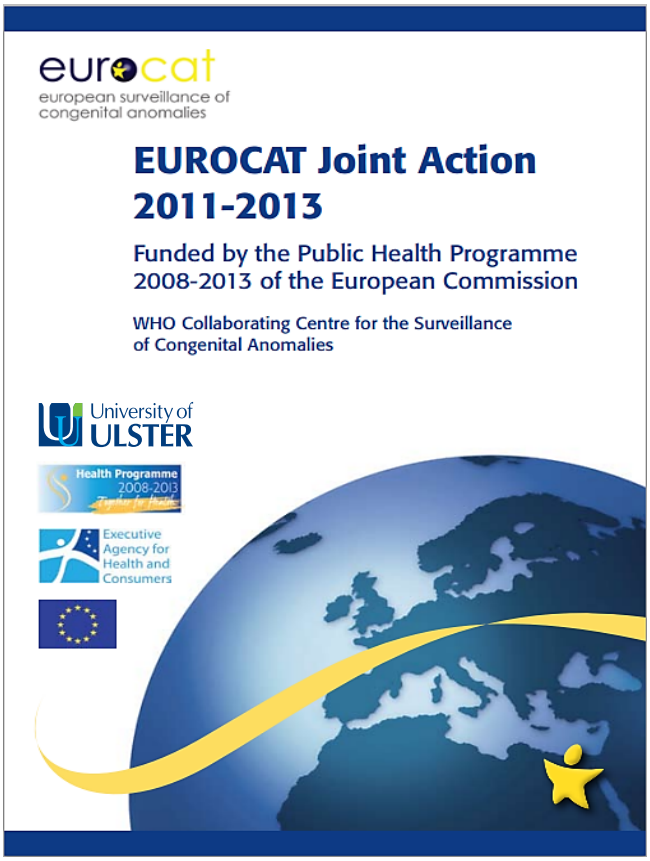
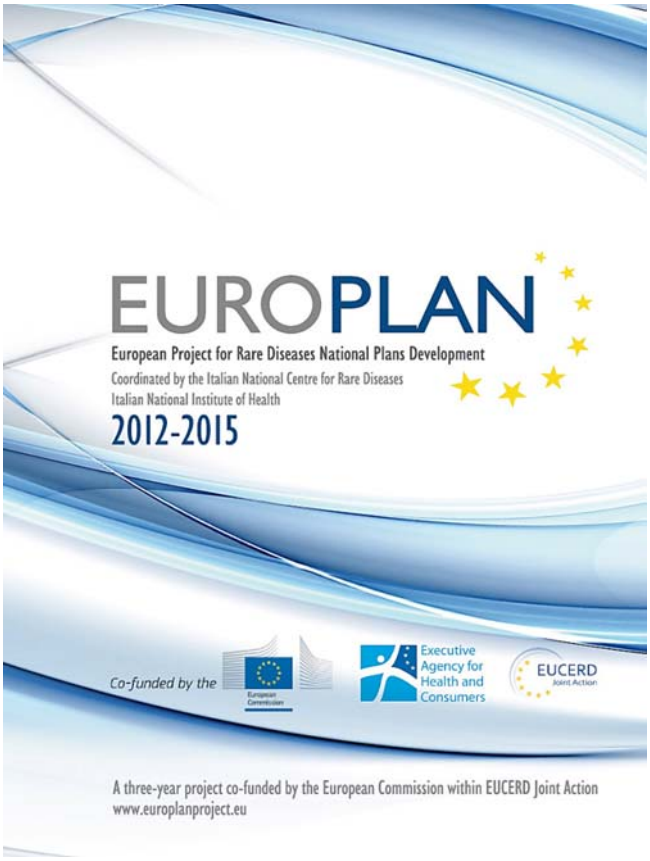
PRIMARY PREVENTION OF CONGENITAL ANOMALIES

EUROCAT (European Surveillance of Congenital Anomalies) and
EUROPLAN (European Project for Rare Diseases National Plans Development)

Recommendations on policies to be considered for the primary prevention of congenital anomalies in National Plans and Strategies on Rare Diseases





Grant No: 2010 22 04

www.eurocat-network.eu

Grant No: 2011 22 01

www.europlanproject.eu

PRIMARY PREVENTION OF CONGENITAL ANOMALIES

EUROCAT (European Surveillance of Congenital Anomalies)/EUROPLAN Recommendations on policies to be considered for the primary prevention of congenital anomalies in National Plans and Strategies on Rare Diseases

Purpose of the Recommendations

Most congenital anomalies are rare and form an important group of Rare Diseases, for which EU Member States are developing National Plans. Primary prevention of congenital anomalies was identified as an important action in the field of Rare Diseases in the Communication from the Commission to the European Parliament, the Council, the European economic and social committee and the committee of the regions of 11th November 2008. However, it has not been included in the Council Recommendation on an action in the field of rare diseases of 8th June 2009. This document aims at providing an outline of evidence-based policy actions for primary prevention of congenital anomalies. It does not seek to recommend specific policy options, rather to indicate the areas that Member States could target in their strategies for Primary Prevention of congenital anomalies. EUROPLAN(1) will support and facilitate Member States to incorporate the recommendations specified here in their National Plans, and will facilitate exchange of experience among Member States, in collaboration with EUROCAT(2).

The causes of congenital anomalies can be environmental, genetic or an interaction involving both genes and environment(3). Within the scope of this document, primary prevention includes any evidence-based action aimed at reducing environmental risk factors for congenital anomalies and increasing protective environmental factors. Such factors act in the periconceptional period, most often before the pregnancy has been confirmed. Whereas actions based on the precautionary principle fall mainly outside the scope of this document, in some cases precautionary actions have been quoted when may bear significant public health and/or social benefits. Primary prevention also includes preconceptional counselling concerning genetic risk, but does not include preimplantation diagnosis.

Primary prevention of congenital anomalies includes factors that are common to other diseases as well as factors specific to congenital anomalies. Policies aimed at promoting safer foods and environment, healthy dietary habits and lifestyles as well as reducing the health impact of chronic diseases are expected to reduce the prevalence of congenital anomalies as well as many other diseases. However, elaboration of these policies needs to pay special attention to their relevance in the pre- and periconceptional period.

Rather than pinpointing specific actions, which may have a limited impact in isolation, it is advisable that Member States would integrate the different recommendations within a strategy for Primary Prevention.

The Scope of Policy Actions Needed for Primary Prevention of Congenital Anomalies

In the field of medicinal drugs

- to advise women taking medication to seek medical advice before trying to get pregnant[4];
- to ensure that guidelines are, or are going to be, made available for physicians regarding risk-benefit balance for use of medications in pregnancy, particularly those medications used for treating chronic diseases[5];
- to provide a teratogen information service where specialized advice can be sought by women and professionals[6];
- to conduct postmarketing pharmacovigilance to detect any risk of congenital anomalies associated with use of medications, with the support of population-based congenital anomaly registries[7].

In the field of food/nutrition and lifestyle

- to improve folate status through periconceptional supplementation with folic acid, promotion of the consumption of foods rich in natural folates, and the appropriate use of fortified foods[8]
- to prevent overweight/obesity and underweight[9-11];
- to promote effective information on diet and nutrition in women at childbearing age, minimizing the risks of deficiency and/or overdosing of vitamins and essential trace elements[12];
- further to the implementation of EU food safety strategies, to prevent food contamination by recognized developmental toxicants[13];
- to reduce active and passive smoking[14];
- to promote alcohol avoidance in women who are pregnant or wishing to get pregnant[15-18]
- to pay special attention to diet and lifestyles in communities with low socio-economic status or of recent immigrants.

In the field of health services

- to make available preconceptional care including genetic testing and counselling for families at risk[19];
- to ensure that women with diabetes, epilepsy and other chronic diseases receive preconceptional care in order to minimize the risk of congenital anomalies[20];
- to ensure evidence based vaccination policies to ensure women are protected against infectious diseases associated with congenital anomalies and avoid contraindicated vaccinations during pregnancy[21];
- to include in school educational programs the awareness that congenital anomalies may be caused very early in pregnancy, often before the pregnancy is confirmed, and hence healthy practices should start preconceptionally;
- to include consideration of specific pregnancy-related actions in public health action plans on all the major health determinants.

In the field of environmental pollution including the workplace

- Further to the implementation of EU policies on high-concern chemicals, to ensure both regulatory actions and risk

communication towards citizens in order to minimize exposure to pollutants identified as teratogens[22];
- to ensure a suitable surveillance system where environmental risks can be identified through the integration of congenital anomaly registers with developments in biomonitoring[23];
- to minimize exposure of pregnant workers in their workplace to risk factors for congenital anomalies (chemical, physical and biological)[24].

Types of primary preventive actions and their effectiveness

A number of types of primary preventive action can be identified:

1. Advice to future parents by health professionals during individual preconceptional and early pregnancy consultations, tailored for high and "low" (average population) risk couples.

2. Health education campaigns targeted to potential future parents.

3. EU-based and/or national regulatory actions which affect risk factors at source such as medicines, chemicals, infectious agents, foods, tobacco and alcohol and other recreational drugs.

4. Surveillance, research and evaluation generating evidence for the initiation or updating of primary preventive measures. This includes also the establishment of expert committees to review evidence.

The effectiveness of targeted actions towards primary prevention of congenital anomalies is expected to be markedly improved by:

- an integrated primary prevention plan involving all relevant health professionals, thus avoiding isolated and/or uncoordinated actions/recommendations;
- Implementation and refinement of EU food and environmental control programs providing special attention to congenital anomaly risk factors;
- proper evaluation and integration of new scientific knowledge into public health actions;
- ensuring preconception health care in local public health programs[25-29], while recognizing that many pregnancies are unplanned;
- availability of epidemiological surveillance data from population-based congenital anomaly registers, to monitor the effectiveness of services and interventions to build a sound evidence base for policy development planning and action;
- to ensure sustainability through national and international funding.

Footnotes and Bibliography

These footnotes are intended as a brief guide to the scientific evidence and its main messages for policy, not as an exhaustive review of the evidence.

1) European Project for Rare Diseases national Plans (EUROPLAN) **-** *website* *http://www.europlanproject.eu*

2) European Surveillance of Congenital Anomalies (EUROCAT) - *website* *http://www.eurocat-network.eu/*

3) In the context of these Primary Prevention recommendations, "environmental" is used in its broadest sense as non-genetic (although interacting with genetic factors), encompassing physical, chemical, biological and social factors, concentrating on factors which are potentially modifiable. This broad definition follows that of the US National Institute of Environmental Health Sciences which defines environmental exposure broadly to include not just chemical environmental pollutants, but also diet, pharmaceuticals, stress, pre-existing disease, and use of addictive substances.

   a) *National Institute of Environmental Health Sciences (2012). Advancing Science, Improving Health: A Plan for Environmental Health Research (Strategic plan 2012-2017) (Available at: http://www.niehs.nih.gov/about/strategicplan/strategicplan2012_508.pdf)*
   b) *National Academies Standing Committee on Use of Emerging Science for Environmental Health Decisions (2010). The Exposome: A Powerful Approach for Evaluating Environmental Exposures and Their Influences on Human Disease. Newsletter 3 of the National Academies' Standing Committee on Use of Emerging Science for Environmental Health Decisions. (Available at: http://nas-sites.org/emergingscience/files/2011/05/newsletter3_exposomes-rev.pdf)*
   c) *Seller MJ in EUROCAT (2004). EUROCAT Special Report: A Review of Environmental Risk Factors for Congenital Anomalies. pp7-29 - (Available at: http://www.eurocat-network.eu/content/Special-Report-Env-Risk-I-and-II.pdf)].*
   d) *Martinez-Frias, M-L (2010). Can our understanding of epigenetics assist with primary prevention of congenital defects? 47: (2). 73-80 (Available at: http://jmg.bmj.com/content/47/2/73.full.pdf+html)*

4) Drugs during pregnancy and lactation, Handbook of prescription drugs and comparative risk assessment. Edited by C. Schaefer. Co-authors: H. Garbis, P. McElhatton, P. Peters, M. Reuvers, E. Robert, M. Rost van Tonningen, A. Scialli. ELSEVIER, AMSTERDAM 2001.

5) Medications of particular concern include antiepileptics, folate antimetabolites, antiblastic agents, warfarin and related anticoagulants, retinoic acid derivatives, ACE-inhibitors and AT1 receptor antagonists.

   a) *Henderson E, Mackillop L. (2011). Prescribing in pregnancy and during breast feeding: using principles in clinical practice. Postgrad Med J; 87(1027):349-54*

   However, information on the human teratogenicity of most medications is limited.

   a) *Rasmussen SA (2012). Human teratogens update 2011: can we ensure safety during pregnancy? Birth Defects Res A Clin Mol Teratol. 2012 Mar;94(3):123-8*

Footnotes and Bibliography

b) *Cassina M at al (2012). Genetic susceptibility to teratogens: State of the art. Reprod Toxicol - Epub ahead of print*

There is extensive literature investigating the relative teratogenicity of different antiepileptic medication (*Available at:* http://www.eurocat-network.eu/preventionandriskfactors/medicationduringpregnancy/medicationpublications)

For antiasthmatics and antidepressants, national guidelines need to take into account the growing evidence base. Medication During Pregnancy pages of EUROCAT (*Available at:* http://www.eurocat-network.eu/preventionandriskfactors/medicationduringpregnancy/medicationintroduction)

6) European Network of Teratology Information Services - *website* *http://www.entis-org.com/*

7) EUROmediCAT Project **-** *website* *http://euromedicat.eu/whatiseuromedicat*

8) Strong scientific evidence showed folate rich diet and periconceptional supplementation with folic acid (the synthetic form) is effective in reducing the prevalence of Neural Tube Defects (NTD) and other congenital malformations, and an adequate folate status in women before pregnancy is a protective factor toward these pathologies. In 2009 EUROCAT published a special report highlighting that the majority of women in Europe were still not taking folic acid preconceptionally and/or were beginning to take it too late to prevent congenital anomalies after their pregnancy had been confirmed. As a result, the impact of policy on the rate of NTD in the population was minimal, and socioeconomic inequalities widen due to differences in knowledge. Furthermore the dietary intake of folates may not be sufficient to protect vulnerable women. Many non-European countries, such as U.S.A. and Canada, have instituted mandatory food (flour) fortification with folic acid as a way forward, with a positive impact in reducing NTD prevalence. However, fortification also raises concerns about the possible "side effects" of high folic acid intake in non-target population groups, which might be related to increased cancer promotion. In 2009 the scientific committee organised by EFSA concluded *"There are currently insufficient data to allow a full quantitative risk assessment of folic acid and cancer or to determine whether there is a dose-response relationship or a threshold level of folic acid intake associated with potential colorectal cancer risk. The current evidence does not show an association between high folic acid intakes and cancer risk but neither do they confidently exclude a risk. The uncertainties in relation to cancer risk highlight the importance of ensuring monitoring systems are set up for assessment of folic acid intake and status and NTD and cancer incidence in countries that decide to introduce mandatory fortification."*

a) *De Wals P et al (2007). Reduction in neural-tube defects after folic acid fortification in Canada. N Engl J Med. 2007; 357(2):135-42.*

b) *EUROCAT (2009). EUROCAT Special Report: Prevention of Neural Tube Defects by Periconceptional Folic Acid Supplementation in Europe. EUROCAT Central Registry, University of Ulster. (available at*

Footnotes and Bibliography

http://www.eurocat-network.eu/content/Special-Report-NTD-3rdEd-Part-I.pdf. *To view all EUROCAT publications on folic acid access the following link* http://www.eurocat-network.eu/AboutUs/Publications/FolicAcid)

c) *EFSA (European Food Safety Authority), 2009. ESCO report prepared by the EFSA Scientific Cooperation Working Group on Analysis of Risks and Benefits of Fortification of Food with Folic Acid. (Available at: http://www.efsa.europa.eu/en/scdocs/scdoc/3e.htm)*

d) *Taruscio D et al (2011). Folic acid and primary prevention of birth defects. Biofactors. 37(4):280-4.*

9) Stothard KJ et al (2009). Maternal overweight and obesity and the risk of congenital anomalies. A systematic review and meta-analysis. JAMA, 301 (6), 636-650. *(Available at: http://jama.ama-assn.org/content/301/6/636.full.pdf+html)*

10) Martinez-Frias ML, Frias JP, Bermejo E, Rodriguez-Pinilla E, Prieto L and Frias JL (2005). Pre-gestational maternal body mass index predicts an increased risk of congenital malformations in infants of mothers with gestational diabetes. *Diabetic Medicine*. 22: 775-781.

11) Siega-Riz AM et al (2009).National Birth Defects Prevention Study. The joint effects of maternal prepregnancy body mass index and age on the risk of gastroschisis. *Paediatr Perinat Epidemiol*. 23(1):51-7.

12) Particular attention should be given to:

- deficiency of Vitamin B12 and B6, since they are needed for proper metabolism of folates;
- Zinc deficiency as a risk factor for neural tube defects in communities from developing Countries.

In addition pregnant women should avoid an excessive exposure to vitamin A associated to liver consumption and taking supplements containing vitamin A.

a) *Simpson JL, et al (2010). Micronutrients and women of reproductive potential: required dietary intake and consequences of dietary deficiency or excess. Part I--Folate, Vitamin B12, Vitamin B6. J Matern Fetal Neonatal Med. 2010 Dec; 23(12):1323-43.*

b) *Simpson JL, et al (2011). Micronutrients and women of reproductive potential: required dietary intake and consequences of dietary deficiency or excess. Part II--vitamin D, vitamin A, iron, zinc, iodine, essential fatty acids. J Matern Fetal Neonatal Med. 2011 Jan; 24(1):1-24.*

c) *Dey AC et al (2010). Maternal and neonatal serum zinc level and its relationship with neural tube defects. J Health Popul Nutr. 28(4):343-50.*

d) *SCF/CS/NUT/UPPLEV/24 (2002) Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Preformed Vitamin A (retinol and retinyl esters) (Available at: http://ec.europa.eu/food/fs/sc/scf/out145_en.pdf)*

e) *Duerbeck NB, Dowling DD (2012). Vitamin A: too much of a good thing? Obstet Gynecol Surv. 67(2):122-8.*

13) A recognized example of a food contaminant highly relevant to the safety of the unborn child is methyl mercury in certain fish groups.

Footnotes and Bibliography

a) *Opinion of the Scientific Panel on Contaminants in the Food Chain on a request from the Commission related to mercury and methylmercury in food (Request N° EFSA-Q-2003-030) The EFSA Journal (2004) 34, 1-14*

b) *US Food and Drug Administration:* http://www.fda.gov/Food/ResourcesForYou/HealthEducators/ucm081877.htm *(7/03/2012)* http://www.fda.gov/Food/ResourcesForYou/HealthEducators/ucm083324.htm *(7/03/2012)*

The developmental hazards (especially urogenital malformations) from dietary exposure to endocrine disrupters also deserve consideration, *see also below Environment*.

a) *Giordano F et al (2008). Maternal diet and the risk of hypospadias and cryptorchidism in the offspring. Paediatr Perinat Epidemiol. 2008 May;22(3):249-60*

14) Active Smoking is a risk factor for congenital anomalies.

a) *Hackshaw, A. et al. (2011). Maternal smoking in pregnancy and birth defects: a systematic review based on 173 687 malformed cases and 11.7 million controls. Human Reproduction, 17 (5), 589-604. (Available at:* http://humupd.oxfordjournals.org/content/17/5/589.full.pdf+html)

The evidence regarding passive smoking is more difficult to establish, but is considered to be biologically plausible

a) *Leonardi-Bee J, Britton J, Venn A. (2011). Secondhand smoke and adverse fetal outcomes in nonsmoking pregnant women: a meta-analysis. Pediatrics 2011;127:734-41]*

15) Clarren SK (1981). Recognition of fetal alcohol syndrome. JAMA; 245:2436-9.

16) Martinez-Frias ML, Bermejo E, Rodriguez-Pinilla E, Frias JL (2004). Risk for congenital anomalies associated with different sporadic and daily doses of alcohol consumption during pregnancy: A case-control study. Birth Defects Research (Part A) 70:194-200.

17) Streissguth AP, Aase JM, Clarren SK, Randels SP, LaDue RA, Smith DF (1991). Fetal alcohol syndrome in adolescents and adults. JAMA; 265:1961-1967.

18) Werler MM, Lammer EJ, Rosenberg L, Mitchell AA (1991). Maternal alcohol use in relation to selected birth defects. Am J Epidemiol;134:691-8.

19) Preconception health refers to the health of women and men during their reproductive years. It focuses on steps that women, men, and health professionals can take to reduce risks, promote healthy lifestyles, and increase readiness for pregnancy.

a) *Yoon P W et al (2002).Can familiy history be used as a tool for public health and preventive medicine? Genetics in Medicine; Vol 4 no. 4 Jul/Aug 2002.*

b) *Jack B W et al (2008). The clinical content of preconception care: an overveiw and preparation of this supplement. Am J Obstet Gynecol;199(6 Suppl 2):S266-79.*

c) *Emery JD, Dunlop AL, Ten Kate LP. J (2012). Community Genet. 2012 Jun 29 - Epub ahead of print.*

Proposed Recommendations from published research and recommendations from the Centers for Disease Control and Prevention (CDC):

1. Individual Responsibility Across the Life Span **-** Each woman, man, and

Footnotes and Bibliography

couple should be encouraged to have a reproductive life plan. Individuals identified as having a family history of developmental delays, congenital anomalies, or other genetic disorders should be offered a referral to an appropriate specialist to better quantify the risk to a potential pregnancy.

2. Health Professionals responsibility - The challenge for health professionals is to reach women and men with these interventions at the time they will be most effective in reducing risks. Suspected genetic disorders might require further workup prior to conception. Known or discovered genetic conditions should be managed optimally before and after conception. As a part of primary care visits, provide risk assessment and educational and health promotion counselling to all women of childbearing age to reduce reproductive risk and improve pregnancy outcomes.

3. Consumer Awareness - Increase public awareness of the importance of preconception health behaviours and preconception care services by using information and tools appropriate across various ages; literacy, including health literacy; and cultural/linguistic contexts.

4. Research - Increase the evidence base and promote the use of evidence to improve preconception health.

5. Monitoring improvements - Maximize public health surveillance and related research mechanisms to monitor preconception health.

Pearls for Practice

- Women should also be informed that preconception care can improve health outcomes for both mother and baby. First, ask every women of reproductive age whether she intends to become pregnant in the next year. Asking every woman about her reproductive intentions promotes the idea that pregnancies should be intended. Second, inform women that health conditions and medications can affect pregnancy outcomes. J Am Board Fam Med. 2007; 20:81-84.

- During preconception screening visits, clinicians should focus on issues such as folate supplementation, hypothyroidism management, obesity control, hepatitis B vaccination for at risk women, and rubella vaccination among previously unvaccinated women.

20) Maternal Diabetes is a well established risk factor for congenital anomalies, but the excess risk can be almost eliminated with good glycaemic control. Health services must be organized to ensure that all women with diabetes have preconceptional care to achieve optimal glycaemic control.

    a) *Garne E et al (2012). Spectrum of congenital anomalies in pregnancies with pregestational diabetes. Birth Defects Research (Part A). 94: 134-140.*
    b) *Martínez-Frías ML et al (2005): Pre-gestational maternal body mass index predicts an increased risk of congenital malformations in infants of mothers with gestational diabetes. Diabetic Medicine 22:775-781*

21) Vaccination against maternal rubella is a core element of any primary preventive strategy as rubella during pregnancy is a strong teratogen. Countries should consider their coverage of women, whether immigrant women are offered

vaccination, and whether women found at first pregnancy not to be immune are offered vaccinations to protect them in subsequent pregnancies. Other vaccinations should also be considered. Vaccination during the first trimester should only be given where there is evidence of safety or evidence of a favourable benefit-risk balance.

a) *Gall SA, Poland GA (2011). A maternal immunization program (MIP): developing a schedule and platform for routine immunization during pregnancy. Vaccine; 29(51):9411-3.*

Guidelines for vaccinating pregnant women available at: http://www.cdc.gov/vaccines/pubs/downloads/b_preg_guide.pdf

22) The "environment" as used here is all the physical, chemical and biological factors external to the human host, and all related behaviours, but excluding those natural environments that cannot reasonably be modified. This definition excludes behaviour not related to environment, as well as behaviour related to the social and cultural environment, genetics, and parts of the natural environment.

a) *Prüss-stün A, Corvalan C (2006). Preventing disease through health environments. Towards an estimate of the environmental burden of disease Geneva: World Health Organization; 2006*

In the field of the environmental causes of congenital anomalies evidence is still limited and inadequate to show a causal association; however, the biological plausibility and special vulnerability of the fetus supports precautionary actions (*Communication from the European Commission on the precautionary principle. Brussels - 2000*). In particular, reduction of the level of exposure to hazards acting on a large-scale, such as air pollutants, byproducts of drinking water disinfection and pesticides should be recommended.

a) *Dolk H. and Vrijheid M. (2003). The impact of environmental pollution on congenital anomalies. British Medical Bulletin, 68, 25-45 (Available at: http://bmb.oxfordjournals.org/content/68/1/25.full.pdf+html).*
b) *Stillerman KP et al (2008). Environmental exposures and adverse pregnancy outcomes: a review of the science. Reprod Sci;15(7):631-50.*
c) *Vrijheid M et al (2011). Ambient Air Pollution and Risk of Congenital Anomalies: A Systematic Review and Meta-analysis. Environ Health Perspect; 119(5): 598-606.*
d) *Shirangi A et al (2011). Living near agricultural pesticide applications and the risk of adverse reproductive outcomes: a review of the literature. Paediatr Perinat Epidemiol. 2011 Mar;25(2):172-91.*
e) *Righi E et al (2012). Trihalomethanes, chlorite, chlorate in drinking water and risk of congenital anomalies: A population-based case-control study in Northern Italy. Environ Res;116:66-73.*

Endocrine disrupters are recognized risk factors for reproductive disorders during puberty and adulthood; however, evidence indicates that higher exposure levels may increase the incidence of urogenital malformations such as chryptorchidism and hypospadia.

a) *Carbone P et al (2007). The possible role of endocrine disrupting chemicals in the aetiology of cryptorchidism and hypospadias: a population-based case-control study*

Footnotes and Bibliography

in rural Sicily. Int J Androl;30(1):3-13.

b) *Fernandez MF et al (2007). Human exposure to endocrine-disrupting chemicals and prenatal risk factors for cryptorchidism and hypospadias: a nested case-control study. Environ Health Perspect;115 Suppl 1:8-14. c) Giordano F et al (2010). Maternal exposures to endocrine disrupting chemicals and hypospadias in offspring. Birth Defects Res A Clin Mol Teratol;88(4):241-50; Toppari J et al (2010). Cryptorchidism and hypospadias as a sign of testicular dysgenesis syndrome (TDS): environmental connection. Birth Defects Res A Clin Mol Teratol;88(10):910-9.]*

23) There is a general consensus that further elucidation of the links between environmental exposures and congenital anomalies must come through linking biomarkers and congenital anomaly surveillance approaches.

a) *Schoeters GE et al. (2011). Biomonitoring and biomarkers to unravel the risks from prenatal environmental exposures for later health outcomes. Am J Clin Nutr. 94(suppl):1964S-9S (Available at: http://www.ajcn.org/content/94/6_Suppl/1964S.full.pdf+html)*

24) Pregnant women at work must be protected from teratogenic exposures. The challenge is to do this in early pregnancy, often before the pregnancy has been confirmed or employers are made aware. This issue should be addressed in occupational health policies. Occupational exposures of concern include pesticides, any endocrine disrupting exposure and organic solvents.

a) *Cordier S et al (1992). Maternal occupational exposure and congenital malformations. Scandinavian Journal of Work, Environment and Health. 18: 11-17.*

b) *Cordier S et al (1997). Congenital malformations and maternal occupational exposure to glycol ethers. Epidemiology. 8: (4). 355-363.*

c) *Figà-Talamanca I. Occupational risk factors and reproductive health of women. Occup Med (Lond);56(8):521-31.*

d) *Chevrier C et al (2006). Occupational exposure to organic solvent mixtures during pregnancy and the risk of non-syndromic oral clefts. Occup Environ Med; 63(9):617-23.*

e) *Ormond G et al (2009). Endocrine disruptors in the workplace, hair spray, folate supplementation, and risk of hypospadias: case-control study. Environ Health Perspect;117(2):303-7*

f) *Nassar N et al (2010). Parental occupational exposure to potential endocrine disrupting chemicals and risk of hypospadias in infants. Occup Environ Med. 2010 Sep;67(9):585-9.*

g) *Vaktskjold A, Talykova LV, Nieboer E. (2011). Congenital anomalies in newborns to women employed in jobs with frequent exposure to organic solvents—a register-based prospective study. BMC Pregnancy Childbirth;11:83.*

h) *Morales-Suárez-Varela MM et al (2011). Parental occupational exposure to endocrine disrupting chemicals and male genital malformations: a study in the Danish National Birth Cohort study. Environ Health;10(1):3*

Footnotes and Bibliography

25) *Health Council of the Netherlands. Preconception care: a good beginning. The Hague: Health Council of the Netherlands, 2007; publication no. 2007/19.* ISBN 978-90-5549-678-5 (Available at: *http://www.gezondheidsraad.nl/sites/default/files/200719E.pdf*)

26) Hani KA et al (2006). Preconception Care for Improving Perinatal Outcomes: The Time to Act. Matern Child Health J. 10(Suppl 1): 3–11.

27) Frey KA, Files JA. Preconception healthcare: what women know and believe. Matern Child Health J. 2006 Sep;10(5 Suppl):S73-7.

28) Johnson K et al; CDC/ATSDR Preconception Care Work Group; Select Panel on Preconception Care (2006). Recommendations to improve preconception health and health care—United States. A report of the CDC/ATSDR Preconception Care Work Group and the Select Panel on Preconception Care. MMWR Recomm Rep. 55(RR-6):1-23.

29) Medline Plus – Preconception care. A service of the U.S. National Library of Medicine NIH (National Institutes of Health) **-** *website* *http://www.nlm.nih.gov/medlineplus/preconceptioncare.html*

These Recommendations were developed as part of Workpackage 7 of the EUROCAT Joint Action 2011-2013, funded by the EU Public Health Programme.

Workpackage Leader: Domenica Taruscio.

With the contribution of: Larraitz Arriola (Basque Country-Spain), Francesca Baldi (Italy), Fabrizio Bianchi (Italy), Eva Bermejo-Sánchez (Spain), Elisa Calzolari (Italy), Pietro Carbone (Italy), Rhonda Curran (NI-UK), Helen Dolk (NI-UK), Ester Garne (Denmark), Miriam Gatt (Malta), Anna Latos-Bieleńska (Poland), Alberto Mantovani (Italy), Maria Luisa Martínez-Frías (Spain), Amanda Neville (Italy), Anke Rißmann (Germany), Stefania Ruggeri (Italy), Domenica Taruscio (Italy).

Amended and approved by EUROCAT Registry Leaders and members of the EUROCAT Project Management Committee June 2012 (Ingeborg Barisic, Elisa Calzolari, Rhonda Curran, Helen Dolk, Ester Garne, Lorentz Irgens, Babak Khoshnood, Domenica Taruscio, Diana Wellesley).

Project Leader of EUROCAT Joint Action: Helen Dolk.

First version: April 30, 2012
Amended version: June 3, 2012
Version post RLM Budapest, July 26, 2012
Final version: September 30, 2012.
Approved by EUROCAT Project Management Committee 13 December 201