

BACKGROUND

PREMESSA

Congenital anomalies (CAs), also known as congenital malformations or birth defects, can be defined as functional or structural anomalies that occur during intrauterine life. It is estimated that each year 8 million babies – 6% of total births worldwide – are born with a severe congenital birth defect. At least 3.3 millions of children aged 0 to 5 years die as a consequence of severe birth defects and each year approximately 300,000 newborns with a diagnosis of birth defect die within the first 28 days of life.¹⁻³ In the United States, where over 3.0% of live births present with a congenital defect, CAs represent the leading cause of paediatric hospitalization and infant mortality.⁴ In Europe, CAs are the leading cause of perinatal mortality: the European Surveillance of Congenital Anomalies (EUROCAT) network estimated a perinatal mortality associated with CAs of 9.2 per 10,000 births in 2008-2012.⁵ The live birth prevalence of CAs does not represent the total CAs prevalence. It is necessary to consider all the cases that do not result in birth in relation to the premature death of the malformed foetus (spontaneous abortion) and therapeutic abortions. In 2010, in Europe, there were 49.16 per 10,000 births recorded as termination of pregnancy following prenatal diagnosis of CA, as reported by EUROCAT surveillance system.⁶ In summary, CAs are considered a major cause of foetal death, infant mortality and morbidity, and long-term disability. CAs are diseases with high impact on the affected individuals, on their families, and on the community in terms of quality of life and healthcare service needs.⁷ As a consequence, CAs represent a significant public health issue and an efficacy primary prevention strategy should be a priority for public policies and healthcare system. CAs vary widely in severity, organs affected, and aetiopathogenesis. The causes of many CAs are complex and multifactorial, but in most cases their aetiology remains unknown. Most CAs are caused by complex gene-environment interactions, mainly still unknown. It is estimated that about 20% of all CAs are due to gene-chromosomal causes, another 10% to exogenous factors, and the remaining 70% to interactions between the two factors.^{8,9} Although genetic factors play an important role, some congenital

anomalies might be preventable through interventions addressed to reduce environmental exposures. Environmental factors (such as chemical toxicants, infection agents, maternal diseases, and exogenous factors) can have mutagenic effects before conception, teratogenic effects, endocrine disruption, and epigenetic action. According to the World Health Organization (WHO), approximately 5% (ranging from 1% to 10%) of CAs are attributable to environmental exposures. Genetic causes are attributable to genetic-chromosomal aberration or dysgenesis.⁸ Pregnant women and their foetuses may be exposed to multiple contaminants present in environmental matrices (water, soil, air) in the living and working environment, as well as to numerous lifestyle risk factors and socioeconomic determinants.^{7,10} Epidemiological studies suggested associations with CAs of various types of environmental exposure, such as air pollutants, cigarette smoke, pesticides, solvents, metals, radiations, contaminants, and chemicals.¹¹⁻¹⁵

The main mechanisms of action of exposure to chemical pollutants are DNA methylation,^{16,17} oxidative stress,^{18,19} inflammatory processes,^{20,21} and epigenetic mechanisms.^{22,23}

Harmful nicotine and other chemicals in cigarettes have teratogenic and carcinogenic effects on human germ cells and are known to have adverse effects on the development of the embryo, especially during organogenesis.^{24,25} Alcohol may enhance the formation of oxygen free radical by inducing apoptosis and modify growth factors by inhibiting or stimulating cell proliferation.²⁶

A previous literature review including CAs (carried out on articles published from 1998 to 2009) had been performed by Pirastu et al.,²⁷ in the framework of the SENTIERI project (the Italian Epidemiological Study of Residents in National Priority Contaminated Sites).²⁸

The aim of the present study was to make available a literature review of the recent epidemiological evidence on the risk of CAs associated with environmental and individual exposures.

Since we addressed a very wide topic, namely all CAs associated to many kind of exposure, a non-systematic review was performed.