INTRODUCTION
In the last few years, the studies on gender medicine (GM) have received considerable attention due to the identification of wide and relevant disparities between women and men in human health and disease. In particular, GM focuses on the impact of the gender differences on human physiology, pathophysiology, and clinical features of diseases [1-8]. Although some confusion has occurred with regard to the terms, the gender-sensitive approach includes “sex” and “gender” characteristics, where “gender” refers to those characteristics of women and men that are socially and culturally determined, whereas “sex” refers to biological and physiological differences. Sex (biology) and gender (the social construction of masculinity and femininity) interact constantly and can lead to gender disparities in a number of human diseases in terms of incidence, prognosis, or response to therapy [4, 5]. The GM can be considered a multifaceted field of investigation integrating various aspects of socio-cultural and biological sciences more than the others areas of medicine [2, 9]. However, the gender sensitive approach is starting to acquire relevance in medicine only in recent years [4, 5, 9] and the situation in the area of Occupational Safety and Health (OSH) is even worse [10]. Probably this is due to social and historical differences in the employment of women and men in the labour market. Starting with the Industrial Revolution to modern times, cultural practices, combined with the inertia of the longstanding religious and educational conventions, restricted to entry and participation of women in the paid work. Generally, women were confined to unpaid work, such as the housewife, family and care-giver roles, and men to paid work [11, 12]. Earning women are part of a modern phenomenon that took place during the World War II. In that period, women participation in the workforce was great as many male soldiers were away fighting and the women had to take up jobs to support economy and warfare efforts of their countries. In addition, social changes during the twenty years following the end of World War II had caused the impossibility returning of women to their past working roles and started to seek employment in work market [13]. In the last few years, and before having understood the relationship between health and gender, health promotion policies in the field of OSH have not taken into account the different long-term health effects on woman and men in the workplaces [14]. In every country, OSH laws have traditionally focused on dangerous work performed by men and in rarely cases on women occupied in related types of work. This gender-neutral legislation is often based on the assumption that it would be equally applied to all workers. The exception has been the protective laws prohibiting of certain types of hazardous work during pregnancy.

At the moment, the European Agency for Safety and Health at Work (EU-OSHA) has encouraged a policy of gender equality in all European member states [15, 16]. In Italy, there were already in place some laws that establish principles and fundamental rights in occupational health, safety and in social security but none of these concerns gender approach. Only in 2008, Italy has adopted European provisions with new specific legislation that integrates the previous laws and introduces the gender differences into the workplace. Despite the fact that gender equal legislation opportunities have been enacted in Italy, their application is delayed by some difficulties. This review examines some of these critical aspects.
islation opportunities have been enacted in Italy, their application still has to take place and the approach of OSH is generally gender neutral. In this review we will try to examine some of these critical aspects.

**TOWARD A GENDER-ORIENTED RISK ASSESSMENT**

**Italian laws in the occupational health**

Starting from 1800 many European countries began to introduce in their legislation some rules on safety at work. In 1880, the Italian Agriculture-Industry-Commerce Ministry, publishing statistical data, revealed that 49% of surveyed workers were women, 27% adult males and 24% children. Meanwhile, in many European countries, rules for protection of children and women at work were laid down; in 1902 also in Italy, according to the Law 242, some limits regarding the work of minors and women were fixed; a pillar rule was the introduction of the prohibition to employ mothers before four weeks after childbirth [17]. The key rules of health and safety at workplace were ratified in Italian Constitution in 1948. In the articles number 32, 35, 38, 41, the right to health and safety in the workplace were established as basic rule for everyone; this issue is also included in the Italian Civil Code (art. 2087), but even today, many of these principles are not applied as the laws require [18]. The story of national legislation on occupational health can be divided into three historical periods:

1. from 1865 to 1950, concerning the Civil Code laws;
2. from 1950 to 1980, regarding the provisions enacted to reconcile the demands of change (both in the social realities and industrial policies), with the increasingly demanding of health protection at workplaces;
3. from 1990 to present, Italy has adopted European provisions with new specific legislation that integrates the dynamic involvement of employees in the enterprise security management.

The issue of gender in occupational safety and health was introduced only in 1995 in the “Beijing World Conference” (UN) and then, it was taken up by the International Labour Office (UN agency) in 1999. Other important contributions came by the data of the University of Quebec, on the effects of occupational gender segregation on health.

The adoption of the Framework Directive on the Security and Safety Law (89/391) for European member states represents a breakthrough in the European security view. The Directive introduces basic important concepts such as the obligation to carry out the risk assessment, the attribution of significant responsibilities and duties to the employers and the objective of defining consistent prevention policies for all job categories. The transposition of this directive in Italy resulted in the Decree 626/94 and later in the present Decree 81/08.

This Decree is to be considered as a Consolidated Act, reforming the current legislation regarding occupational health, with the aim of ensuring “uniformity of the protection of women and men workers throughout the country by respecting the basic level of benefits relating to civil and social rights, even with regard to gender differences, age and migrant workers” (art. 1); moreover, it is specified that both the risk assessment and the labor medical reports should take into account “gender differences” (art. 28, 40).

In particular, the Decree declares “to promote the consideration of the gender difference in relation to the risk assessment and the development of preventive measures” (art. 6, let. 1).

Art. 8 defines the institution of the National Information System for Prevention in the Workplace (SINP), aimed to orientation, programming, planning and evaluation of prevention of accidents and occupational diseases. Art.8 also states that SINP has to manage the flow of information related to the prevention, taking into account (let. b and c art. 8) “the risk framework also from a gender perspective and health framework and safety of male and female workers”.

**Risk assessment process**

The adoption of the directive on security and safety implicate the prevention of occupational hazards and risks. The directive 89/391/CEE introduces as a duty for the employer the development of a document assessing the work-related risks; the employer also decides the protective measures to be taken and provides documents regarding accidents recording and analysis (art. 9). The directive transposing in the national legislation of the member states of the European Union leads to a sufficiently uniform policy on the OSH topic. The central point of this common vision is the Risk Assessment process. The analysis of the operational documentation and of the national legislation allows to produce a synthetic “conceptual map” (Figure 1). The map helps the employer and the workers approaching to the OSH topic [19].

The approach to OSH imply three phases: i) hazard identification; ii) risk assessment; iii) actions and procedures to minimize risk.

i) Hazard identification is a process involving the acknowledgement that a hazard exists and that the description of its characteristic is available [20]. A hazard is any situation, substance, activity, event or environment that could potentially cause injury or occupational disease. In this first step it is important to identify every single hazard, through the development of an organizational model, which emphasizes the most relevant processes for the OSH. France has mapped all the so called “unités de travail” [21] on its territory; they are defined as “homogeneous groups of hazard situations”, are not necessarily workplace-related (activities, tasks) but are conditions shared by one or more workers.

ii) Risk assessment considers the effectiveness of existing OSH controls and then evaluates the probability and the potential severity of specific hazardous events and exposures. On the basis of such an assessment, an enterprise decides whether or not the risk is acceptable.

It is important to understand that the concept of “risk assessment” demands the answer to two future-oriented questions: 1) What is the probability that a particular hazardous event or exposure will actually occur in the future? 2) How severe would the impact on health and safety be, if the hazardous event or exposure actually occurred?
An event or an exposure is labeled as “high risk” if it is likely to cause severe injury or ill conditions.

The risk assessment is a qualitative-quantitative process, composed by the “risk measurement” and the “risk evaluation” processes [22]. At the end of the process, it is possible to assign priorities at measures to subsequently realize.

iii) Measures consist in actions, controls and procedures, including the provision of information, education and training. Information should also concern the best practices in the workplace, the emergency procedures and the use of special protective equipments. Finally, OSH practice includes health surveillance of workers. Every measure is assigned to suitable staff and its effectiveness on the risk reduction has to be monitored, since each action, control or procedure, is aimed to produce a benefit. Benefits are possible in the prevention standpoint (reduction of hazard probability) and/or in the protection one (reduction of hazard severity).

Each of the phases of the OSH process described above requires the completion of the previous step (and demands for the subsequent one).

In the above described overview, the “gender issue” cannot be considered in a specific phase of the process, as it is pointed out in the Italian work legislative regulation (D.Lgs.81/08). Issues regarding gender are present in the information flows, which can influence the hazard identification phase; moreover, the potential severity on an hazard may differ from male to female and the risk assessment could include these evaluations. Therefore, the gender information is included in the aggregated data flows in the health surveillance process.

In conclusion, the “gender issue” is a cross element in OSH, lowering the hazard aggregation degree by doubling the “homogeneous group of hazard situations” that an enterprise has to take into account.

WORK-RELATED RISKS: ARE MEN AND WOMEN EXPOSED TO THE SAME RISKS?

As previously mentioned, the health promotion policies in the workplaces have not taken into account the different long-term health effects on both sexes. The participation of women at the workforce has significantly increased in the last years and European guidelines suggest the inclusion of the gender issue in the OSH flows [15, 16, 23, 24]. The initial efforts to address gender bias in occupational area were based primarily on social inequalities. Probably, this attitude was conditioned by the numerous studies that have linked discrimination at the workplace with the effects on health [25]. Consequently, occupational studies about women have been focused on gender inequalities, work organization hazards and psychosocial stressors, with a deficit in toxicological and physiological studies. Consequently, there are only a few studies that have analyzed sex susceptibility to the same hazardous substances and biological agents. It is therefore in need of new scientific approaches about gender differences at workplace to design appropriate intervention strategies to the prevention of chemical and biological work-related risks. Regard to these two fields of intervention, the OSH should take into account the diversity among female and male workers related to both biological (sex) and socio-economic differences (gender). Hereinafter a brief summary of current knowledge in the area of OSH will be reported.

The socio-cultural differences (gender differences)

The socio-cultural differences are a complex subject that implies knowledge of political and social sectors, which are outside the discussion of this text. Nevertheless, some considerations must be done to define the risk assessment in a gender perspective.

Occupational segregation and work related risks

In the design of all risk management strategies and their implementation in the workplace the characteristics of both female and male jobs, the specific features of the jobs (who does what, when, how and for how long), the different responsibilities that women and
Gender issues on occupational safety and health

Men have at workplace should be considered. How we will see later, these gender inequalities could influence the hazard identification phase and cause confusion regard to the risk assessment. Actually, there is strong segregation of women and men into different jobs and tasks. Unequal distribution of jobs is one of key factors on gender differences when observing the exposure to occupational hazards, accidents and diseases. Consideration should be given to exposure level of hazards that change according to different jobs sectors and tasks as well as to number of hours worked [25]. Socio-economic and cultural factors, as well as gender stereotypes, have affected occupational segregation, which is the underlying reason for so many gender inequalities [26]. Gender stereotypes have restricted women and men in “feminized and masculinized” sectors of activity (horizontal segregation). This is also true where women and men have the same job, but perform different tasks [27]. In addition, men are more likely to work in jobs higher up in the occupational hierarchy than women (vertical segregation) [25, 28]. Hence gender segregation at the same workplace strongly contributes to an unequal distribution of working conditions and exposure to different physical and psychological risks between sexes also in the same workplace. Generally, men are exposed to longer working hours, physically demanding work, noise, and have higher job status role. Men are more likely to work in management and manual and technical jobs associated with machinery or plant operations [28]. Men are exposed to noise to a much higher degree due to the activities in the heavy industry such as mining, shipbuilding, and metal works together with the agriculture sectors [29, 30]. Women are also likely to have part-time or temporary contracts more than men [25]. In addition, vertical segregation places women in the lowest positions excluding them from the decision making process. [15, 16, 28]. Women are more likely to work in jobs involving child and frail care, private and public service activities, or for small firms and manufacturing industries. Job segregation strongly contributes to different hazards exposure and consequently to different health outcomes. Examples of these could include skin diseases that women suffer when working with wet hands and the chemical cleaning and sterilizing agents as well as protective gloves containing latex dust. Asthma and allergies appear to be more common among women than men [31, 32]. Other sources of respiratory hazards in female jobs include dusts in textile and clothing manufacture. In care work, catering, private and public service activities and education sector, women are more exposed to infectious diseases than men [33].

Musculoskeletal disorders are the most common work-related health problems for both women and men and they are on the increase in European member states [16]. Several studies have also reported male-female differences in the prevalence of symptoms of work-related musculoskeletal disorders, some arising from workplace exposure differences [34].

Musculoskeletal disorders can affect workers in all sectors but an additional risk factor for many women is the use of tools and equipment not always designed for the female work population [35]. Across the world, work equipment, tools and personal protective equipment (PPE), have been traditionally designed for the male body size. As a result, not only women, but also many men try problems finding suitable and comfortable PPE because they do not conform to standard male worker model. Uncomfortable work equipment and tools can lead to poor working posture, leading to an increased risk of musculoskeletal disorders. These can occur in relation to exposure to poor ergonomic conditions in both women and men [36-38].

Work-related stress

Both women and men report high levels of work-related stress but there are certain stressors to which women are more likely to be exposed due to social aspects because of the jobs they typically do. Some causes of work-related stress are known as stress women are as well as women are more exposed to specific stressor [39]. Generally, work-related stress is due to the type of work, position in the hierarchy, horizontal and vertical discrimination; sexual harassment and the situation outside of work [40]. Another social aspect far from being ignored, regards the greater proportion of unpaid work carried primarily out by women (especially at home) [12]. In addition, when paid and unpaid work are added together, women are seen to work longer hours than men. This puts extra pressure on many women workers [39, 41]. Women may be excessively exposed to work-related stress due to job segregation and their increased caring and home responsibilities.

Although the reactions to the same psychological exposures may vary between individuals, stress can be linked to a number of mental and physical effects [30, 41, 42]. It is known that stress raises blood pressure and increases the risk of heart disease [41], it can also weaken the immune system making all more vulnerable to illness. It can cause depression and even lead to suicide. In addition, stress can increase drinking or smoking as well as reduce the attention during specific working phases and increasing the risk of a potential hazard. According to available scientific evidence, the work-related stress can be dealt with as other occupational health and safety issues, adapting the control cycle already well established for the assessment and management of physical risks [16].

The biological differences (sex differences)

During the last few decades of the twentieth century, GM studies saw the development of a growing awareness that the physiology as well as the same diseases were significantly different for men and women [6-9, 43, 44]. Nevertheless, differences between sexes due to anatomy, physiology, biochemistry and toxicology have not received adequate attention in OSH. It has only recently been defined that gender-related biological differences may result in differential vulnerability of women and men to physical workplace factors such as hazardous substances and biological agents [29, 34, 45-47]. To date, many studies, on which much of our understanding of occupational risk is based, have been performed on men excluding women [5]. For many years,
Food and Drug Administration guidelines specifically precluded participation of women in many toxicological studies [48]. Currently, it is believed that women and men differ in many aspects of biological vulnerability to occupational hazards. This section provides a brief survey on biological differences between women and men in their exposure to occupational chemicals.

**Occupational chemical exposure and physiological differences between sexes**

Chemicals may carry out variable toxic action according to the amount absorbed by the body (or Body Burden) [49]. Toxicological studies have defined the level to which it is believed a worker can be exposed day after day for a working lifetime without adverse health effects. This level is named threshold limit value (TLV). However, TLV has been calculated on men [50] and few studies have measured exposure for men and women in the same occupational setting. Generally, chemical susceptibility varies depending how quickly and efficiently toxic agent is metabolized. Regarding to chemical susceptibility, some biological differences between sexes could play roles in the real risk associated with occupational exposure [46, 47, 51]. There are various ways of classifying biological differences between sexes regarding to occupational exposure to toxic agents: they can be broken down into: i) body size and composition; ii) genetic-molecular-biochemical and iii) hormonal.

The most obvious are the anthropometric differences between sexes according to muscle mass, fatty tissue, and bone mass. Especially adipose tissue may make women more susceptible to substances that accumulate in fat, such as organic solvents (e.g. benzene and trichloroethylene and so on all the liposoluble substances). They have been identified a number of chemical agents for which the body burden is different in women and men even when they carry out the same job [49]. Generally, the relationship between exposure dose, absorbed dose and effective dose of chemical agents is complex and depending on various factors that are studied by pharmacokinetics or toxicokinetics. Generally, chemical susceptibility varies depending how quickly and efficiently toxic agent is metabolized. The four different phases of the toxicokinetic are all subject to sex differences [45, 46, 53]. These are the 1) absorption across the body barriers (e.g., skin and hair), 2) the distribution into the body 3) the metabolism and 4) the excretion.

Absorption probably differs between women and men due to the condition of the skin (with or without cosmetics), number of hair follicles, breathing rates and respiratory volume. Absorption of chemicals from the stomach is affected by gastrointestinal motility that in turn is influenced by sex hormones. Stomach transit time may also change throughout phase of the menstrual cycle in women [53]. In addition to the higher body fat composition, women have a lower average body weight, smaller plasma volume and lower average organ blood flow than men. All together these factors affect the extent of distribution of the chemical into the body compartments [46, 53]. However, the greater role in toxicokinetic variability is played by differences in xenobiotic metabolism [45, 46, 53]. Primarily these reflect the differences in gene expression for enzymes of the CYP450 superfamily, the major family of enzymes involved in the metabolism of chemical agents. Sex-based variance in the expression and activity of CYP isoenzymes have been reported in different studies [45, 46, 53]. In addition, CYP450 activity is also modulated by hormones [45]. Finally, renal excretion of compounds is higher in men than women [45, 46, 53].

It is clear that the limits defined by TLV should be monitored according to gender differences, in order to determine appropriate procedures in OSH. It should also be emphasized that over one-third of the agents classified by the International Agency for Research on Cancer (IARC) as certain or probable human carcinogens, have been identified from studies of workplace exposure. These studies are predominantly performed on men and not sufficient to describe risks among women [54-56]. Occupational cancers among women, as well as men, are largely preventable. Future studies should incorporate analyzes that account for biological measures of susceptibility for sexes because of potential gender differences in body size, work tasks and physiology.

Hormonal influences, such as menstruation, pregnancy, lactation and menopause can be important physiological determinants of the biologically active dose [57]. Analyses comparing exposure to disease risk should consider biological time windows of exposure, especially those related to hormonal changes. Some studies indicate that timing of exposure has an important impact on risk [49]. Hormonal variability also occurs in men and variation within a sex over time can sometimes exceed average sex differences [58]. An emblematic example is related to the effect of gender on lung capacity and sensitivity to asthmatic attacks. At all ages, it is possible to recognize differences depending on hormonal changes [31, 32, 59-61]. Men are highly sensitive in prepubescent age while women become more sensitive in post pubertal age. This condition continues until menopause. Epidemiologic studies have shown that sensitivity to asthmatic attacks increases in the premenstrual phase and airway reactivity to allergens and irritants varies over time and with hormones [60, 61]. These differences could make women more susceptible than men to occupational asthma and indicate the need for additional prevention measures during the premenstrual phase (e.g. particular PPE).

**Epidemiologic data**

This latter topic allows us to introduce other critical points regarding to the neutral risk assessment. Epidemiologic studies are an important tool that should help us to identify risk factors for disease in accordance to evidence-based practice. Consequently, the collected data could help to identify the targets for preventive healthcare. Unfortunately, in many occupational studies, the epidemiological data are affected by the gender bias since they were not collected as a sex-disaggregated data. Sex-disaggregated data reflects roles, real situations, general conditions of women and men in different contexts. Occupational segregation without sex-disaggregated data analysis could reduce the development of effective
policies related to OSH as it is more difficult to identify hazards and risks specifically affecting each sex. Many collected epidemiological data on employment may not fully represent female and male workers. For example, death certificates and other routinely collected administrative data may be of poorer quality for women than for men. For example, the labor of “housewife” is often entered on death certificates of women, even when they were employed outside the home for long time and especially among older women who are retired at the time of death [62]. In addition, it seems even more difficult to trace the job of married women due to name changes. All together this data may be confounders. Gender discrimination could also influence the collection of useful data. For example, special attention has always been given to women exposed to chemicals that could be hazardous to their reproductive health while this has been little emphasized in men, although many chemical agents could also damage the sperm production and motility.

CONCLUSION

In the last years, the EU-OSHA has promoted a policy of gender equality in all European member states. Gender inequalities in occupational health can be related to both socio-cultural (gender differences) and biological differences (sex differences). At present, it seems very difficult to develop standardized methods of gender risks assessment and security managers are confused. In this article we have described some critical points that can be reasons of this disorientation. To overcome confusion and create strategies that take into account the gender differences in OSH it will be necessary to face some aspects in order to implement a correct prevention strategy. In this section we summarize some biological aspects that we believe to be crucial in OSH strategies.

It is essential to evaluate occupational risks in women and men separately, therefore changing the concept of homogeneous groups of hazard. The management of diversity in the workplace requires measures, directed at specific risks faced by women and men. In reality, measurements of occupational exposure on women are rare. New methods are needed to establish a relationship between the risk factor for women and the occupational exposure. To examine environmental interactions at the workplace, the analysis of susceptibility should be performed taking in account occupational exposure related to hormonal time frames. In particular, it should draw attention to recognized biological differences between women and men to ensure they are equally protected in the workplace. Risks related to the reproductive health should be evaluated in workers, both women and men, to prevent any exposure that could be hazardous to their health. The inclusion of women and men in sector studies should be proposed to investigate other aspects of biological vulnerability. Additionally, standardized interviews on the wellbeing at work place could also be undertaken. Studies on occupational exposure should encompass a significant proportion of atypical workers that have not been in employment for long time, namely women being the most important category. Developing a comprehensive picture of the role of gender in occupational health will require a close interaction between gender medical studies and occupational epidemiological information. In this regard, there is still a need to improve gender sensitivity in collecting and analyzing data in sex-disaggregated manner on occupational injuries and diseases. Finally, to plan, monitor and evaluate the impacts of preventive measures and policies related to OSH, the health gap between men and women at work should be overcome by utilizing the collection, management and analysis of sex-disaggregated data.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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