of drug cocktails is difficult and depends substantially on the analysis of the duration of the effect and the maintenance of a situation of psycho-physical stability after the suspension of the drugs (7-9). The certain information reported by the subject is that the therapy established in first aid, Lorazepam 5 F 1 mL 4 mg/mL intravenously was successful, allowing a quick effective and prolonged recovery. Vice versa, the drug cocktail, orally taken at home 4 days before the hospitalization, was ineffective. The psychiatric examination defines the patient as quiet and collaborative. There are no disturbances of thought or alterations of the perceptual sphere. No self-inflicted and hetero-inflicted conception in progress (Appendix A1.7). The patient reports that the psychiatric evaluation during the hospitalization was limited to a few interviews lasting several minutes in which she concentrated her reasons for psychological suffering. The hospitalization lasted about 24 hours to which are added about another 24 hours spent in observation in the emergency room during the therapy with Lorazepam. No psychiatric tests were administered and the specialist did not provide any explanation for the principal and first diagnosis of International Code of Disease (not submitted for privacy reasons) in the hospital discharge form. Although the diagnosis was not explained to her and her family, the patient signed the discharge form. Even if the diagnosis refers only to that single episode, as the psychiatrist explained several weeks after, it was a further source of anxiety and frustration, but she was able to contain it. In fact, about a week after the event, the patient returned to work, successfully completing the unfinished activities which involved also direct contact with the audience.

Due to the initial marked side effects (daze and skidding/wobbling gait) hardly compatible with an active life, she agreed to adhere to the prescribed psychoactive drug therapy only for about a week from hospitalization, but accepted a few months of a supportive psychotherapy program.

After about 7 monthly sessions, considering both the relative absence of drugs intake (sporadically, less than 1 mg of anxiolytic to facilitate nightly rest), and the stable improvement in mood, the cycle ended with an informal agreement to contact the psychotherapist service in case of problems. In these interviews, the woman reconfirmed the problems encountered in the workplace, in an empathic atmosphere that facilitated the total and lasting functional recovery. In this context, it should be noted that the healthcare network has been efficient and proactive, guaranteeing, at least in that period, priorities for complete and free support, including the follow-up phase. She cannot tell if the prescribed drugs (sedative/anxiolytic) or their dosages were wrong, or if her physical conditions did not allow their use during an anxiety episode. Weakness, drowsiness and dizziness are the first physical symptoms to which gastrointestinal problems are sometimes associated. After the hospital discharge, considering that some psychotropic drugs only take positive effect after a few weeks of use, adherence to therapy is difficult both for the side effects, and in the absence of certainty about its effectiveness and the real need to continue it. This topic could become object of attention, especially if the diagnosis had been correct and the illness increasingly disabling. In this case, the problem has not recurred with such severity, although there have been some other occasions of psychological stress.

Alongside a moderate psycho-behavioural fragility such as performance anxiety, highlighted in this circumstance, there is also the suspicion of a greater sensitivity to certain categories of drugs (antibiotics, psychoactive substances, etc.) with increased possibility of incurring side/adverse effects (10-12). It should also be noted that if the drugs taken in home therapy had achieved a reasonable effect, no hospitalization and psychiatric diagnosis would have been made. Therefore, there is the possibility of relapses caused by psychological stress rather than by chemical substances, although for more than 4 years since this episode, no other event of a certain clinical importance has occurred. A general limbic hyperarousal to every kind of stressor, even without fault of reasoning, can lead to a feeling of almost constant anxiety and insecurity, increasing the possibility of kindling phenomena.

In any case, the symptom most complained by the worker were tachycardia, apparently often without stress. For this reason, it should be evaluated on a case-by-case basis what the source of the problem in order to set up the best prevention measure. The risk/benefit evaluation of drugs, as well as of environmental pollutants is therefore very important, as hypothesized also by the results coming from the analysis of some isoenzymatic families (Appendix B).

Between August and October 2018, following further investigations of a generic gastroenteric illnesses, she performed an abdominal ultrasound with a diagnosis of hyperdistant gallbladder lithiasis and a mild hepatic steatosis but without dilation of the intra and extrahepatic biliary tract.

Following a new admittance to the ER (Appendix A1.8), at the beginning of June 2019, for a gastroenteric disease with no clear correlation for an acute cholecystic attack, the patient was enlisted for cholecystectomy and was prescribed a therapy of ursodessosicolic acid (450 mg) once/day for some months. The recovery of the episode was rather rapid, as there were no significant notes in the analyses carried out in the ER and the situation was stationary. The researcher points out that so far she has not detected any acute side effects immediately linked to the intake of both thyroid hormone and ursodesossicolic acid, despite being chronic intakes and at medium-high dosages. The patient considers the decision to undergo cholecystectomy a difficult one, although acid therapy has had no effect on lithiasis as shown by the last ultrasound check carried out in December 2019. No acute symptoms from several months (June 2019–December 2021) but sometimes mild non-specific gastrointestinal discomfort, especially by night. On the one hand there is the risk of an acute cholecystitis or, albeit with a lower probability, an obstruction pancreatitis, as partially suggested by the specialist considering the relatively young age of the patient. On the other hand, there is the possibility of postoperative complications, in addition to the risks related to general anaesthesia. The concern about anaesthesia is accentuated

in the patient by the unresolved doubt of chemical substance sensitization either by inhalation and other routes of administration, as described above (13-15).

These considerations, together with a seeming lack of complete agreement in the scientific field on the need to operate on a patient with no acute specific symptoms (16, 17), and the current COVID-19 pandemic, makes the patient lean towards the decision of "control and reassessment" in a vicious circle, waiting for a worsening. Expanding the general picture of health, the researcher also points out that she has been wearing soft contact lenses since the early 1990s and that around 1996, probably coinciding with her laboratory activity and the use of electron microscopy, she had detected a slight left eyelid ptosis that worsened over years, so much so as to think in 2006 of a blepharoplasty surgery. This intervention was finally discouraged by the doctor because it was considered un-resolving. Following the abstention from lab activity, also this situation seems to be partially restored and no apparent problem in the use of contact lenses until April 2019. In that period, after applying a specific sun cream to her face, she had a strong irritation to both eyes that prevented her from continuing to wear contact lenses. She was diagnosed with corneal de-epithelialization due to both the cream and probably also to prolonged contact lens wear. After about 3 years from the episode, she still cannot wear contact lenses because, despite a marked improvement, the eyes tend to irritate easily, due to various agents: pollen, dust, pollution, excessive use of the PC, etc. The same fluorescein used by ophthalmologists in the test to verify the healing process of corneal de-epithelialization determined the phenomena of irritation and lasting and annoying redness that require treatment with hyaluronic acid, cortisone and antibiotics –eye drops.

The latest diagnoses (Summer 2020) provided by the patient are of suspected vitiligo/dyschromia localized to some areas of the fingers, toes and neck and a suspected onset of insulin resistance, currently untreated. The subject reports that, however, she has now recovered to a fairly good and more stable state of health than the critical period that lasted about 2 years (2012-2014). She avoids exposure to concentrated chemicals, in particular some solvents (e.g., ethanol, trichloroethylene, benzene and paints containing solvents) and for an extended period of time.

In general, she has no evident problems in the moderate use of common sanitizers, household detergents, body soap, cosmetics and perfumes both personal and environmental. She has noticed a partial improvement in the health of epidermis (xerodermia) and hair and has gradually resumed a slight physical activity.

Nonetheless, the situation is still fluctuating with sudden exacerbations and remissions of various symptoms of which the most common and annoying are: tachycardia with or without anxiety almost exclusively at night, rarely burning and itching of the skin, mild muscle tension and slight breathing difficulty that can cause insomnia. Sometimes she takes simple herbal products, or anxiolytic or analgesics, like ibuprofen. Sleep quality is relatively low, maybe due to the onset of menopause. Sometimes there is also an increase in localized water retention, mainly in the lower limbs, and abdominal swelling and poor tolerance to heat and cold. It should be noted that, till December 2021, all the symptoms described above are partly reduced during periods of rest, especially summer and staying in less polluted areas than in the metropolis where she lives. Both factors, stress and pollution reduction, contribute to improvement.

Legal action

The legal action that the subject presented at the end of 2013, to obtain a more precise evaluation that could justify the certificate of unsuitability for chemical risk, did not lead to any further analysis targeted by the Technical Consultancy Office and by the Judge. In the report of the medical-legal consultant (July 2014), listing all the investigations presented by the subject and the objective examination of the Official Technical Consultant, is stated that the "MCS topic" is still controversial both nationally and internationally, with a substantial difficulty of nosological classification:

> "[…] once the sensitisation system is activated, reactions may occur following exposure to multiple chemicals including solvents, volatile organic compounds, building products, [...], drugs, anaesthetics, etc. Reactions also occur after strong natural odours, light and sound, intense heat and cold, electromagnetic fields, thus suggesting a common mechanism of neurological sensitization." [*This part is faithfully translated from Italian language*].

The technical dissertation on MCS continues quoting both the work of Dr Martin Pall (18, 19), who proposed a toxicological etiopathogenesis of the disease with activation of a vicious biochemical circle NO-ONOO in the brain, and others articles that reinforced the hypothesis of biochemical mechanisms underlying the disease with reduction of glutathione -s-transferase, alterations in the composition of fatty acids in the cell membrane.

Summarizing what is written in the report of the medical-legal consultant, the causal link between occupational exposure and the hypothesis of sensitization formulated in the lawsuit is not satisfied in a probabilistic way.

The report makes it clear that the current state of scientific knowledge and diagnostic tests cannot find a direct link between exposure to low-dose, detected symptoms and nosological framework, as written in the report of the occupational medicine doctor of the polyclinic that the patient had spontaneously contacted.

A defensive response by the State Attorney's Office, according to which the quantities of substance, the index of volatility and toxicity and the daily use times, did not justify, according to the provisions of the software A.R.Chi.M.E.D.E., the request for personal electronic instruments capable of alerting the exceeding of the threshold limits. The lawsuit was therefore dismissed due of:

1) the current lack of scientific evidence supporting the causal link between exposures and the damage;
2) no evidence of demotion in the activity carried out, despite the requirement not to use it for tasks with potential chemical risk had resulted in several work activities' blocks.

Toxicological assessment

In the case described, the core to be unravelled is how much any chemical exposure and the onset of symptoms and diseases can be interrelated and determine the situation described above. The various Occupational physicians that, in about 20 years of service, have followed one another in the Body, have taken note of the problems and have carried out only common clinical and laboratory tests and, based on the result, have defined the path to be taken. The last decision in June 2012 was judgment of permanent unsuitability for chemical risk not supported by any precise diagnosis but only as a precautionary measure.

In view of a toxicological evaluation of the events, it is worth noting the previous use of some solvents and acids at high concentrations: absolute methanol, absolute ethanol, DMSO, Triton X 100, Hydrochloric acid 37% and finally xylene mixed with glue (*see* Tables 1-3). Xylene, although used for a shorter time than other substances, seems to have been responsible for the main event. Chronic exposure to volatile solvents without precautions, causes an increase in the permeability of the nerve cell membrane, making the nervous system more vulnerable to toxic effects (20). For practical reasons, attention has been paid below to only a few of the substances used in the trials. Much of the information for the substances listed in Table 4, was obtained by consulting the open free website: https://pubchem.ncbi.nlm.nih.gov. For the sake of brevity and in due to the greater severity of symptoms observed in relation to exposure, only xylene is presented in detail.

Table 4. Most used substances by the study case, classification and code.
Fore more information: https://pubchem.ncbi.nlm.nih.gov/ (last visited 5/19/2022)

Classification	Category	Code (%substance)
Absolute Methanol (MEOH), CAS no. 67-56-1*		
Flammable liquids	2	H225
Acute toxicity, Oral	3	H301
Acute toxicity, Inhalation	3	H331
Acute toxicity, Dermal	3	H311
Specific target organ toxicity - single exposure	1	H370
Absolute Ethanol (EtOh), CAS no. 64-17-5*		
Flammable liquids	2	H225
Dimethylsulphoxide (DMSO), CAS no. 67-68-5**		
Skin corrotion/irritation	2	H315 (93.42%)
Serious eye damage/irritation	2	H319 (96.87%)
Specific target organ toxicity, single exposure; Respiratory tract irritation	3	H335 (39.81%)
Hydrochloric acid, CAS no.7647-01-0*		
Acute toxicity, Inhalation	3	H331
Skin corrosion/irritation	1A	H314
Triton X-100, Cas no. 9002-93-1***		
Acute toxicity, oral	4	H302 (84.64%)
Skin corrosion/irritation	2	H315 (38.26%)
Serious eye damage/eye irritation	2	H319 (38.84%)
Serious eye damage/eye irritation	1	H318 (51.88%)
Hazardous to the aquatic environment, acute hazard	1	H400 (11.59%)
Hazardous to the aquatic environment, long-term hazard	1	H410 (24.06%)
Hazardous to the aquatic environment, long-term hazard	2	H411 (24.35%)
Hazardous to the aquatic environment, long-term hazard	3	H412 (21.16%)
Xylene, CAS no. 1330-20-7****		
Flammable liquids	3	H226 (100%)
Acute toxicity, inhalation	4	H332 (99.64%)
Skin corrosion/irritation	2	H315 (100%)
Serious eye damage/irritation	2A	H318 (31.84%)
Aspiration hazard	1	H304 (37.33%)
Acute toxicity, dermal; acute toxicity, inhalation	2	H312+H332 (34.66%)
Acute toxicity, dermal	4	H312 (99.64%)

* The risk phrases essentially agree with what is reported on the website of the ISS Chemicals Database according to Annex VI of the Regulation (EC) 1272/2008, known as CLP (Classification Labelling and Packaging).

** Aggregated GHS information provided by 865 companies from 21 notifications to the ECHA C&L Inventory. Each notification may be associated with multiple companies. Reported as not meeting GHS hazard criteria by 546 of 865 companies. For more detailed information, please visit ECHA C&L website.Of the 19 notification(s) provided by 319 of 865 companies with hazard statement code(s). Information may vary between notifications depending on impurities, additives, and other factors. The percentage value in parenthesis indicates the notified classification ratio from companies that provide hazard codes. Only hazard codes with percentage values above 10% are shown.

*** Aggregated GHS information provided by 362 companies from 32 notifications to the ECHA C&L Inventory. Each notification may be associated with multiple companies.Reported as not meeting GHS hazard criteria by 17 of 362 companies. For more detailed information, please visit ECHA C&L website.Of the 31 notification(s) provided by 345 of 362 companies with hazard statement code(s). Information may vary between notifications depending on impurities, additives, and other factors. The percentage value in parenthesis indicates the notified classification ratio from companies that provide hazard codes. Only hazard codes with percentage values above 10% are shown.

**** Aggregated GHS information provided by 1385 companies from 18 notifications to the ECHA C&L Inventory. Each notification may be associated with multiple companies.Information may vary between notifications depending on impurities, additives, and other factors. The percentage value in parenthesis indicates the notified classification ratio from companies that provide hazard codes. Only hazard codes with percentage values above 10% are shown. The risk phrases on the site of the ISS Chemicals Database according to Annex VI of Regulation (EC) 1272/2008 (CLP) are: flammable liquid category 3 (H226); acute inhalation toxicity category 4 (H332); harmful in contact with skin (H312); skin irritant (H315).

Xylene

Xylene (three isoforms o, m, p) is an aromatic solvent, colourless liquid with a pungent sweet smell and widely used in glues, paints, lacquers, inks, pesticides and degreasers (21). It is also present in petrol and therefore is diffusely polluting. The risk phrases are shown in Table 4. The TLV-TWA is 100 ppm. Toxicity can be caused by inhalation, dermal contact even through intact skin, and ingestion. Inhaled may cause dizziness, nausea, asthenia. Although its smell is characteristic, it is able to block the olfactory nerve causing temporary anosmia. At toxic concentrations, sensitization of the myocardium to endogenous catecholamines with tachycardias and arrhythmias as well as pulmonary oedema, respiratory arrest and death may occur. There is neither sufficient data nor evidence to classify it as a human carcinogen, but xylene just as toluene passes through the placenta and is absorbed by the embryo.

The diagnosis of acute intoxication is based both on symptoms, history and laboratory tests such as electrolyte picture, glycaemia, azotaemia, creatininemia, CPK creatinine phosphatase hepatic, urine examination etc. It is also useful to check the level of methyl hippuric acid, metabolite of xylene, excreted with urine generally in the first 24 hours. Only in the first few hours is possible to detect traces of xylene in the blood. Due to the different interferences that can play a role in biotransformation processes, the levels detected in body fluids are not always indicative of the severity of the clinical picture and symptoms (21).

Nevertheless, they can still be qualitative indicators of exposure to toxic substances, but it is necessary to intervene with a certain speed and carry out appropriately cadenced dosages. Acute and chronic exposures can cause organic psycho syndrome and toxic encephalopathy. The symptomatology noted in this case report is partially overlapping with the effects of these substances. The neuro and cardiological system, as well as the respiratory and dermal systems, although apparently free of irreversible damage, are nevertheless more reactive.

Psychological issue

The subject presented a brief description of psychological problems preceding and contemporary to the mentioned events. It does not appear that any psychological assessment has been carried out, even temporally, related to the above scenario in the work context. She reports that during particularly stress full life events (mourning, separation, business problems, etc) she sometimes experienced some periods of mild anxiety and depression. These emotions were, instead, more pronounced during the final stages of her degree experimental thesis and in the period immediately following. During this period (about 1995 to 1999) she spontaneously decided to perform a few occasional sessions of psychotherapy and to take sporadically some psychotropic drugs. The initial reasons were work difficulties during the experimental thesis phase and then work precarity. However, she emphasized that there was no work stoppage nor of daily activities, despite the difficulties and no health problems that required an emergency room visit.

This period was followed by a long period of relative calm without psychotherapy and any drugs' intake, with changes and improvements in personal life and partially also in work activities. The researcher confirms that she has difficulty in maintaining serenity especially when there are several prolonged stressful events at the same time and where the relational contrast component is predominant. She also believes, however, that some chemical substances in indefinite doses can cause her situations of malaise more or less serious even in the absence of stressors and not directly related to anxiety phenomena.

Discussion and conclusions

There are various points of discussion to highlight.

The absence of a diagnosis that justifies a declaration of permanent unfitness for chemical risk, drafted as a precautionary measure, highlights an unresolved health problem and is therefore an issue to be examined in depth because of the different implications that it could determine in health, work and socio-economic fields. Faced with the above history, the physician/researcher can decide whether to evaluate each individual aspect in isolation as a stand-alone event without any correlation, or whether there is a common denominator that can explain the situation, detecting possible markers of active biological dose and effect and placing these events in relation, when possible, both to chemical exposure and to other existing diseases. It is important to be able to detect the aetiology of symptoms, whether fully or partially reversible or irreversible, in order to set the correct therapy and seek appropriate preventive measures. An accurate analysis of the case history will help to delineate with greater precision the mode of onset of symptoms, the duration and co-presence of other diseases raising similarities and differences in the subjects considered.

In this case report, the only certainty is that, starting from a situation of apparent tolerance to chemical risk, known as stage 0 according to the theory of clinical ecologists for MCS, and accredited by about ten years of experimental activity, we have come, after several semi-controlled re-settings and interspersed with periods of almost total absence of occupational exposure, to a gradually more disabling situation leading to the certification of permanent unfitness to chemical risk. In the absence of environmental monitoring through individual electronic instruments, and of real time toxicological analyses able to detect the presence in body fluids of chemical substances potentially responsible of the symptoms detected in the "acute" phase (22), it is even more difficult to determine which factors have determined the situation aforementioned.

Although it seems unlikely that this was one or more lab incidents with even partial overcoming of the TLV legal limits, the absence of environmental and biological measurement determines a situation in which at least four hypotheses can be assumed:

a) lab accident with exceeding of the limit;
b) psychosomatic and psychiatric diseases of dubious aetiology (23-26);
c) sensitization to chemicals (3, 18, 27-30);
d) pathologies that may lead to decreased chemical tolerance.

The correct evaluation of these points would require environmental and biological monitoring. This is for at least to exclude the possibility that a lab accident, even without exceeding the TLV, may have a role in the onset of the specific symptomatology on someone who is not in perfect health or presenting some unclear genetic predisposition. It also should be verified whether chronic exposure to specific substances can lead to small, repeatable and gradual changes in important parameters, such as: sensitization to catecholamines with episodes of prolonged tachycardia and extrasystole, wheezing, increase in anaemia, maybe increasing haemorrhagic phenomena during menstrual cycle, blood pressure and hormonal imbalances, and anything else that is considered a possible risk factor compared to the chemicals used.

It should also be borne in mind that, due to individual susceptibility, about 2.5% of the exposed population may suffer health damage even under environmental conditions that comply with the set threshold limit, in addition to the possible synergistic action resulting from mixtures of compounds whose toxicological properties are not always known with accuracy.

Points (b) (c) and (d) are the object of extensive research into the effects of low-dose inhalation of lipophilic solvents that pass through the blood-brain barrier leading to a rapid onset of symptoms (31). There are already several evidences regarding the mechanism of action of some

solvents. Following chronic abuse, they initially determine an increase in the permeability of nerve cell membranes and changes in the modulation of Gamma-aminobutyric acid (GABA-A) and N-methyl-D-aspartate (NMDA) receptors, autoimmune and inflammatory states, psychiatric diseases and other pathologies including the MCS (18, 27, 32, 33-36). Tachycardia, dizziness, difficulty breathing, sense of fainting, agitation and tremors, fatigue and weakness, difficulty in memorizing and coordination are non-specific symptoms if analysed individually and are common both to neuropsychiatric diseases and to other pathologies (37).

An analysis limited to the episode can lead to a diagnosis carried out exclusively on the basis of the symptoms detected at the specific time and therefore potentially without explanations. It is emphasized that the presence of other pathologies, including psychiatric and psychosomatic pathologies, does not in itself exclude the possibility of a greater sensitivity to chemical substances or something else (37). In this context, MCS may in turn represent an additional problem whether it is assumed to be a form of chemophobia or, even more so, whether it is assumed that these patients have a greater reactivity to low dose chemicals. In the reported example, the toxicological, psychiatric and neuro-cardiological aspects are areas of choice. Once the morbid phenomenon has been accurately described in terms of symptoms, both through the analysis of bio-physiological parameters and through the subjective perception of the patient, it is therefore important to evaluate which factors determine the onset of symptoms and according to which modalities.

The diagnosis of a disease, identified by a specific code – ICD or DSM-5 (*Diagnostic and Statistical Manual of mental disorders, fifth edition*), may not provide accurate information about the aetiology of the morbid phenomenon and may increase the possibility of therapeutic errors on the long time, especially with respect to the need for prolonged administration of drugs. In the case herein described, the acute symptoms had completely disappeared after the single administration, so there was no real need to continue with a further intake of multiple psychotropic drugs (Evidence based medicine). For the patient it becomes fundamental that the physician verifies the real necessity of proceeding with a prolonged pharmacological treatment without having previously been able to adequately evaluate the patient after the acute symptomatology. Otherwise, there is a risk of over-medication, with the possibility of abnormal reactions and side effects that could increase confounding factors.

The DSM5 states that (38):

> "The case formulation for any given patient must involve a careful clinical history and concise summary of the social, psychological, and biological factors that may have contributed to developing a given mental disorder. Hence, it is not sufficient to simply check off the symptoms in the diagnostic criteria to make a mental disorder diagnosis. Although a systematic check for the presence of these criteria as they apply to each patient will assure a more reliable assessment, the relative severity and valence of individual criteria and their contribution to a diagnosis require clinical judgment. The symptoms in our diagnostic criteria are part of the relatively limited repertoire of human emotional responses to internal and external stresses that are generally maintained in a homeostatic balance without a disruption in normal functioning. It requires clinical training to recognize when the combination of predisposing, precipitating, perpetuating, and protective factors has resulted in a psychopathological condition in which physical signs and symptoms exceed normal ranges […]" (p. 59)

This could also reduce possible over- or underestimates of undefined etiological phenomena, resulting for example from statistical-epidemiological analysis based exclusively on the counting of specific codes, without evaluation of the causes.

In the neurotoxicological field it is known that (37):

a) mood disorders may be the first indicators of damage to the central nervous system. The latency time can also be quite long. Initially, if the damage is severe, the individual can make up for it with his own resources, but as he ages, this process of compensation can diminish, revealing the problem;
b) neurological diseases, such as Parkinson's disease, Amyotrophic Lateral Sclerosis (ALS), Alzheimer's disease, could therefore be added to mood disorders;
c) people suffering from mental disorders may be more susceptible to neurotoxic substances and aggravate their symptoms of anxiety, mania, depression, psychosis etc.;
d) problems to the liver, to the biliary system rather than to the kidneys can diminish the capacity of detoxification making the individual more susceptible to the chemical insult including the neurotoxic one;
e) Hashimoto thyroiditis with many related symptoms: heart palpitation, fatigue, memory problems, etc.;
f) other unidentified pathologies.

It should be noted that subjective symptoms with reversible or irreversible signs of exposure are accepted as signs of neurotoxicity, particularly if dose-response correlation is detected (25). In the case presented, following the principles of Cullen (39) and Lacour (40), the elements that lead to the hypothesis of MCS with other forms of comorbidity are, on the one hand, the time connection between exposures to chemicals and acute effects of a mainly neuro-cardiological and respiratory type, and on the other hand, the almost complete remission in the absence of further direct exposures (27, 33, 41, 42).

In 2003, the first symptoms that the subject had related to chemical exposure, led to the diagnosis of Hashimoto's thyroiditis, whose etiopathogenesis is still controversial. It is an autoimmune organ specific disease, characterized by a chronic inflammatory state with lymphocytic infiltration and antibodies to TPO and thyroglobulin (43, 44). Gradually the thyroid, attacked by antibodies, loses its function by reducing its mass and becoming fibrotic. In addition to a genetic predisposition, various etiological hypotheses as follows: high iodine intake, infections, radioactive exposure, psychophysical stress, pregnancy, as well as exposure to drugs and pollutants. According to this last aetiological hypothesis, some chemical substances could modify the surface haptens, determining the misrecognition of the organ by the immune system with subsequent auto-attack. A genetic predisposition, together with environmental factors, would contribute to the development of autoimmune diseases by altering the immune system with different mechanisms and influencing both the phenotype and severity of thyroiditis (43, 45). Women are up to 10 times more likely than men to develop autoimmune thyroiditis with a higher risk in post-partum and perimenopause (43). However, chronic hormone replacement therapy does not appear to have completely solved the specific problem identified as a result of occupational exposures. Avoidance of lab substances also seems to have led to an improvement but not a complete recovery of tolerance. In fact, from the analysis of the "three re-exposures" it seems that after a certain period of time a process of bioaccumulation with exacerbation of polyhedral symptoms is triggered. The most serious episode of 2012, which led the patient to repeated access to the ER of several hospitals over the course of a week and which led to relapses even in the following period, did not lead to any definite diagnosis but to hypotheses of malaise or anxious syndrome. The hypothesis that the complained symptoms, tachycardia and sense of fainting, sometimes tremors as well strong agitation interspersed with drowsiness, diarrhoea and sporadic pangs at the level of the central solar plexus were attributable to exposure to xylene, was partially taken into account in the emergency room.

On the other hand, xylene and the complex mixture of substances present in the laboratory during the 2012 episode could have played an important role especially with respect to the main

symptoms complained by the subject: tachycardia and agitation. Sensitization of the myocardium to endogenous catecholamines is a characteristic effect of several organic solvents including xylene (21, 46-48).

The severity of the effect depends not only on the intrinsic characteristics of the substance, the exposure time and the concentration, but also on the particular conditions of vulnerability of the individual (46, 48).

In the case described, it is possible that the effect, although disabling, determined prolonged tachycardia and reactivation of the system perhaps also due to endogenous release of catecholamines, for example after coffee or even simply more stressful situations or physical activity. In the scientific literature it is suggested that, following inhalation exposure (high dose) to some organic solvents, the imbalance in electrical conduction on the myocardium together with a possible release of catecholamines concur in increasing the possibility of the onset of arrhythmias that, in some cases, can determine the sudden death of the subject for cardiovascular arrest after ventricular fibrillation (46). Several animal experiments (beagle dogs) performed under controlled conditions allowed to evaluate the mechanism of action noting that even short exposures to certain chemicals can cause arrhythmias (46). It is also important to note that the event of sudden death does not normally have characteristic pathophysiological markers that can be detected at autopsy (46), and this problem has required more accurate analyses to try to determine the mechanism of action. Although myocardial sensitization is a recognized risk during acute exposures to different classes of hydrocarbons the scientific literature on this subject is quite limited (48) compared with the greater number of articles present for volatile anaesthetics for human use. The subject confirms that at that time, she had no conscious reason for psychological stress, despite the general difficult work situation. Of course, a psychiatric phenomenon of removal and conversion can always be subtended, but no pre-defined psychotherapeutic path was marked as a priority, but only a rough indication. There is the doubt of an intoxication with organic low-dose psycho-syndrome.

Finally, analysing the last event of 2017, it is noted that the triggering nervous problem was work-related stress, but its continuation could have been a paradoxical reaction following the oral intake of a mix of drugs between anxiolytic-hypnoinducents, as also described in the illustrative insert of some of the drugs taken. In the ICD code there is no mention of this possibility, although the medical record shows both the negative evolution despite the oral intake of various types of drugs compared to the positive outcome of treatment at the ER. From a toxicological and psychiatric point of view, different hypotheses could be conjectured. It can be assumed that oral drugs have not had the desired effect because of dosage and time errors or because they have not been adequately metabolized by the body at a hepatic level. The body may not have been able to detoxify and subsequent assumptions, besides not producing the hypnotic effect, have aggravated exhaustion, irritability and nausea. Higher dosage combined with intravenous administration bypassing the first pass and making the drug quickly 100% bioavailable increased its efficacy. Probably other important factors were both the choice of the drug and, from a psychological point of view, the safety of the patient in being in an adequate environment to cope with any side effects, avoiding a negative impact on family life in the event of further problems. The above is clearly evident from the description in the medical record. By checking the results of the analyses of isoenzymatic families (Appendix B), it is written that:

> "Cyp 2C19 is one of the members of the P-450 family of cytochromes, and it is responsible for the metabolism of about 5-10% of the drugs currently on the market, among which the most important are some benzodiazepines, omeprazol (anti-acidity) and phenytoin (anti-epileptic), citalopram, clomipramine, diazepam, propranolol, omeprazole, tricyclic antidepressants, anti-malaria, barbiturates and anticancer drugs. It is a rapid metabolizing phenotype with activity increased by 50% and more. A lack of response to treatment is

possible. Need to increase control over concomitant drugs adverse events and pharmacological efficacy. If necessary, change the dosage by dosing the plasma concentration of the active substance or implement alternative methods.
PON 1 A575G genotype G/G with reduction of enzyme activity and increase in oxidative damage.
GSTT1 Glutathione S-trans Genotype null.
MT1A rs8052395 genotype A/A whose likely effect is a reduction in protein function with an increased risk of accumulation of heavy metals".

However, at the current state of knowledge it is not possible to ascertain the responsibility of these findings as a "necessary and sufficient condition" for a specific diagnosis of MCS. For these reasons it is important to gather evidence on individual clinical cases accurately reported (2, 3).

In order to carry out a proper epidemiological study on MCS, it is first of all necessary to agree on the existence of the syndrome as an entity apart from other diseases and closely linked to exposure to chemicals.

How many factors must be taken into account to perform a correct differential diagnosis (24)? If the worker also had a tendency to somatise problems of varying order and degree, in this context the "chemophobia" (42, 49, 50) should not have played a decisive role, at least in the early stages, given that she herself had asked to be reinserted into experimental activity and had complained of health problems only a few months after re-employment. As previously expressed, from the clinical and research point of view, it is however necessary to identify those parameters and markers that can lead to a precise differential diagnosis between psychological and toxicological problems in a condition in which the two categories can mutually increase.

It should be noted that some of the symptoms complained of could be due to both Hashimoto thyroiditis and an anaemia condition. We do not even know the further possible negative contribution provided by a gallbladder with randomly discovered but probably long-standing lithiasis. It is therefore possible that any unbalance factor in a system that is not in perfect homeostasis, may result in a worsening of the physiological conditions that manifests itself with anomalous responses that are only partly pointed out by the analysis performed in the E.R. In this case it would be appropriate to highlight the direct link between the acute symptoms, with moderate alterations of some parameters (heart rate, pressure changes etc), the subtoxic chemical exposure and the underlying diseases. The origin of the syndrome is most likely multifactorial involving both the genetic, epigenetic and ability to respond to psychophysical stress, but the trigger must still be caused by, evident or not, exposure to chemicals (51).

A reduction in the tolerance thresholds to some chemicals, evidenced by acute symptoms of discomfort, may be both the alarm bell of a difficulty in rebalancing the system and an obvious secondary effect of a pathological picture. In both cases, in my opinion, it would become a specific nosological framework which would legitimise inclusion in the ICD with a dedicated code, justifying the certificate of unsuitability for chemical risk pending further scientific knowledge.

It is also right to mention the importance of how risk factors are assessed.

In this case, the evaluation by the system of prevention and protection of workers has been entrusted to the Ar.Chi.ME.DE. algorithm, as can be seen from the lawsuit brought to the fore. At least in ambiguous cases such as this, it would be appropriate not to rely exclusively on the calculation of algorithms to assess the risk of the individual, but to analyse the entire work process and in the revaluation phases of the suitability of supporting at least another worker to avoid further risks.

In any case, some electronic instruments such as electronic nose, can prevent the possible stay in contaminated workplaces, also in consideration of the fact that some laboratories and tools are in common and that both the concentration and the quantity of the products used even if under chemical hood are not always reduced as, instead, was written in response to the lawsuit.

Work related stress factors

The analysis of work-related stress is another important point in the law on the safety and protection of workers. An inadequate management of work, both in terms of human and economic resources, can determine an excessive burden of responsibility on a single individual, aggravating an already complicated situation.

Furthermore, it is underlined that the issues related to the organization of work, lack of funds and adequate tools rather than even litigation in the workplace are among the main recognised causes of requests for compensation to INAIL as shown in Figure 1, relating to the period in question (2012-2016). The scheme concerns psychic problems and for the greatest number of these cases, the cause has not been determined further confirming what has been stated above on the need to investigate the topics in order to prevention as well.

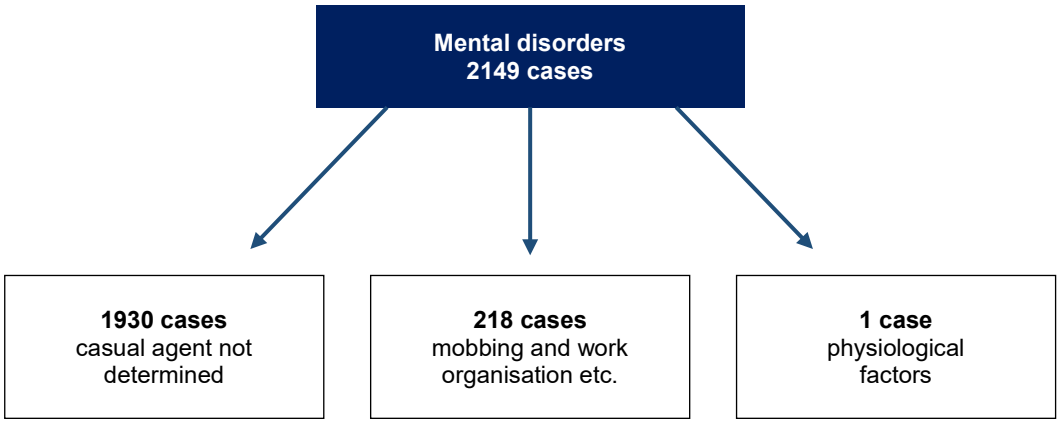

Figure 1. Summary of INAIL data information for mental disorders cases (ICD-10: F00-F99), years 2012-2016 in Italy

Special attention deserves the possibility of a psychiatric mis-diagnosis that could lead to a code e.g. of psychosis etc., instead e.g. a severe work-related stress etc., whose symptoms may have been accentuated by the ineffectiveness and side effects of the drugs taken.

In the presence of a potentially debilitating psychiatric diagnosis, the role of the worker protection and safety service is fundamental in outlining the most appropriate way of applying the law on safety in respect of privacy (Regulation EU 2016/679, General Data Protection Regulation), of the dignity of the worker and in the protection of the employer. This is a point that needs to be explored for the many economic, social and psychological implications it can have on the person concerned.

Possible future implications

In order to carry out a correct epidemiological analysis on workers subjected to health surveillance due to exposure to chemical risk, a complete clinical and risk documentation of the worker is needed where everything that characterizes the subject is specifically reported (51).

From the beginning of the work activity and for the correct drafting of the certificate of suitability to the task, an in-depth evaluation must be performed to identify particular pathologies in progress.

If, for example, the worker is expected to be exposed to specific VOCs in a semi-controlled manner, it would be appropriate to periodically evaluate all the parameters that may change as a possible result of the exposure, including psycho attitudinal-neurological, psychiatric tests and the myocardial function. In case of suspected subacute poisoning, or in case of suspected MCS, it would be advisable to evaluate the presence of the substance or its metabolites in the blood, in the urine and the environmental pollution.

The substances must be analysed according to their specific toxicokinetics.

All the main physiological parameters for at least 48-72 hours from the onset of symptoms or exposure must be evaluated: cardiac Holter; oximetry; blood pressure assessment; basic and specific blood tests for damage. If the substance causes effects on the nervous system both chronically and, with greater evidence, following an uncontrolled exposure or in presence of a possible disorder like MCS, it is hypothesized that after an exposure there is an abnormal release of neurotransmitters such as catecholamines (adrenaline, noradrenaline, serotonin, and so on) at levels higher than the expected but probably limited to the intoxication period. In case of intoxication or of MCS, being the latter not detectable even through the analysis of specific metabolites, it is hypothesized an increase both in the duration of the release and in the achieved level of endogenous catecholamines and any reversible or non-reversible cardiac problems. From the analysis of all the aforementioned factors it could be possible to detect the difference between an “endogenous” panic attack or similar psychiatric diseases both for duration, severity, absence of circulating metabolites, single parameter relief, etc. from a low dose or uncontrolled dose intoxication.

The assessment of the psychological well-being of the individual in the workplace can be performed routinely like the other exams, both for direct interview and through neurological and psychometric tests able to evaluate not only any cognitive or neurological disorders but also particular psychoneurotic pathologies. Work-related stress, burnout syndrome, organizational difficulties must be assessed and, if it is possible, quickly addressed and solved.

If it is possible to discern between the three objectives set out above (intoxication due to accident, MCS or endogenous psychological disorder) the fallout on the National Health System and in the field of safety at work would consist in the correct evaluation of incidents and to avoid work suspensions or judgments of unsuitability to chemical risk due to uncertain diagnosis or partial application of the law.

The workers’ safety act provides for the use of all the most innovative technological means to limit the risk. In general, a more thorough analysis of any similar situations might also raise issues regarding the appropriate classification of chemicals or their mixtures. Not all chemicals have been accurately evaluated for hazard in *in vitro* and *in vivo* testing. Sometimes the labelling was lacking in information or was not unambiguous, but depended on the manufacturing company, revealing an absence of harmonization.

This issue may result in an underestimation of the associated risk. Expanding the context, the neuro- and cardiotoxic properties of common environmental pollutants in combination with the possibility of developing MCS, may be responsible for the increased incidence, especially in polluted areas, of reversible/ irreversible cardiac and psycho-neurological disorders.

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APPENDIX A
Medical sheets and work anamnesis with risk folders*

* All information in these documents corresponds to the Italian original. For confidentiality reasons, personal data has been deleted as well as those relating to hospitals and health care personnel involved.

A1. ER sheets

A1.1. ER sheet; admittance: 02-15-2003; 9:24 am • discharge 9:52 am

ER code: green (mild degree)

Anamnesis

Elective laboratory activity with semi-controlled exposure to different solvents (DMSO, HCl 37%, MeOH, Tris, Triton X, NaOH, Na_2EDTA, Ethidium bromide).
She is monitored by the prevention and protection service.
Inflammatory airways from 2 days and malaise, asthenia, palpitations and dizziness after exposure to chemicals during laboratory experimentation.
No previous pathology or chronic therapy.
Non-smoker.
No relevant allergies

Physical examination

Vigilant collaborator, no focal neurological deficits or motor deficits.
Abdomen treatable. Romberg: more pronounced swing to the right. Signs of rhinitis.

Vital parameters

maximum pressure: 130; minimum pressure: 70; heart rate: 75 bpm; SaO_2: 100

Outcome

discharge to home

Diagnosis

rhinitis

Notes and prescriptions

1. Inform the primary care physician
2. temporary refusal from exposure not protected by solvents deemed to be responsible for the symptoms;
3. Inform the prevention and protection service of your membership structure;
4. Visit the occupational health clinic.

A1.2. ER sheet; admittance: 03-12-2003; 3:06 pm • discharge 6:12 pm

ER code: yellow (severe degree)

Anamnesis

dizzying syndrome after solvent exposure

Physical examination

good general conditions, rhythmic cardiac action, no relevant note.

Vital parameters

maximum pressure 110; minimum pressure 70; heart rate: 76 bpm.

Outcome

discharge to home

Diagnosis

dizzying syndrome

Notes and prescription

occupational medicine visit

A1.3. ER sheet; admittance 04-16-2012; 2:28 pm • discharge: 7:52 pm

1. ER Code 2:34 pm: green (mild degree-deferrable)

2. ER code 2:53 pm: white (not urgent)

Anamnesis

She reports that while working under a hood with xylene a few ml of substance (about 2 mL), dripped out from the canister. She experienced generalized malaise and temporary anosmia. Hashimoto thyroiditis and not other noteworthy diseases.

Physical examination

vigilant and eupnoic and collaborative and oriented with indifferent decubitus. Chest MV physiological, not pathological noises. Heart ACR clear tones, free pauses, peripheral pulses present, valid and symmetrical. Abdomen, painless, valid peristalsis, hypocondriac organs not palpable.

Vital parameters

2:28 pm: maximum pressure 110; minimum pressure 70; heart rate 99 bpm; SaO_2 99
4:17 pm: maximum pressure 110, minimum pressure 60; heart rate 85 bpm

Observed in Emergency and Acceptance Department

7.47 pm: The patient is informed of the need to remain in clinical observation for possible admission. The patient refuses to wait for the results of the examinations and eventual hospitalization.

Diagnosis

reported malaise with temporary absence of smell after exposure to xylene.

Outcome

refuses hospitalization

Urgency outcome

green

A1.4. ER sheet; admittance 04-17-2012 6.29 pm • discharge 04-18-2012; 00.55 am

1. ER Code 6.30 pm: green

2. ER Code 8.39 pm: yellow

Agitation and sleepiness

Anamnesis

Patient with Hashimoto thyroiditis treated with Eutirox. Yesterday morning around 10.30 am, contact with xylol-based solvents in the workplace. Denies the possibility of pregnancy in progress. Denies known allergies.
She arrives in ER due to a feeling of discomfort, abdominal discomfort, epigastric pain after caffeine intake, associated with breathing difficulties. Yesterday she was visited in another hospital for temporary loss of smell after contact with xylene.

Contacted Poison control center: ECG-RX chest-dosage parameters of liver and kidney function.

Patient reports state of accentuated agitation while waiting for the exams performed. It is proposed lexotan by os. The patient refuses.

Physical examination
agitated, alert and oriented patient. Valid cardiac tones and free breaks. Not bronchospasm. Hypochondriacal organs within limits.

Vital parameters
6.30 pm: maximum and minimum pressure: not detected, heart rate 110 bpm; SaO_2 98
9.18 pm: maximum pressure 140; minimum pressure 80; heart rate 100 bpm; SaO_2 100

Chest x-ray: normal

ECG: in the standard.

Blood count analysis: normal

Biochemical test: normal

Diagnosis
anxious reaction, reported contact with xylene.

Outcome
discharge to home

Notes and prescriptions
Lexotan 15 gtt on need in case of agitation up to 4 times a day (avoid driving after taking medication). Medical examination for anxiety disorder.

Prognosis
2 days barring any complications

Remarks
Intolerance to arterial sampling in radial artery for blood gas analysis

A1.5. ER sheet admittance 04-20-2012; 2.08 pm • discharge 8.40 pm

1. ER Code 2.10 pm: green

2. ER Code 4.04 pm: green

Anamnesis
In the previous days inhalation of xylene with repeated admittances in the ER. She reports that this morning while she was on duty sitting at her own workstation, a sudden dry cough and, after a few minutes, the appearance of sweating, a feeling of cold [...] after the appearance of dry mouth, difficulty in swallowing and breathing. She drank water and turned to the ER.

Physical examination
glossy, oriented, rhythmic cardiac action, treatable abdomen with peristalsis, no deficit of strength and sensitivity to the limbs, no neck stiffness. Normally transmitted tactile vocale tremor thorax vesicular murmur.

Vital parameters
2.08 pm: max pressure 110; minimum pressure 70; heart rate 90 bpm; SaO_2 98
4.05 pm: max pressure 115; minimum pressure 70; heart rate 88 bpm; SaO_2 100

Request: neurological-psychological-anesthesiological examination

Neurological examination
no relevant note

Psychological visit
[...] the different controls seem not to highlight particular organic problems related to the substance. The emphasis with which she recounts her “illnesses” would seem to point to a somatoform disorder with a significant dose of anxiety. A psychiatric approach is useful after neurological evaluation.

Anesthetic response: ECG, chest X-ray, routine blood tests, EGA. Clinical observation.

Hematoclinic tests: mild microcythemia, slight increase in white blood cells, lymphocytes reduction and mild hypokalemia. She refuses glycosate solution with potassium chloride but accepts KCl tablet

Outcome
discharge to home

Diagnosis
malaise, hypokalemia with suspected inhalation of vapors

Note and prescriptions
potassium and magnesium therapy 3 times/day

A1.6. ER sheet entrance 04-21-2012, 06.17 pm • discharge 04-22-2012, 11.39 pm

ER code: yellow

Notes: strong agitation

Anamnesis: patient reports contamination with toxic substances (xylene) from Monday. It has already been visited at this polyclinic. Subsequently anxiety crisis in the workplace.

Today (Saturday) she returns to ER for anxious state for alleged new contact with toxic substances. Patient suffering from hashimoto thyroiditis on eutirox therapy, denies recent fever. Yesterday in ER she performed both psychiatric and anesthetic evaluation. Normal tests except hypopotassemia. Denies the possibility of pregnancy.

Physical examination
agitated patient. EOG in the standard. Required exams: urgent psychiatric visit and Tac skull

Psychiatric counselling response
accidental exposure to xylene with previous 4 visits to the ER during the week. At the moment it seems that this exposure has not produced significant internal changes, however it has resulted in a condition of high psychic stress characterized by strong anxiety, intense fears of having suffered metabolic damage, an intense and prevalent idea of being able to face irreversible organismic alterations. Given the current condition of the patient, I agreed with her that she remain in observation with our ER; that in the case of negative internalistic objectivity she may leave ER, who in the next few days will contact DH neuropsychology for a finer diagnostic evaluation that fully clarifies the existence or not of neuropsychological deficits. The patient currently refuses anxiolytic therapy proposed for the night; in the case you subsequently accept, I advise administering diazepam 5mg / slow e.v infusion

Skull CT result
examination performed using axial scans in an emergency regime without contrast medium. Not recent endocranial hemorrhages, nor Tc findings of expansive endocranial lesions. Minute hypodensic areolae liquoral lacunar character in the putaminal area probably bilaterally inexact. The ventricular system and the periencephalic liquor spaces are of morphology and amplitude within the limits of the norm.

Outcome
resignation to other facilities

Diagnosis
malaise

Notes and requirements
she was entrusted to her husband.

A1.7. Psychiatric hospitalization; admittance 09-17-2017 • discharge 09-19-2017

Clinical diary

09/18/17
She is admitted in the Psychiatric Diagnosis and Treatment Service in voluntary health treatment, following access to the ER on her own initiative.

09/19/17
quiet, cooperative […]. No evidence of disturbances in thinking, nor alteration of the perceptual sphere. No self or heterolesive ideation in progress.

A1.8. ER sheet; admittance 06-06-2019 4:49 am • discharge 12:56 am

ER code: green

Anamnesis
She comes in ER for palpitations followed by nausea, abdominal pain, diarrhea. Patient with Hashimoto's thyroiditis and gallbladder stones, she follows home therapy with eutirox 100 µg (increased dosage by about 4-5 months after endocrinology). She does not report known allergies to drugs.

Objective examination
vigilant and oriented patient. She complains of nausea. Rhythmic cardiac activity, valid tones, free pauses. Abdomen treatable, painless, painful to palpation at mesogastric level.

Remarks
Watchful, asymptomatic, treatable abdomen, painless, no signs of peritonism.

Outcome
discharge to facilities

Diagnosis
gallbladder stones.

Notes and requirements
deursil 450 µg/die. She is listed for cholecystectomy.

APPENDIX B
Genotyping tests

Results of the case study's tests of advanced molecular diagnostics - Nucleic acid sequencing using MALDI-ToF technology

Test	Result	Reference values / possible genotype
CYP2C9*3 A1075C Polymorphism	Genotype C/A	Homozygous A/A Heterozygous A/C Homozygous C/C
VKORC1 G-1639A Polymorphism	Genotype G/G	Homozygous G/G Heterozygous G/A Homozygous A/A
CYP1A2*1F Polymorphism	Genotype A/A	Homozygous C/C Heterozygous C/A Homozygous A/A
GSTP1 A313G (glutat.S-tran) Polymorphism	Genotype A/G	Homozygous A/A Heterozygous A/G Homozygous G/G
CYP3A4* 1B 392 A>G Polymorphism	Genotype AIA	Homozygous A/A Heterozygous A/G Homozygous G/G
CYP3A5 * 3 6986 A>G Polymorphism	Genotype G/G	Homozygous G/G (*3/*3) Heterozygous G/A (*3/*1) Homozygous A/A (*1/*1)
ABCB1 C3435T Polymorphism	Genotype C/C	Homozygous C/C Heterozygous C/T Homozygous T/T
eNOS3 Glu298Asp Polymorphism	Genotype G/G	Homozygous G/G Heterozygous G/T Homozygous T/T The presence of the T allele results in reduced enzyme activity and consequently increased oxidative damage.
TSER 28bp VNTR Polymorphism	2R/3R	R2/R2 R2/R3 RJ/RJ Most frequent haplotypes in the Caucasian population
ABCC2 C24T Polymorphism	Genotype A/G	Homozygous C/C Heterozygous C/T Homozygous T/T
CYP2C19 Genetic polymorphisms	Genotype: *1/*17 Rapid metabolising phenotype. Enzyme activity increased by 50% or more. This situation leads to more rapid elimination of drugs metabolised by CYP2C19: non-response to treatment is possible. Increase monitoring of concomitant drugs, adverse events, and drug efficacy. Consider appropriate dosage modification, if possible, dose the plasma concentration of the active substance implement alternative treatments	
*17 (-806C>T)	Genotype C/T	
*4 (1A>G)	Genotype A/A	
*2 (19154G>A)	Genotype G/G	
*3 (17948G>A)	Genotype G/G	
*5 (90033C>T)	Genotype C/C	
*10 (1953C>T)	Genotype C/C	
*7 (19294T>A)	Genotype T/T	
"9 (12784G>A)	Genotype G/G	
*8 (1271H>C)	Genotype T/T	
*6 (12748G>A)	Genotype G/G	

Test	Result	Reference values / possible genotype
CYP2D6 Genetic polymorphisms	Genotype: *1/*1 Phenotype: normal metaboliser Normal enzyme activity (probability >95%). Remote possibility that unknown allelic variants not known can alter the metabolism. Use the drug doses recommended by normal clinical practice.	
*2 (2850C>T) *41 (2988G>A) *3 (2549delA) *4 (1846G>A) *6 (1707delT) *9(2615_2617delAAG) *8 (1758C>T) *7 (2935A>C) *1O (100C>T) *2A (-1584C>G) *17 (1023C>T) *29 (1659G>A) *XN (multiple CYP2D6)	Genotype C/C Genotype G/G Genotype A/A Genotype G/G Genotype T/T Ins/Ins Genotype C/C Genotype A/A Genotype C/C Genotype C/C Genotype C/C Genotype G/G Absent	
UGT1A1*28 Polymorphism	Heterozygous	(7 repetitions TA): Normal homozygous 6/6 rip Heterozygous 6/7 rip Mutated Homozygous 7/7 rip
MTHFR - C677T Polymorphism	Genotype C/C	Normal homozygous C/C Heterozygous C/T Mutated Homozygous T/T
MTHFR - A1298C Polymorphism	Genotype A/A	Normal homozygous A/A Heterozygous A/C Mutated Homozygous C/C
APO E Genetic polymorphisms	Present Genotype E2/E3	E2/E2 E2/E3 E2/E4 E3/E3 E3/E4 E4/E4
Factor V Leiden G1691A Polymorphism	Genotype G/G	Normal homozygous G/G Heterozygous G/A Mutated Homozygous A/A
Factor II G20210A Polymorphism	Genotype G/A	Normal homozygous G/G Heterozygous G/A Mutated homozygous A/A
CBS I278T Polymorphism	Genotype T/T	Homozygous T/T Heterozygous T/C Homozygous C/C
DNA or RNA sample storage (DIMA)		
DNA or RNA extraction (DIMA)		
PAI-1 4G/5G Polymorphism	Heterozygous 4G/5G	Homozygous 4G/4G Homozygous 5G/5G Heterozygous 4G/5G
Beta-Fibrinogen G455A Polymorphism	Genotype G/G	Normal homozygous G/G Heterozygous G/A Mutated homozygous A/A

Test	Result	Reference values / possible genotype
MPO G-463A Genetic polymorphism	Genotype A/G	Homozygous G/G Heterozygous G/A Homozygous A/A The presence of the A allele leads to a reduction in enzyme activity and consequent increase in oxidative damage
GSTM1 (glutathione S-Trans.) Polymorphism	Normal genotype	Normal genotype Null genotype
GSTT1 Glutathione S-Trans. Polymorphism	Null genotype	Normal genotype Null genotype
SOD2 Ex2+24T>C rs4880 Polymorphism	Genotype T/T	Homozygous T/T Heterozygous T/V Homozygous V/V**V=C,G or A
CAT C262T Genetic polymorphism	Genotype C/C	Homozygous C/C Heterozygous C/T Homozygous T/T The presence of the T allele leads to a reduction in enzyme activity and consequent increase in oxidative damage
OGG1 C315G Polymorphism	Genotype C/C	Homozygous C/C Heterozygous C/G Homozygous G/G The presence of the G allele leads to a reduction in enzyme activity and consequent increase in oxidative damage
PON1 A575G Genetic polymorphism	Genotype G/G	Homozygous A/A Heterozygous A/G Homozygous G/G The presence of the G allele leads to a reduction in enzyme activity and consequent increase in oxidative damage
PON1 C-108T Genetic polymorphism	Genotype C/C	Homozygous C/C Heterozygous C/T Homozygous T/T The presence of the T allele leads to a reduction in enzyme activity and consequent increase in oxidative damage
DNA mutation analysis (DIMA)		
Metallothionein polymorphisms (MTSN)		
MT1A rs8052394 A>G	Genotype A/A	Probable effect of the polymorphism A/A = Reduced protein functionality with increased risk of heavy metal accumulation A/G =Partial reduction in protein function G/G =Normal protein function
MT1A rs11640851 A>C	Genotype A/A	A/A = Absence of variation of gene expression A/C = Partial reduction of gene expression C/C = Reduction of gene expression with lower protein levels

Test	Result	Reference values / possible genotype
MT1A rs11076161 A>G	Genotype G/G	G/G = Normal protein function G/A = Partial reduction in protein function A/A = Reduced protein functionality with increased risk of heavy metal accumulation
MT1M rs9936741 T>C	Genotype T/T	T/T = Normal protein functionality T/C = Partial reduction in protein functionality C/C = Reduced protein functionality with increased risk of heavy metal accumulation
MT1M rs2270836 G>A	Genotype A/A	G/G = Reduction in protein functionality with increased risk of heavy metal accumulation G/A = Partial reduction in protein functionality A/A = Normal protein functionality
MT2A rs28366003 A>G	Genotype A/A	A/A = No change in gene expression A/G = Partial reduction in gene expression G/G = Decreased transcription efficiency of the gene with increased sensitivity to metals
MT2A rs1610216 A>G	Genotype A/A	A/A = No change in gene expression A/G = Partial reduction in gene expression G/G = Decreased transcription efficiency of the gene with increased sensitivity to metals
MT2A rs10636 C>G	Genotype G/G	G/G= Normal protein functionality G/C = Partial reduction in protein functionality C/C = Reduced protein functionality with increased risk of heavy metal accumulation
Metallothionein expression (MTEX)		Expression values in copies/µL normalised on Beta Actin (Housekeeping gene). 6-month follow-up recommended
MT1A (quantitative analysis) MT2A (quantitative analysis) MT1E (quantitative analysis) MT1F (quantitative analysis) MT1G (quantitative analysis) MT1M (quantitative analysis) MT1X (quantitative analysis)	0,00 copies/µL 2,42E-04 1,73E-04 5,99E-04 1,06E-05 2,31E-04 1,07E-03	Metallothioneins (MT) are proteins with a high affinity for metals. They perform several actions including transport and storage of metals; they participate in the metabolism of essential metals and protect against heavy metal intoxication. MT expression can increase following physiological stimuli and due to exposure to a number of agents, including metals, that activate gene expression. Expression levels of MT-I (1A,1E,1F,1M,1X) and I-I (2A) in the blood can be used as biomarkers of an individual's ability to express MTs in other organs.

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