

**DISCUSSION AND CONCLUSIONS**  
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# DISCUSSION

## DISCUSSIONE

**E**pidemiological studies, as well as experimental studies, are providing a growing amount of information for recognized or potential risk factors for single or groups of CAs and are useful to generate hypotheses for future research investigating the relationship between environmental exposures and the development of birth defects.

Currently, there is no unified monitoring system for birth defects worldwide. Information on the prevalence of CAs come from birth certificates and from State birth defects monitoring systems. CA prevalence data come from population-based registries of CAs, which are the most reliable sources. CA registries are tools used to identify genetic and teratogenic exposures, as well as evaluating and planning health care services and prevention policies.<sup>127,128</sup> In Europe, the European Joint Action EUROCAT considered CA registries an effective tools for epidemiological assessments in polluted areas.<sup>129</sup> Moreover, primary prevention of CAs in the population based on controlling environmental risk factors is a crucial policy priority, including preconceptional care and whole population approaches. An updated on the state of the art on prevention of CAs has recently been published by a EUROCAT and EUROPLAN working group.<sup>130</sup>

### ENVIRONMENTAL EXPOSURES ESPOSIZIONI AMBIENTALI

#### Industries / Industrie

The epidemiological evidence collected in this review on the association between industrial sources of prenatal exposure and the increased risk of CAs are still limited, as few analytic epidemiological studies have been performed and most of these studies have used an ecological design unable to infer a causal relationship. The ecological design does not allow the exploration of possible individual confounders related to maternal and paternal risk factors. Another limitation that needs to be considered in the interpretation of the results is that evaluating health impact in industrially polluted areas is a very complex process due to the multiple and heterogeneous sources of pollution, the role of non-environmental risk co-factors and the multifactorial aetiology of CAs. Finally, the CA prevalence estimates are highly variable across the different registries due to different diagnostic practices and methods of gathering and coding data. Another important consideration is that the risk estimate may be underestimated since, in several studies, cases were ascertained only in live births. Despite these limitations, slight associations

of CAs as a group among offspring to mothers living in proximity to industrial activities – such as chemical, petrochemical, steel and power plants, and ports – were detected. Based on scientific literature, the evidence of association in relation to selected CA subgroups is still inadequate, although the potential teratogenic effect of chlorinated solvents, especially on CHDs and NTDs, have already been reported, suggesting a relationship between maternal occupational exposure to specific chlorinated solvents and the development of birth defects.<sup>110</sup> An excess for genital defects, namely cryptorchidism and hypospadias, were observed suggesting a correlation with the presence of petrochemical plants.<sup>131</sup> In the literature, there is already evidence of the harmful effects of hydrocarbon exposure on spermatogenesis,<sup>132</sup> including reduced sperm mobility<sup>133</sup> and sperm chromosome abnormalities.<sup>134</sup> The hypothesis of cumulative effects to multiple low-dose environmental risk factors exposure with a prevalent endocrine disruptor effect is currently proposed.<sup>135</sup>

#### Mines / Miniere

Due to sparse epidemiological data collected in the examined period, evidence on the association between maternal residential proximity to mines and the risk of CAs as a group in offspring is inadequate. In addition, the current epidemiological evidence on the causal relationship between residential exposure and increased risk of specific subgroups is inadequate, both due to the limited number of studies and to the ecological approach being unable to estimate individual exposure to specific categories of pollutants. Extraction activities of shale gas with surface techniques are uniquely practiced in the United States, where, according to estimates, 15 millions of Americans live within one mile from unconventional natural gas extraction wells.<sup>136</sup> During 1982-2005, surface mining activities in West Virginia have been increased from 19% up to 42%,<sup>137</sup> while the International Energy Agency reports that unconventional gas production accounts for 18% of gas production.<sup>138</sup> Fracking operations are accountable for the release of BTEX (benzene, toluene, ethylbenzene, xylene), PHA (polyhydroxyalkanoates), volatile organic compounds, ozone, suspended particulate, sulphur and nitrate oxides, and heavy metals seeping into the groundwater.<sup>139-141</sup> Hence, geographic specificity should be addressed by future research assessing the relationship of exposure over time, in addition to adopting surveillance programmes or analytical study designs.

#### Landfills / Discariche

Two reviews concluded that epidemiological evidence on associations between both total CA and selected subtypes, such as

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CHDs, NTDs, hypospadias, and skin disorders, and the maternal residential proximity to industrial or hazardous waste land-fill sites are still to be considered limited. Though several multiple-site studies supported a plausible linkage between residence near waste disposal sites and adverse reproductive effects, literature investigating links between land contamination and CA risk often provides no consistent results.

Moreover, just recently, a systematic review evaluated the causal relationship between exposure to hazardous waste and risk of CAs, overall and for specific subgroups (i.e., urogenital, connective and musculoskeletal system and neural tube anomalies), as limited.<sup>142</sup> In the Provinces of Naples and Caserta (Southern Italy), illegal toxic waste disposal is responsible for emissions of dioxins, furans, and polychlorinated biphenyls, but the body of evidence is still inadequate and only slight associations for urogenital system and CNS defects alone were detected.

The difficulty in exactly identifying waste arrangement and locating illegal waste dumping implies that the population at risk is hard to identify. Low-dose exposures affect the relative risk in small increments that are difficult to distinguish from the ones introduced by confounding factors.

Overall, the wide geographical and demographic dimension of these areas, the heterogeneity of the sources of exposure, and the limitation due to the ecological design need to be considered in the interpretation of the results.

### Incinerators / Inceneritori

The evidence of a causal relation between residential proximity to incinerators and increased CA risk is still inadequate. Most of the epidemiological studies used an ecological approach based on the distance from the source of emissions or on the exposure to incinerators estimated with dispersion models, but none of the studies included biomonitoring data able to validate the exposure models. Experimental data show that dioxins are highly lipophilic and they partition preferentially in adipose tissue.<sup>143</sup> Overall, in the field of environmental causes of CAs, evidence is often limited or inadequate. Epidemiological studies are hard to compare since they often differ in the type of population (total births including foetal deaths, stillbirths, pregnancy termination, or only live births), the source of data, and the considered confounding factors.

Therefore, future studies should try to adhere to very strict standards in order to avoid underestimation of the risk estimates.

## INDIVIDUAL EXPOSURES ESPOSIZIONI INDIVIDUALI

### Cigarette smoke / Fumo

The analysed literature provides sufficient evidence that maternal smoking is associated with increased risk of CHDs among offspring, in particular for septal defects and right ventricular outflow tract obstruction (RVOTO), especially in the case of maternal exposure before and after conception. Smoking was a

significant risk factor even considering potential confounding factors. The calculated pooled risk estimates were homogeneous, despite studies conducted in different geographical areas and on women with different lifestyles factors may influence the prevalence of CHDs. The association between maternal smoking in pregnancy and the risk of CHDs in the foetus had already been demonstrated by previous work.<sup>144,145</sup>

Pooled analyses showed evidence of significant association between maternal smoking exposure during pregnancy and orofacial clefts, NTDs, and gastrointestinal anomalies, above all, when women smoke in the periconceptional period and in the first trimester of pregnancy. Smoking was also a significant risk factor for less severe CAs, such as cryptorchidism. These results further support public health recommendations to completely abstain from smoking both before and during pregnancy.

### Alcohol / Alcol

The use of alcohol during pregnancy can lead to multiple health and social problems for both the mother and the child. High alcohol consumption among pregnant women can cause life-long disabilities in the offspring known as foetal alcohol spectrum disorder, together with other adverse pregnancy outcomes.

The Action plan for the prevention and control of non-communicable diseases in the WHO European Region addresses alcohol use and aims to prevent alcohol exposure during pregnancy. Recently, the WHO published a report to give an overview of the literature on interventions to prevent alcohol exposure during pregnancy addressed to pregnant and non-pregnant women.<sup>146,147</sup>

However, collected evidence regarding CAs and maternal mild-to-moderate alcohol consumption during pregnancy is considered too limited to show a causal association. In particular, while the evidence of an association between mild-to-moderate alcohol intake and risk of CHDs is weak, there is more persuasive evidence of the harmful effect of high levels of alcohol consumed either on weekly bases or on a single binge drinking occasion. As to other specific CA subtypes, it appears that anomalies in the nervous system, particularly anencephaly and spina bifida, are more likely to occur in association with high levels of alcohol consumption both on a constant consumption and on binge drinking occasion during the first trimester of pregnancy. However, the statistical analysis of the data collected in this review confirms the association between alcohol consumption and age, smoke, and SES, strengthening its use as a confounding factor.

### Socioeconomic status / Livello socioeconomico

To date, few studies have evaluated if socioeconomic inequalities could be associated with the risk of CAs, as the epidemiological evidence of associations between SES and CAs are still limited. In particular, findings suggest that the risk of CAs increases in the most disadvantaged classes. An important consideration is that lower socioeconomic status is associated with health-damaging lifestyles, such as heavy smoking, increased alcohol consumption, and poor health care.

### **Occupational exposure /** Esposizione occupazionale

Concerning occupational exposure, the epidemiological studies collected in this review were suggestive of an association between NTDs and paternal exposures to solvents, although they are not strong enough to infer a causal relationship, as well as between maternal exposure to pesticides and increased risk of oro-facial clefts among offspring.

Conversely, evidence of association between maternal and paternal exposure to pesticides and urogenital defects, such as cryptorchidism and hypospadias, are to be considered inadequate; the evidence of causal relation between occupational exposure of both parental to chemical agents or PAH and increased risk of selected CAs is also inadequate.

In conclusion, even if the evidence is still limited or inadequate, pregnant women at work must be protected from teratogenic exposure as pesticides and organic solvent. This issue should be addressed in occupation health policies.<sup>130</sup>

### **Air pollution /** Inquinamento atmosferico

A limited number of studies investigated the causal relation between birth defects and prenatal exposure to air pollution, specifically CO, O<sub>3</sub>, PM<sub>10</sub> and PM<sub>2.5</sub>, NO<sub>2</sub>, and SO<sub>2</sub>. Most of these analytical epidemiological studies have focused on cardiac and oral cleft birth defects; for cardiac defects, only a slight association was detected, for oral cleft defects no evidence was identified. Anyway, evidence of a positive association between specific CHDs and maternal exposure to high concentrations of NO<sub>2</sub> and SO<sub>2</sub> has been reported in a recent pooled analysis. However, inconsistencies and uncertainties concerning the effects of specific pollutants and pollutant mixtures and critical exposure periods remain. In particular, the major limitations of air pollution studies are exposure misclassification, low statistical power, and unmeasured confounding. Further studies which include more accurate exposure assessment and spatial analyses, better case ascertainment, and adjustment for a large number of potentially confounding effects are needed.

## CONCLUSIONS

### CONCLUSIONI

In conclusion, despite a growing number of studies suggests a link between CAs and specific environmental contaminants and individual risk factors, such association appears to be limited to some birth defect subgroups. Furthermore, environmental epidemiology suffers from limitations leading to inadequate or contrasting results: since most diseases are “rare” in populations, a large number of individuals have to be observed

for a long-time period to identify a potential determinant, and studies carried out in small communities for a limited number of years lack statistical power. Hence, improved exposure assessment methods – in particular more accurate spatial measurements or modelling – standardized definition of cases, a more accurate control of the main or putative confounders, and a larger sample size are highly recommended for future epidemiological studies.