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# Final Report
# September 2007 to August 2010

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## EXECUTIVE SUMMARY

EUROCAT (European Surveillance of Congenital Anomalies) is the European network of population-based congenital anomaly registries for the epidemiologic surveillance of congenital anomalies. It has been in existence since 1979, and co-funded by DGSanco's Rare Diseases and Public Health Programmes since 2000. This report concerns the funding contract Sept 2007 to August 2010.

Registries transmit an electronic file of anonymous standardised information on cases of congenital anomaly to the Central Registry each year, with which the central database is updated. In Feb 2010, the central database was updated with 2008 (births) data. The central database now includes X cases of congenital anomaly (livebirths, fetal deaths from 20 weeks gestation and terminations of pregnancy following prenatal diagnosis) from 1980-2008 from full member registries.

Four new registries joined the network during 2007-2010, to bring coverage to 41 registries in 21 countries, covering 1.7 million births per year. 31% of births in the European Union are covered by the surveillance system.

Notable achievements Sept 2007-August 2010:

- European Symposium on the Prevention of Congenital Anomalies, Bilbao, June 2009.
- Redesign and relaunch of the EUROCAT website at www.eurocat-network.eu
- EUROCAT Report 9: Surveillance of Congenital Anomalies 1980-2009 submitted for publication in the journal Birth Defects Research.

# A Progress Report for each Work Package

## A1 Work Package No. 1 – Co-ordination of the Project

EUROCAT is organised as follows:

- The Central Registry at University of Ulster co-ordinates the network, carrying out administration, financial management, database management, website management, report preparation, surveillance and research activities, and liaison with other organisations.

- EUROCAT member registries send data annually for inclusion in the EUROCAT Central Database at University of Ulster (see Work package 4).

- Working Groups are responsible for specific work packages (Work package 5 Folic Acid and Prevention of Neural Tube Defects; Work package 6 Drugs during Pregnancy; Work package 7 Prenatal Screening and Diagnosis), led by partners. These Working Groups are given help accessing or analysing the Central Database data by Central Registry staff. In addition there is a Coding and Classification Committee which deals with evaluation and advising on harmonisation of coding of congenital anomalies in ICD10 (see WP 4).

- The Central Registry is advised by the Project Management Committee, which includes the six Registry Leaders elected as the EUROCAT Steering Committee (see Section B2), as well as Workpackage leaders. For meetings held, see Section C1.

- Registry Leaders Meetings (RLM) are held once a year, with in addition an open scientific symposium "European Symposium on the Prevention of Congenital Anomalies" every two years. The purpose of the RLM is to introduce new registries and registry leaders, discuss harmonisation of methodology, the results of statistical monitoring and investigation of trends and clusters (WP4), the work of the Working Groups (WP5,6,7) and the progress of research projects using the EUROCAT database. The RLM also presents an opportunity for training, either on a one to one basis (e.g. EDMP Clinics are held where training is given in the use of the EUROCAT Data Management Programme software, and induction sessions for new registries), or in workshops (e.g. in malformation coding or statistical monitoring methods). A Registry Leaders Meeting was held June 2008 in Helsinki, June 2009 in Bilbao and June 2010 in Dublin, (see C2, C3 and Appendix 4). The 10th European Symposium on the Prevention of Congenital Anomalies was held in Bilbao on June 10, 2009 (see C2, C3 and Appendix 4).

- There is a Members Only section of the EUROCAT website, where all minutes of meetings, draft and internal documents, EDMP software for downloading (see WP4) and data management instructions, are available, managed by Central Registry.

Since EUROCAT is funded under the Rare Diseases strand of the EU Public Health Programme, participation in the Rare Diseases Task Force (RDTF) is an important part of ongoing work. Prof Helen Dolk (Deputy Leader of the RDTF) and Dr Vera Nelen have represented EUROCAT at RDTF meetings in Luxembourg, particularly with respect to preparation of the Commission Communication on Rare Diseases: Europe's challenges in Nov 2008 and Council Recommendation in June 2009. EUROCAT was also represented in two of the RDTF Working Groups: the Coding WG (Dr Ester Garne and Dr Diana Wellesley) improving the coding of rare disease, and the Health Indicators WG (Prof Helen Dolk and Dr Babak Khoshnood) considering minimum information sets regarding rare diseases in Europe. Prof Dolk is on the Editorial Board of Orphanews, an e-newsletter disseminating research and policy news on rare diseases worldwide. Dr Ester Garne spoke about EUROCAT at the Children Workshop in Luxembourg November 2007, where DGSanco sponsored projects regarding the health of Children were discussed. Dr Fabrizio Bianchi represented EUROCAT at the ICORD Feb 2009 meeting on Rare Disease Registries. Dr Bianchi also represents EUROCAT in the EUROPLAN project on national plans for Rare Diseases. A special role for EUROCAT in relation to rare diseases policy has been to emphasise the opportunities and needs for primary prevention of congenital anomalies and other rare diseases. In 2009, EUROCAT published a letter in the Lancet (see Section D) defining primary prevention based on reduction of environmental risk factors, in order to clear the way in the policy agenda of countries who have confused "prevention" with prenatal screening or preimplantation diagnosis.

EUROCAT currently has 29 full members, 6 associate members and 7 affiliate members operating in 21 countries of Europe. Full Members transmit individual anonymised case data to the EUROCAT Central Registry and Associate members transmit aggregate case numbers. Population coverage in 2007 is shown in Table 1. EUROCAT covers 31% of births in the EU-27 population and 29% of births in the European countries shown i.e. a coverage of approximately 1.7 million births in 2007.

EUROCAT approved new membership applications from UK South West, French West Indies and Slovenia, and the registries were accepted as Affiliate Member registries. When these registries transmit data which conforms to EUROCAT Guide 1.3, they will transfer to Full Member status. EUROCAT also received new membership applications from Valencia and Slovakia, which require further clarification before membership is granted.

Czech Republic joined EUROCAT as an Associate Member in 2009.

The former Central East France registry was restricted to Rhone-Alpes region in 2007 and was renamed Rhone-Alpes registry (Associate Member).

Two full members (Campania and Sicily) passed to affiliate status due to inability to transmit data to the central database for administrative reasons. Seven members moved from Affiliate to Past membership status (Auvergne, Galway, NE Italy, Asturias, Glasgow, NW Thames and England NCAS).

Interest in becoming a EUROCAT member was received from Moldova and Latvia. A representative from Moldova attended the RLM, Helsinki 2008 and presented plans to establish a register. The President of the EUROCAT Association visited Moldova in March 2009 on their invitation to consolidate and help with their membership application. A representative from Latvia attended the RLM, Dublin 2010 and is a partner in the EUROCAT Joint Action 2011-2113 with the intention of establishing a full member register during that period.

**Table 1: Coverage of the European Population, birth year 2007, by EUROCAT Full or Associate Member Registries**

| Country | EUROCAT Registry | Year started EUROCAT data transmission | Annual Births 2007, Registry | Annual Births 2007, Country[1] | % Country Covered * |
|---|---|---|---|---|---|
| **EU** | | | | | |
| EU (Present EU Member States) | | | 1,347,841 | 5,249,863 | 25.7 |
| EU-15 (EU Member Countries since before 2004) | | | 839,283 | 3,325,950 | 25.2 |
| EU-NMS (Countries acceded in 2004-2007) | | | 508,558 | 1,923,913 | 26.4 |
| Belgium | Antwerp | 1990 | 19,874 | | |
| | Hainaut | 1980 | 12,717 | | |
| | Total | | 32,591 | 120,664 | 27.0 |
| Bulgaria | | | | 75,257 | 0.0 |
| Czech Republic | Czech Republic[2, 3] | 2000 | 114947 | 114,947 | 100.0 |
| Denmark | Odense | 1980 | 5,429 | 63,731 | 8.5 |
| Germany | Mainz | 1990 | 3,323 | | |
| | Saxony-Anhalt | 1987 | 17,470 | | |
| | Total | | 20,793 | 683,214 | 3.0 |
| Estonia | | | | 15,840 | 0.0 |
| Ireland | Cork & Kerry | 1996 | 9,953 | | |
| | Dublin | 1980 | 26,370 | | |
| | South East | 1997 | 7,468 | | |
| | Total | | 43,791 | 69,863 | 62.7 |
| Greece | | | | 111,717 | 0.0 |
| Spain | Barcelona | 1992 | 14,862 | | |
| | Basque Country | 1990 | 20,681 | | |
| | Spain hospital network[2] | 1980 | 102,540 | | |
| | Total | | 138,083 | 489,221 | 28.2 |
| France | Isle de la Reunion | 2002 | 15,002 | | |
| | Paris | 1981 | 26,339 | | |
| | Rhone-Alpes[2] | 2006 | 57,744 | | |
| | Strasbourg | 1982 | 21,962 | | |
| | Total | | 121,047 | 814,377 | 14.9 |
| Italy | Emilia Romagna | 1981 | 40,662 | | |
| | Tuscany | 1980 | 30,957 | | |

| | | | | | |
|---|---|---|---|---|---|
| | Total | | 71,619 | 561,747 | 12.7 |
| Cyprus | | | | 8,488 | 0.0 |
| Latvia | | | | 23,269 | 0.0 |
| Lithuania | | | | 32,495 | 0.0 |
| Luxembourg | | | | 5,429 | 0.0 |
| Hungary | | | | 97,642 | 0.0 |
| Malta | Malta[3] | 1986 | 3,898 | 3,898 | 100.0 |
| Netherlands | Northern | 1981 | 17,678 | 181,574 | 9.7 |
| Austria | Styria | 1985 | 10,209 | 76,203 | 13.4 |
| Poland | Wielkopolska | 1999 | 38,302 | | |
| | Rest of Poland[2, 3] | 1999 | 351,411 | | |
| | Total | | 389,713 | 389,713 | 100.0 |
| Portugal | South | 1990 | 18,874 | 102,811 | 18.4 |
| Romania | | | | 215,651 | 0.0 |
| Slovenia | | | | 19,702 | 0.0 |
| Slovakia | | | | 54,476 | 0.0 |
| Finland | Finland[2] | 1993 | 58,574 | 58,574 | 100.0 |
| Sweden | Sweden[2, 3] | 2001 | 101,688 | 101,688 | 100.0 |
| UK | Northern England | 2000 | 33,054 | | |
| | Thames Valley | 1991 | 29,716 | | |
| | E Mid & S York | 1998 | 72,549 | | |
| | Wales | 1998 | 34,585 | | |
| | Wessex | 1994 | 29,003 | | |
| | Total | | 198,907 | 771,923 | 25.8 |
| **Non EU** | | | | | |
| *Candidate countries in EUROCAT* | | | | | |
| Croatia | Zagreb | 1983 | 7,351 | 41,748 | 17.6 |
| *EFTA countries in EUROCAT* | | | | | |
| Norway | Norway | 1980 | 58,046 | 58,046 | 100.0 |
| Switzerland | Vaud | 1989 | 7,620 | 74,337 | 10.3 |
| Ukraine | Ukraine[4] | 2005 | 29,253 | 472,657 | 6.2 |

[1] Source: Crude birth rate (accessed 29-06-2010) http://epp.eurostat.ec.europa.eu/portal/page/portal/population/data/main_tables

[2] Associate EUROCAT Registries (transmit aggregate data only)

[3] Source of annual births in country provided by registry rather than EUROSTAT

[4] http://www.ukrstat.gov.ua/operativ/operativ2007/ds/pp/pp_e/pp1207_e.html (accessed 29-06-2010)

[*] Including the 6 EUROCAT Affiliate registries (French West Indies, Hungary, Campania, Sicily, Slovenia, South West UK) coverage of the EU population increased from 25.7% to 30.5%

## A2 Work Package No. 2 – Dissemination of the Results

The central means of dissemination of EUROCAT results is the EUROCAT website. The old website (www.eurocat.ulster.ac.uk) was relaunched under a new address(http://www.eurocat-network.eu) in January 2010, with a new thematic design and new logo. The old website had an average of 1121 hits per month for absolute unique visitors in the period Sept 2008-Feb 2009 from 130 countries/territories. The new website.....

A major feature of the EUROCAT website is the facility to produce tables according to user requirements, now at http://www.eurocat-network.eu/ACCESSPREVALENCEDATA/PrevalenceTables. Specific website hits for these pages……

There are a number of standard report layouts available (with Examples in Appendix 1):

**An A1 table**: This displays the number of live births (LB), the number of fetal deaths (FD) and the number of terminations of pregnancy for a congenital anomaly (TOPFA) for each of the 96 EUROCAT congenital anomaly subgroups, combining data from all user-selected registries. It also provides overall prevalence rates per 10,000 births per subgroup. Prevalence rates are given including or excluding cases with a chromosomal anomaly, which are aetiologically different. The user can choose to look at figures for just one registry or a number of registries combined. The user can choose to look at figures for one year or for a number of years combined. See Table 2 below for an example of an A1 table.

**An A5 table:** This displays prevalence rates over time for ONE chosen anomaly. The user can choose any time period from 1980-2008, and any number of registries. The report will display the number of LBs, FDs and TOPFAs per registry, per year for the user- specified anomaly. It also displays the yearly population per registry. Total prevalence rates are calculated as before with and without inclusion of chromosomal cases. If the user has chosen to look at more than one registry, the combined figures will be at the bottom of the report. For an example please see Appendix 1.1.

**An A6 table:** This table will provide the user with prevalence over time for ONE chosen registry. The user can specify the time period (any years from 1980-2008) and choose the anomaly (or anomalies) of interest. For an example please see Appendix 1.2

**A B3 table:** This table will show the LB prevalence, LB+FD prevalence, and LB+ FD+TOPFA prevalence rate for ONE chosen anomaly in a time range. The LB+FD+TOPFA prevalence is also shown excluding chromosomal cases. It also

gives the number of LBs, the number of FDs and the number of TOPFAs for each of the registries that the user chooses. For an example please see Appendix 1.3

There are also 3 tables that show data specifically related to prenatal diagnosis.

**A PD1 table:** This shows the total number of cases and the percentage of cases prenatally diagnosed for 7 selected anomalies: anencephalus and similar, spina bifida, transposition of great vessels, hypoplastic left heart, gastroschisis, bilateral renal agenesis (including Potter syndrome) and Down syndrome. To be included in the PD tables, each registry must have transmitted 4 years complete data to EUROCAT within the period and the "When discovered" variable (i.e. indicating whether the case was prenatally diagnosed) should be 80% complete. The table by default provides figures for the last 5 year period. For an example please see Appendix 1.4.

**A PD2 table:** This provides the total number of cases and the number prenatally diagnosed for ONE of the 7 anomalies (listed above). This allows the user to compare % of cases prenatally diagnosed between registries. For an example please see Appendix 1.5.

**A PD3 table:** This table shows the gestational age (GA) at termination and the TOPFA prevalence rate for the All Anomalies subgroup. The GA categories are <14 weeks, 14-19 weeks and 20+ weeks. This allows comparison of GA and prevalence of TOPFA for All Anomalies, between registries. For an example please see Appendix 1.6.

The prevalence data available on the website are updated in March/April and October/November of each year, and these updates are accompanied by updated Member Registry Descriptions http://www.eurocat-network.eu/ABOUTUS/MemberRegistries/MembersAndRegistryDescriptions/AllMembers and Data Quality Indicators (see WP 4)

All EUROCAT Special Reports are downloadable from the website, as well as publication lists for journal publications and links to abstracts of journal publications. A full publication list for 2007-2010 can be found in Section D.

New versions of the EUROCAT Data Management Program (see WP4) are downloadable from the Members Only section of the website.

The EUROCAT website has been redesigned (subcontracted to Biomedical Computing Ltd) so that its structure is theme-based. The 4 main themes of Prevalence, Prevention & Risk Factors, Prenatal Screening & Diagnosis and Clusters & Trends make it easier for the user to navigate the site.

The 10th European Symposium on the Prevention of Congenital Anomalies took place on June ? in Bilbao, 2009. The programme and attendance list is shown in Appendix X.
Two e-newsletters have been issued (see Section D1), sent to 1,674 subscribers in 62 countries worldwide.

In 2008, EUROCAT published a short article describing EUROCAT in the European Parliament Magazine (see Section D1).

EUROCAT has had a number of requests for general chapters to contribute to European reports or books. Chapters were written for de la Paz and Croft "Rare Diseases Epidemiology" 2010; for the EUROPERISTAT-SCPE-EUROCAT European Perinatal Health Report (data from 2004); and for EUGLOREH Health of the European Union Report (see Section D).

EUROCAT is a WHO Collaborating Centre for the Epidemiologic Surveillance of Congenital Anomalies. EUROCAT was represented at WHO Geneva, August 2008 (Dr Patricia Boyd) at a meeting to determine "A Prioritized Research Agenda for Prevention and Control of Noncommunicable Diseases" and by Prof Dolk at a subsequent meeting in September 2010. A revised set of terms of reference have been agreed with WHO, and EUROCAT looks forward to working with WHO to implement the May 2010 World Health Assembly resolution on birth defects. EUROCAT is contributing data to the new Global Burden of Diseases (GBD) Project. Prof Dolk represents EUROCAT on the GBD Congenital and Genetic Disorders Expert Group. As part of EUROCAT's work for this Project, a EUROCAT Special report on Congenital Heart Defects was published (see Section D1).

EUROCAT worked with Surveillance of Cerebral Palsy in Europe to analyse whether there is an association between risk of cerebral palsy and risk of cerebral and non-cerebral congenital malformation. This resulted in a journal publication (see Section D1), and was followed by a project funded by the Fondation Motrice of France investigating this issue in more detail by linkage of registries of both groups of conditions, which co-exist in three regions of Europe. A resulting scientific paper has been published in Dev Med Child Neurol (see Section D) and conference presentations have been given (see Section C4).

EUROCAT was invited by EUROPERISTAT to submit a chapter on congenital malformations to the European Perinatal Health Report, now available at [www.eurocat.ulster.ac.uk/pdf/EUROPERISTAT-Report.pdf] (see Section D1). This will now lead to joint work on perinatal and infant mortality due to congenital malformations.

EUROCAT was also invited by the DG Sanco funded EUGLOREH project, European Global Report on Health Status of the European Union, to submit a chapter on Congenital Malformations, now available at http://www.eugloreh.it/ActionPagina_993.do and given in Section D1.

EUROCAT contributed a chapter on “The Prevalence of Congenital Anomalies in Europe” in: Rare Diseases Epidemiology, Springer, published in 2010. (see Section D1).

For contributions to meetings of other organisations, see Section C.

## A3 Work Package No. 3 – Evaluation of the Project

Two types of evaluation are carried out at Project Management Committee meetings, supported by documentation prepared by Central Registry:

**1. Progress Evaluation**

Progress on all work packages is reviewed three times a year by the PMC (for meeting details see C1). Progress in terms of new membership and increase in size of the European birth population covered by surveillance is described in section A1.

**2. Dissemination Evaluation**

Number of scientific publications, submitted, in press and published – see Collaborative Publications List in Section D1.

Number of website hits per month, generally and specifically for prevalence Tables, see A3.

Number and type of citations of EUROCAT publications. A Scopus citation search for all publications in the medical and scientific literature mentioning EUROCAT in their Reference lists found 150 citations 2007 to 2010 in a range of journals. The most cited EUROCAT collaborative papers published during 2007 to 2010 were Loane et al 2007 on gastroschisis (36 citations), Calzolari et al 2007 on cleft lip and palate (19 citations), Dolk et al 2009 on the antiepileptic drug lamotrigine (18 citations), Boyd et al 2009 on prenatal screening policies in Europe (14 citations), Barisic et al 2009 on Cornelia de Lange syndrome (11 citations).

A further indication of the use of EUROCAT data are the number of requests for EUROCAT information from non-EUROCAT organisations (see Appendix 6).

In October 2010, EUROCAT carried out a web-based survey of EUROCAT newsletter recipients and website users. There were 142 respondents and the results are given in Appendix 8. Results show that EUROCAT sources of information across all three of its main themes, and across all types of congenital anomaly, are being accessed and found valuable. However, the low response rate limits interpretation.

## A4 Work Package No. 4 – Core Surveillance and Data Management

The Objectives of this Work Package are:

To provide essential epidemiological information on congenital anomalies in Europe

a) To provide updated prevalence rates for major congenital anomalies among livebirths, stillbirths and terminations of pregnancy following prenatal diagnosis, and perinatal mortality due to congenital anomalies
b) To describe and interpret major trends in prevalence and geographical differences
c) To provide new epidemiological information on very rare genetic syndromes diagnosed prenatally or in the first year of life
d) To promote better coding and classification of congenital anomalies and syndromes
e) To measure and improve data quality and standardisation
f) To agree and measure up to five key fetal health and related service indicators to be included among rare disease indicators

To co-ordinate the establishment of new registries throughout Europe collecting comparable, standardised data. Advise and train applicant and new member registries on EUROCAT methodology, evaluate their data and integrate their expertise.

To co-ordinate the detection and response to clusters and early warning of teratogenic exposures

a) To conduct annual statistical monitoring for trends and temporal clusters, and advise and co-ordinate their investigation
b) To prepare for the integration of congenital anomaly information into a comprehensive environmental health information system

**Description of the Work**

**Data Management, Data Quality and Coding**

Data Management

Data are transmitted to Central Registry using EUROCAT Data Management Program (EDMP) on 15th February and/or 15th October each year. These data are uploaded to the membership-only website so that registries can confirm that the data are correct and agree excluded cases (cases that do not meet EUROCAT's definition of a congenital anomaly case).

Central Registry continues to organise EDMP training workshops at the annual Registry Leaders Meeting to answer queries and solve EDMP-related problems. At different times throughout the meeting, 3 members of Central Registry staff are available to demonstrate the latest features of the EDMP package. Registry leaders are encouraged to book a one-to-one session and bring any problems that they may have experienced in the previous year for discussion. Also anyone attending the conference who is thinking of starting collection of congenital anomaly data is invited along to see the main features of the package and to see if it would meet their needs.

Two new versions of EDMP were released in June 2008 and May 2010. EDMP is constantly being improved taking into account user requests if sufficient demand. The main features in these updates were:

a) user defined location subgroups and associated denominators. This enables the registries to now run reports and statistical surveillance by location.
b) improved and more user-friendly statistical surveillance for clusters and trends.
c) an updated navigation screen. This has been designed to help easily access all of the available features in EDMP.
d) output of data to Excel has been modified to ensure consistency, especially for date fields

Data Quality

A range of data quality indicators (DQI) were designed to measure the quality and characteristics of data transmitted from participating registries (http://www.eurocat-network.eu/ABOUTUS/DataCollection/DataQuality/DataQualityIndicators). This increases the transparency of data collected within the EUROCAT network. These DQI are divided into five groups: Completeness of Case Ascertainment, Accuracy of Diagnosis, Completeness of information on Core and Non-Core Variables, Timeliness and Denominator Data Availability. Comparisons can be made between each individual registry and the EUROCAT average (see Appendix 2).

In 2009-2010, a new DQI was added assessing Down syndrome (DS) ascertainment. The DS DQI calculates the ratio of Observed to Expected DS cases, assuming a uniform maternal-age specific DS prevalence across Europe. Observed (O) is the number of livebirth (LB) + the number of TOPFA corrected for survival to LB. Expected (E) is based on 5 year age-specific LB +corrected TOPFA estimates[1] applied to the maternal age profile of each registry birth population.

[1] Savva GM, Walker K, Morris JK. 2010. The maternal age-specific live birth prevalence of trisomies 13 and 18 compared to trisomy 21 (Down syndrome). Prenatal Diagnosis 30: 57-64

Over time the quality is edging ever upward. Some interesting improvements are detailed below:

a) If we compare the 5 year period 2000-2004 with 2004-2008, we see that the timeliness of data transmission has improved immensely. 21 registries submitted 2008 for the February deadline in 2010 compared to only 7 with 2005 data in February 2007. This makes annual surveillance more meaningful and timely.

b) The most important indicator is of course the overall congenital anomaly rate. The overall EUROCAT prevalence rate is currently 239.3 per 10,000 births, an increase from 225.9 in the 2000-2004 period. There were 12 registries below the rate of 200 per 10,000 (2%) in the older time period but only 8 registries now. Achieving an ascertainment rate of >2% should be the foremost aim.

c) The overall percentage of cases with syndrome text completed increased from 34% to 68% and malformation 1 text from 56% to 73%. Many registries maintain 100% completeness, but some registries are changing local practice to enable capture of this information. The number of registries below 90% completeness has decreased to only 6. 3 years ago twice as many registries were below the 90% completeness.

d) With the prevalence of selected postnatally diagnosed conditions, the overall rate has increased from 8.9 per 10,000 births to 18.0 per 10,000. This is a large increase. In the older time period there were 15 registries below a rate of 1 per 1000, whereas currently only 3 registries are below this rate

e) Use of unspecified Q codes - obviously we want the prevalence rate of unspecified codes to be as low as possible. The overall rate has come down from 9.4 to 8.9 per 10,000 births. In the time period 2000-2004, 10 registries made use of unspecified codes at a rate of >1 per 1000. However, only 4 registries currently have a rate of >1 per 1000

An added benefit of statistical monitoring (see below) is that it identifies errors in the data which are then corrected by the registry – so it is an indirect tool for improving data quality.

Coding

The EUROCAT Coding and Classification Committee have:

a) extended the list of minor anomalies for exclusion.
b) refined EUROCAT's multiple malformation computer algorithm to identify children with more than one (unrelated) major malformation on the basis of ICD codes. Information presented at Helsinki RLM 2008, showed that the computer algorithm identified 9% of approximately 22,000 cases as potential multiples. When these cases were reviewed by the medical geneticists, 6% were considered to be true multiples. Further work is needed to refine the algorithm. revised the EUROCAT Syndrome Guide to include all syndromes that are included in the ICD10 Q chapter and skeletal dysplasias.
c) developed coding guidelines addressing specific malformation coding difficulties in response to coding queries from local registries
d) organised two half-day coding workshops held in Helsinki June 2008, and in Dublin, June 2010.
e) created a new Severe Congenital Heart Defects (CHD) anomaly subgroup

All relevant documentation is available on EUROCAT website http://www.eurocat.ulster.ac.uk/pubdata/Malformation-Coding-Guides.html

The EUROCAT Coding and Classification Committee regularly submit proposals to improve existing classification practices to WHO ICD10 for approval, and also contribute to the Rare Diseases Coding Group preparing for WHO ICD11. A Coding & Classification Committee Report on WHO ICD10 updates was uploaded on EUROCAT website in December 2007: http://www.eurocat.ulster.ac.uk/pdf/Ester/Report-on-WHO%20ICD10-Updates.pdf ?Ester

**Liaison with Registries**

Contact with new member registries is ongoing and assistance with coding queries is provided by Central Registry. The French West Indies registry has submitted data and is striving for full membership status. Slovenia, Latvia and Valencia have each received EDMP and instructions on how to use the program to code congenital anomalies according to EUROCAT specifications, as outlined in Guide 1.3. Representatives from these 3 registries also attended the EUROCAT conference in June 2010. Central Registry is also in contact with Slovakia and Moldova who are both interested in EUROCAT membership. The registry in Cyprus have a particular interest in CHD. They were provided with a newly designed demonstration version of EDMP and it is hoped that we will find a mode of collaboration with Cyprus. The South West England registry is currently affiliate status and they hope to submit case data for the deadline in October 2010.

**Provision of Prevalence Information**

Prevalence of EUROCAT congenital anomaly subgroups is updated biannually to the EUROCAT website at www.eurocat-network.eu. The website tables http://www.eurocat-network.eu/ACCESSPREVALENCEDATA/PrevalenceTables show the most recent upload of data (13 April 2010) up to and including cases born in the year 2008. The prevalence rates for each of the 95 EUROCAT congenital anomaly subgroups are shown below in Table 2.

**Table 2: An A1 table showing prevalence rates for all EUROCAT anomaly subgroups, 2004-2008, all full member registries**

| | | | | | | Excluding Chromosomal | |
|---|---|---|---|---|---|---|---|
| **Anomaly** | **LB N** | **FD N** | **TOPFA N** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** |
| **All Anomalies** | 55973 | 1498 | 12164 | 69635 | 233.43 | 58971 | 197.68 |
| **Nervous system** | 3292 | 337 | 3553 | 7182 | 24.08 | 6503 | 21.80 |
| Neural Tube Defects | 769 | 150 | 2082 | 3001 | 10.06 | 2870 | 9.62 |
| Anencephalus and similar | 92 | 85 | 951 | 1128 | 3.78 | 1104 | 3.70 |
| Encephalocele | 107 | 19 | 246 | 372 | 1.25 | 353 | 1.18 |
| Spina Bifida | 570 | 46 | 885 | 1501 | 5.03 | 1413 | 4.74 |
| Hydrocephaly | 848 | 94 | 761 | 1703 | 5.71 | 1532 | 5.14 |
| Microcephaly | 595 | 26 | 60 | 681 | 2.29 | 628 | 2.11 |
| Arhinencephaly/holoprosencephaly | 82 | 23 | 303 | 408 | 1.37 | 271 | 0.91 |
| **Eye** | 1027 | 7 | 74 | 1108 | 3.71 | 1010 | 3.39 |
| Anophthalmos/micropthalmos | 233 | 5 | 45 | 283 | 0.95 | 237 | 0.79 |
| Anophthalmos | 45 | 2 | 15 | 62 | 0.21 | 57 | 0.19 |
| Congenital cataract | 308 | 0 | 4 | 312 | 1.05 | 299 | 1.00 |
| Congenital glaucoma | 78 | 0 | 0 | 78 | 0.26 | 76 | 0.25 |
| **Ear, face and neck** | 487 | 14 | 176 | 677 | 2.27 | 512 | 1.72 |
| Anotia | 83 | 1 | 9 | 93 | 0.31 | 87 | 0.29 |
| **Congenital heart disease** | 18985 | 405 | 1932 | 21322 | 71.47 | 18674 | 62.60 |
| Common arterial truncus | 171 | 11 | 69 | 251 | 0.84 | 224 | 0.75 |
| Transposition of great vessels | 889 | 15 | 76 | 980 | 3.29 | 954 | 3.20 |
| Single ventricle | 93 | 10 | 73 | 176 | 0.59 | 162 | 0.54 |
| Ventricular septal defect | 8583 | 115 | 534 | 9232 | 30.95 | 8274 | 27.74 |
| Atrial septal defect | 5115 | 40 | 121 | 5276 | 17.69 | 4652 | 15.59 |
| Atrioventricular septal defect | 848 | 59 | 304 | 1211 | 4.06 | 499 | 1.67 |
| Tetralogy of Fallot | 798 | 16 | 124 | 938 | 3.14 | 810 | 2.72 |
| Tricuspid atresia and stenosis | 144 | 8 | 37 | 189 | 0.63 | 181 | 0.61 |
| Ebstein's anomaly | 98 | 19 | 25 | 142 | 0.48 | 135 | 0.45 |
| Pulmonary valve stenosis | 1074 | 3 | 22 | 1099 | 3.68 | 1060 | 3.55 |
| Pulmonary valve atresia | 204 | 3 | 63 | 270 | 0.91 | 254 | 0.85 |
| Aortic valve atresia/stenosis | 305 | 6 | 27 | 338 | 1.13 | 322 | 1.08 |
| Hypoplastic left heart | 413 | 33 | 349 | 795 | 2.66 | 725 | 2.43 |

| | | | | | | Excluding Chromosomal | |
|---|---|---|---|---|---|---|---|
| **Anomaly** | **LB N** | **FD N** | **TOPFA N** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** |
| Hypoplastic right heart | 76 | 9 | 46 | 131 | 0.44 | 120 | 0.40 |
| Coarctation of aorta | 924 | 16 | 69 | 1009 | 3.38 | 898 | 3.01 |
| Total anomalous pulm venous return | 158 | 1 | 10 | 169 | 0.57 | 161 | 0.54 |
| **Respiratory** | 1118 | 99 | 425 | 1642 | 5.50 | 1443 | 4.84 |
| Choanal atresia | 219 | 4 | 10 | 233 | 0.78 | 216 | 0.72 |
| Cystic adenomatous malf of lung | 222 | 6 | 31 | 259 | 0.87 | 258 | 0.86 |
| **Oro-facial clefts** | 4091 | 78 | 490 | 4659 | 15.62 | 4303 | 14.42 |
| Cleft lip with or without palate | 2427 | 52 | 356 | 2835 | 9.57 | 2608 | 8.80 |
| Cleft palate | 1654 | 26 | 134 | 1814 | 6.12 | 1685 | 5.69 |
| **Digestive system** | 3881 | 145 | 670 | 4696 | 15.74 | 4187 | 14.04 |
| Oesophageal atresia with or without tracheo-oesophageal fistula | 552 | 28 | 63 | 643 | 2.16 | 575 | 1.93 |
| Duodenal atresia or stenosis | 333 | 22 | 23 | 378 | 1.27 | 264 | 0.88 |
| Atresia or stenosis of other parts of small intestine | 251 | 3 | 7 | 261 | 0.87 | 258 | 0.86 |
| Ano-rectal atresia and stenosis | 673 | 16 | 183 | 872 | 2.92 | 800 | 2.68 |
| Hirschsprung's disease | 346 | 0 | 2 | 348 | 1.17 | 313 | 1.05 |
| Atresia of bile ducts | 73 | 1 | 4 | 78 | 0.26 | 77 | 0.26 |
| Annular pancreas | 46 | 0 | 8 | 54 | 0.18 | 39 | 0.13 |
| Diaphragmatic hernia | 582 | 51 | 152 | 785 | 2.63 | 706 | 2.37 |
| **Abdominal wall defects** | 1160 | 88 | 663 | 1911 | 6.41 | 1649 | 5.53 |
| Gastroschisis | 766 | 34 | 124 | 924 | 3.10 | 907 | 3.04 |
| Omphalocele | 361 | 53 | 460 | 874 | 2.93 | 637 | 2.14 |
| **Urinary** | 7263 | 200 | 1353 | 8816 | 29.55 | 8336 | 27.94 |
| Bilateral renal agenesis including Potter syndrome | 79 | 34 | 247 | 360 | 1.21 | 355 | 1.20 |
| Renal dysplasia | 999 | 30 | 294 | 1323 | 4.43 | 1260 | 4.22 |
| Congenital hydronephrosis | 2963 | 25 | 142 | 3130 | 10.49 | 3026 | 10.14 |
| Bladder exstrophy and/or epispadia | 125 | 4 | 38 | 167 | 0.56 | 165 | 0.55 |
| Posterior urethral valve and/or prune belly | 202 | 1 | 75 | 278 | 0.93 | 270 | 0.91 |
| **Genital** | 5044 | 40 | 196 | 5280 | 17.70 | 5146 | 17.25 |
| Hypospadias | 4228 | 8 | 39 | 4275 | 14.57 | 4224 | 14.40 |

| | | | | | | Excluding Chromosomal | |
|---|---|---|---|---|---|---|---|
| **Anomaly** | **LB N** | **FD N** | **TOPFA N** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** |
| Indeterminate sex | 154 | 13 | 48 | 215 | 0.72 | 194 | 0.65 |
| **Limb** | 10040 | 261 | 1149 | 11450 | 38.38 | 10790 | 36.17 |
| Limb reduction | 1158 | 90 | 404 | 1652 | 5.54 | 1538 | 5.16 |
| Upper limb reduction | 847 | 56 | 270 | 1173 | 3.93 | 1093 | 3.66 |
| Lower limb reduction | 374 | 42 | 186 | 602 | 2.02 | 559 | 1.87 |
| Complete absence of a limb | 14 | 4 | 37 | 55 | 0.18 | 55 | 0.18 |
| Club foot - talipes equinovarus | 2653 | 94 | 323 | 3070 | 10.29 | 2916 | 9.77 |
| Hip dislocation and/or dysplasia | 1893 | 3 | 5 | 1901 | 6.37 | 1879 | 6.30 |
| Polydactyly | 2318 | 30 | 162 | 2510 | 8.56 | 2362 | 8.05 |
| Syndactyly | 1210 | 37 | 88 | 1335 | 4.55 | 1244 | 4.24 |
| Arthrogryposis multiplex congenita | 116 | 8 | 69 | 193 | 0.65 | 191 | 0.64 |
| **Musculo-skeletal** | 1652 | 112 | 822 | 2586 | 8.67 | 2398 | 8.04 |
| Thanatophoric dwarfism | 13 | 6 | 81 | 100 | 0.34 | 100 | 0.34 |
| Jeunes syndrome | 9 | 1 | 16 | 26 | 0.09 | 26 | 0.09 |
| Achondroplasia | 82 | 2 | 22 | 106 | 0.36 | 104 | 0.35 |
| Craniosynostosis | 467 | 7 | 34 | 508 | 1.70 | 467 | 1.57 |
| Congenital constriction bands/amniotic band | 72 | 21 | 101 | 194 | 0.65 | 189 | 0.63 |
| **Other malformations** | 1441 | 109 | 494 | 2044 | 6.85 | 1841 | 6.17 |
| Asplenia | 19 | 3 | 20 | 42 | 0.14 | 38 | 0.13 |
| Situs inversus | 140 | 4 | 35 | 179 | 0.60 | 176 | 0.59 |
| Conjoined twins | 11 | 9 | 33 | 53 | 0.18 | 53 | 0.18 |
| Disorders of skin | 547 | 6 | 44 | 597 | 2.00 | 542 | 1.82 |
| **Teratogenic syndromes with malformations** | 301 | 23 | 66 | 390 | 1.31 | 380 | 1.27 |
| Fetal alcohol syndrome | 131 | 1 | 3 | 135 | 0.45 | 134 | 0.45 |
| Valproate syndrome | 27 | 0 | 2 | 29 | 0.10 | 28 | 0.09 |
| Warfarin syndrome | 0 | 0 | 0 | 0 | 0.00 | 0 | 0.00 |
| Maternal infections resulting in malformations | 104 | 14 | 49 | 167 | 0.56 | 165 | 0.55 |
| **Genetic syndromes + microdeletions** | 1401 | 45 | 267 | 1713 | 5.74 | 1645 | 5.51 |
| **Chromosomal** | 4441 | 420 | 5803 | 10664 | 35.75 | 0 | 0.00 |

| | | | | | | Excluding Chromosomal | |
|---|---|---|---|---|---|---|---|
| **Anomaly** | **LB N** | **FD N** | **TOPFA N** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** |
| Down Syndrome | 2923 | 133 | 3091 | 6147 | 20.61 | 0 | 0.00 |
| Patau syndrome/trisomy 13 | 116 | 24 | 430 | 570 | 1.91 | 0 | 0.00 |
| Edward syndrome/trisomy 18 | 236 | 125 | 1087 | 1448 | 4.85 | 0 | 0.00 |
| Turner's syndrome | 188 | 46 | 424 | 658 | 2.21 | 0 | 0.00 |
| Klinefelters syndrome | 170 | 3 | 92 | 265 | 0.89 | 0 | 0.00 |
| Cru-du-chat syndrome | 30 | 1 | 10 | 41 | 0.14 | 0 | 0.00 |
| Wolff-Hirschorn syndrome | 22 | 1 | 14 | 37 | 0.12 | 0 | 0.00 |

LB= Livebirth
FD= Fetal death from 20 weeks gestation
TOPFA= Termination of Pregnancy following prenatal diagnosis of a congenital anomaly

Some year 2008 data was uploaded to the website in April 2010 and we hope to complete 2008 for the majority of registries at the next deadline (15th October 2010). Year 2008 data was received from the following 23 registries: Styria (Austria), Antwerp, Hainaut (Belgium); Zagreb (Croatia); Odense (Denmark); Isle de la Reunion, Paris (France); Saxony-Anhalt (Germany); Dublin, SE Ireland (Ireland); Emilia Romagna, Tuscany (Italy); Malta, N Netherlands; South Portugal, Spain Hospital Network Sweden, East Midlands & South Yorkshire, Northern England, Thames Valley, Wales, Wessex (UK); and Ukraine.

Year 2007 data are available on the website for the 23 registries listed above and the following 6 registries Czech Republic, Rhone-Alps (France), Wielkopolska, Poland (Poland); Barcelona (Spain) and Vaud (Switzerland) For the 5 year time period 2004-2008, the prevalence of all congenital anomalies was 233.4 per 10,000 births and all non-chromosomal anomalies was 197.7 per 10,000 births. Congenital heart defects excluding chromosomal anomalies accounted for 31.6% of these anomalies, chromosomal anomalies 15.3% and neural tube defects (NTD) 4.3%.

Data on prenatal diagnosis (PD) was uploaded to the website tables for the first time in January 2008 (see WP2 and Appendices 1.4, 1.5 and 1.6). The PD tables are currently available for the following 21 registries: Styria (Austria); Hainaut (Belgium); Zagreb (Croatia); Odense (Denmark); Ile de la Reunion, Paris (France); Emilia Romagna, Tuscany (Italy); Malta; N Netherlands; Poland, Wielkopolska, (Poland); South Portugal; Barcelona (Spain); Vaud (Switzerland); East Midlands & South Yorkshire, N England, Thames Valley, Wales and Wessex (UK) and Ukraine. The PD tables cover the period 2004-2008. Some interesting statistics are detailed below:

a) overall, 73% of the following 6 anomaly subgroups (excluding cases with additional chromosomal anomalies) were prenatally diagnosed: anencephalus, spina bifida, transposition of great vessels, hypoplastic left heart, gastroschisis, bilateral renal agenesis (including Potter syndrome). The proportion prenatally diagnosed ranged from 33% for transposition of great vessels to 96% for anencephalus.
b) 51% of Down syndrome cases were prenatally diagnosed. The rates of prenatal diagnosis vary greatly between registries from 3% to 92%.
c) the rate of TOPFA per 1,000 births for All Anomalies combined varied between registries from 0.47 - 10.19.

**Statistical Monitoring and Investigation of Trends and Clusters**

Statistical monitoring to identify clusters and trends that may alert participants to changing teratogen exposures in the environment is run by Central Registry in February/ March each year. The methodology continues to be refined. All statistical programming at Central level is available locally via the EDMP. Trend detection is now run on short term trends (5 years) and long term trends (10 years). A minimum of 5 expected cases and 2 observed cases in any two year interval is required. This improvement in methodology means that fewer subgroups of congenital anomalies are excluded from analysis due to insufficient numbers. In addition, the output now shows both the test for trend and the test for non-linearity. Finally, to aid investigation reports, a new subgroup "Down syndrome adjusted" was created for monitoring purposes which corrects Down syndrome for survival and maternal age when testing for trends.

A new feature of Statistical Monitoring was introduced in the February 2009 version of the EUROCAT Central Registry database (ECD). This new feature enables us to run a trend analysis considering all registries combined ("pan-Europe analysis"), which is particularly useful for the rarer anomalies with too few data for analysis of trend for each registry separately. This general trend analysis allows us to see if a trend is unique to an individual registry or is more commonly experienced in Europe.

A new version of EDMP was released in June 2008 which allowed registries to run reports and statistical surveillance by region using the "User defined location" function. This improvement was particularly useful for large registries wishing to restrict analysis to a particular region covered by the registry. In addition, the statistical surveillance user interface was made more user-friendly to encourage registries to conduct statistical surveillance for clusters and trends locally.

EUROCAT Statistical Monitoring Report 2007 was uploaded to the website in May 2010 http://www.eurocat-network.eu/content/Stat-Mon-Report-2007.pdf This Report identifies clusters using the scan method and both pan-Europe and individual registry increasing trends that may alert participants to changing teratogen exposures in the environment (see Section D1).

Ten registries were included in a cluster analysis based on estimated date of conception identifying time clusters with date of conception from April 2005 to March 2007 (births 2006-2007), covering 0.5 million births per year. 23 clusters were detected where cases were unusually close together in time, more clusters than would be expected by chance. There was no pattern of time clusters in any one congenital anomaly subgroup occurring across Europe. Five of the clusters were identified in previous Statistical Monitoring Reports, but are no longer continuing. Of the remaining 18 clusters, diagnostic or data quality issues were thought to explain nine and 3 were not reported on. Preliminary registry

investigations confirmed an excess of cases in a further 6 and continued surveillance was recommended (choanal atresia, Edward syndrome, anencephalus, coarctation of aorta, bladder exstrophy, cleft palate).

In Pan-Europe monitoring, trend tests were performed for 94 of the 95 EUROCAT subgroups of congenital anomalies covering 4.0 million births in 22 EUROCAT registries, 1998-2007. Significant increasing trends over time were identified for the following anomalies: Hypoplastic left heart, total anomalous pulmonary venous return, cystic adenomatous malformation of lung, abdominal wall defects, gastroschisis, omphalocele, renal dysplasia, hypospadias, Edward syndrome/ Trisomy 18. Further investigations into these increasing trends are ongoing centrally.

Twenty-two registries were included in a time trend analysis, covering a population of 4.1 million births in 1998-2007. A total of 259 significant trends (89 increasing and 170 decreasing) were reported from surveillance of 95 anomaly subgroups, many more than would be expected by chance. Some of these confirmed known time trends, for example increases in gastroschisis, and in Down syndrome (the latter due to maternal age increases). Other trends were related to increasing use of prenatal or neonatal screening and diagnosis, or changing inclusion criteria. Registry preliminary investigations recommended further local surveillance for the following congenital anomalies: Respiratory anomalies, cleft palate, renal dysplasia, gastroschisis, upper limb reduction, Down syndrome and Edward syndrome/ Trisomy 18.

The EUROCAT Statistical Monitoring Report 2008 will be uploaded to the website in winter 2010 (see Section D1). Monitoring was conducted for 21 Full Member EUROCAT registries with population coverage varying between 4,000 to 74,000 births per year. The results of the long term trend monitoring are presented in EUROCAT Report 9, Paper 4 (see Section ??).

Sixteen registries were included in a cluster analysis identifying time clusters based on estimated date of conception from April 2006 to March 2008 (births 2007-2008), covering approximately 0.78 million births. Twenty-two clusters were detected where cases were unusually close together in time. Half of these clusters were based on older data and ended by December 2006, so there was less emphasis on these as they were not considered “recent”. Registry data were examined to determine whether there was cause for immediate concern for the remaining 11 “new” clusters. Registry investigation reports were available for 9 of the 11 clusters. An excess of cases was confirmed for 4 clusters, and the registries concluded that close further monitoring was necessary, but no immediate action was needed. The remaining five clusters were due to diagnostic or data quality issues.

**Scientific Papers**

(i) Trends and geographical differences in prevalence

In 2008, a study investigating maternal age specific risks of non-chromosomal anomalies 2000-2004 was conducted using data from 23 EUROCAT registries in 15 countries. Overall, the study showed that teenage mothers had an increased risk of non-chromosomal anomalies while older mothers 35-44 years had no increased risk compared to mothers aged 25-29 years. The pattern of maternal age-related risk varied significantly between countries: France, Ireland and Portugal had higher relative risks for teenage mothers, Germany and Poland had higher relative risks for older mothers.

> Loane M, Dolk H, Morris J and a EUROCAT Working Group (2009). Maternal age specific risk of non-chromosomal anomalies. British Journal Obstetrics & Gynaecology 116: 1111-1119
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> .

The prevalence of pyloric stenosis in livebirths was investigated in 7 European regions, 1980-2002. An overall prevalence of 2.0 per 1,000 livebirths was reported, ranging from 0.9 to 4.0 per 1,000 births. There was significant geographical variation with decreasing prevalence in two regions and increasing prevalence in two other regions. Young maternal age (<20 years) adjusted for region significantly increased the risk of pyloric stenosis by 29%.

> Pedersen RN, Garne E, Loane M, Korsholm L, Husby S and a EUROCAT Working Group **(2008)**, "Infantile Hypertrophic Pyloric Stenosis: A Comparative Study of Incidence and Other Epidemiological Characteristics in Seven European Regions", *The Journal of Maternal-Fetal and Neonatal Medicine*, Vol 21, No 9, pp 599-604.

Analysis of congenital heart defects 2000-2005 was conducted in 2008 which contributed to the "Global Burden of Disease, Injuries and Risk Factors" (GBDIRF) project 2007-2010, led by the WHO and Universities of Harvard, Washington, Johns Hopkins and Queensland (see A2). A EUROCAT Special Report on congenital heart defects 2000-2005 was uploaded to the EUROCAT website in March 2009: http://www.eurocat.ulster.ac.uk/pdf/ML/Reports/EUROCAT-Special-Report-CHD.pdf and a paper has been accepted for publication in CIRCULATION….

The total prevalence rate for non-chromosomal congenital heart disease (CHD) in Europe is 7 per 1,000 births.

The average rate of livebirths affected by CHD surviving the first week of life is 6.4 per 1,000 births. Differences between countries in perinatal mortality rates

and termination of pregnancy rates associated with CHD have little impact on this rate. An estimated 6% of these babies die before the age of 1 year.

Ventricular Septal Defect (VSD) and Atrial Septal Defect (ASD) are the most frequent CHD subtypes, accounting (with Pulmonary Valve Stenosis - PVS) for approximately three-quarters of non-chromosomal CHD cases. The vast majority of these children are liveborn and survive the first week, with 10% requiring surgery. A reasonable prevalence estimate for VSD/ASD/PVS combined is 5 per 1,000 births surviving the first week of life.

The remaining quarter of CHD mainly include conditions with higher perinatal mortality, high surgery rates, and conditions for which termination of pregnancy is the outcome for a significant proportion in some countries. The rate of cases surviving the first week of life for these conditions is 1.3 per 1,000 births, of whom an estimated 80% require surgery and 7% are too severe for surgery.

The average combined CHD mortality rate (perinatal deaths + terminations of pregnancy) in Europe is currently 0.7 per 1,000 births. However, a few countries have rates 50% or more in excess of this.

The main health service needs to reduce CHD burden are primary prevention, successful early treatment (possibly involving also improved prenatal diagnosis), and ongoing care for affected children and adults.

A case-control study reported a 35% increased risk of fathering a pregnancy with Klinefelter's syndrome (XXY) associated with older paternal age. The larger positive associations of Klinefelter and XYY syndromes with paternal age compared with Patau and Edwards syndromes are consistent with the greater percentage of these sex chromosome anomalies being of paternal origin.

de Souza E, Morris JK and a EUROCAT Working Group (2010), "Case-Control Analysis of Paternal Age and Trisomic Anomalies", Arch Dis Child,

A paper reporting the risk of NTD in teenage mothers is currently in preparation.
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(ii) Prevalence of rare genetic syndromes

Preliminary data analysis on Fraser syndrome (FS), a rare autosomal recessive condition, using EUROCAT database reported a prevalence of 0.23 per 100,000 births:

Odak LJ, Barisic I, Tokic V, Loane M, Bianchi F, Calzolari E, Garne E, Wellesley D, Dolk H, EUROCAT Working Group **(2008)**, "Epidemiological

Study of Fraser Syndrome in Europe", *European Journal of Human Genetics*, Vol 16, (Suppl 2), 375-376.

Cornelia de Lange syndrome has been the first of a list of rare syndromes to be fully described in terms of its epidemiology in Europe with EUROCAT data. Its prevalence was found to be 1.2 per 100,000 births.

Barisic I, Tokic V, Loane M, Bianchi F, Calzolari E, Garne E, Wellesley D, Dolk H and EUROCAT Working Group **(2008)**, "Descriptive Epidemiology of Cornelia de Lange Syndrome in Europe", *American Journal of Medical Genetics Part A*, Vol 146A, pp 51–59.

# A5 Work Package No. 5 – Prevention of Congenital Anomalies by Raising Periconceptional Folate Status

The objectives of this Work Package are:

a) To evaluate the effectiveness of primary prevention of congenital anomalies by raising periconceptional folate status
b) To survey policy and practice in European countries regarding folic acid supplementation/fortification
c) To evaluate temporal trends in prevalence of neural tube defects and other potentially preventable congenital anomalies in relation to prevention strategies

**Description of Work**

We have updated the individual country chapters on periconceptional folic acid supplementation in the EUROCAT Report "Prevention of Neural Tube Defects by Periconceptional Folic Acid Supplementation in Europe, December 2009". This updated Survey of Folic Acid Policy and Practice in European Countries also includes a chapter for Slovenia and Hungary which were not included in the previous reports: http://www.eurocat.ulster.ac.uk/pubdata/Folic-Acid.html#December%202007

We continue to collect data enabling us to calculate the birth prevalence of specified congenital anomalies including NTDs and other anomalies that might be prevented by periconceptional folic acid. We have analysed the NTD data 1980-2006 in the light of prevention strategies in individual countries and investigated trends over time in relation to policy changes which would indicate success in prevention. The current situation with regard to NTDs will be included in the opening chapter of the EUROCAT Report "Prevention of Neural Tube Defects by Periconceptional Folic Acid Supplementation in Europe, 2009" which will appear on the EUROCAT website in May 2009.

Data on periconceptional folic acid use has been collected since 2005, but the variable has not been completed for the majority of cases. The updated Report 2009 will show the distribution of periconceptional use of folic acid throughout Europe in so far as it has been reported. In general this item has a low degree of completeness and for the Registries that have access to these data the uptake of folic acid in general is low. The Working Group is reviewing the coding of the Folic Acid variable, in order to improve reporting of this variable. We are in the process of conducting a survey to ascertain what information about folic acid use in pregnancy is being routinely collected during antenatal care.

We are in the process of designing a new Folic Acid section for the website to be incorporated under Prevention. Lenore Abramsky and Hermien de Walle will work on this together with the registry Leader of Malta, Dr Miriam Gatt. This will be done in co-operation with the persons working under section A2.1 (redesigning the EUROCAT website).

## A6 Work Package No. 6 – Maternal Disease and Drug-Exposure During Pregnancy

The objectives of the work package were:

a) To develop and implement postmarketing surveillance of teratogenic risks of drugs taken during pregnancy
b) To focus on risk associated with maternal chronic diseases such as epilepsy, diabetes, asthma, as well as maternal myasthenia gravis

**Description of Work**

Pharmacovigilance

We are building a reproductive pharmacovigilance system "EUROmediCAT" based on the successful recent developments in EUROCAT. The aims of the system are to provide early warning regarding risk of congenital anomaly related to medication use in early pregnancy, to test signals generated by pregnancy registers and other sources, and to monitor whether known teratogens have been successfully avoided during pregnancy. For 2 years, the University of Groningen has collected information about non-malformed controls using the same data collection methods as for the malformed registrations. We initiated an antiepileptic drug utilisation study in pregnancy among different countries. Italy (Emilia Romagna), Norway, Germany, France and the Netherlands are currently involved and we hope that Belgium and Denmark will also join this project. This project is the first step in setting up the expanded dataset with non-malformed pregnancies. A publication can be expected December 2009.

EUROCAT Central Registry and the University of Groningen is also involved in the ENCCeP network of the European Medicines Evaluation Agency (EMEA). This is an important forum for pharmacovigilance. At the moment, work is ongoing to develop a code of conduct for scientific independence and transparency, particularly in industry funded pharmacovigilance studies, and to catalogue the databases and expertise existing around Europe. Helen Dolk and Lolkje de Jong van de Berg represent EUROCAT at EncePP. University of Groningen are partners in the PROTECT consortium bid for IMI funding led by EMEA. As partner to this project, the University of Groningen will seek to make it relevant to EUROCAT's work on improving information about drug exposure during pregnancy.

Anti-epileptic Drug Studies

In 2007, EUROCAT created a EUROCAT Antiepileptic dataset including data from 19 registries, 1995-2005. This dataset was used to conduct a case-control study evaluating the risk of orofacial clefts in relation to lamotrigine exposure. The study found no evidence of a specific increased risk of isolated orofacial clefts relative to other malformations due to lamotrigine monotherapy.

Dolk H, Jentink J, Loane M, Morris J, de Jong-van den Berg LTW and EUROCAT Antiepileptic Drug Working Group **(2008),** "Does Lamotrigine Use in Pregnancy Increase Orofacial Cleft Risk Relative to Other Malformations?", *Neurology,* Vol 71, pp 714-722.

In 2008, we analysed the anti-epileptic drugs Valproic Acid (VPA) in relation to increased risk of specific birth defects using the AED dataset. The study found VPA use in the 1st trimester of pregnancy significantly increased the risk of six specific congenital anomalies, and that the increased risk remained for VPA exposure compared to exposure to other anti-epileptics drugs.

Jentink J, Loane MA, Dolk H, Barisic I, Garne E, Morris JK, de Jong-van den LTW and the EUROCAT Antiepileptic Drug Working Group (2010). Valproic acid monotherapy in pregnancy and major congenital malformations. New England Journal of Medicine 362: 2185-2193

A third study assessing the risk of congenital anomalies in relation to carbamazepine has been accepted for publication (BMJ). This study found that carbamazepine teratogenicity is relatively specific to spina bifida, though the risk is less than with valproic acid.

Jentink J, Dolk H, Loane MA, Morris JK, Wellesley DG, Garne E, and de Jong-van den Berg LTW. Intrauterine carbamazepine exposure and specific congenital malformations. BMJ (in press)

A study of the risk of congenital anomaly in relation to lamotrigine exposure, with updates data of a previously published study, is ongoing

Training

ATC-coding workshops were held in Helsinki 2008, Bilbao 2009 and Dublin 2010. The aim of the workshops is to instruct members how to use the ATC-codes and advise on the local availability of codes in their country. During the workshops feedback was given about data transmitted to the central database.

We continue to improve the validity and completeness of first trimester drug exposure in pregnancy. Since 2005, the existing drug variables in EDMP were modified to collect information on the actual ATC drug code. Nineteen registries transmitted ATC drug codes used in the first trimester for the years 2005 and 2006. We are checking and summarising this data to develop quality indicators to improve drug data collection within the EUROCAT database.

Arthrogryposis Multiplex Congenita (AMC)

A study on AMC was conducted using data from 23 registries, 1980-2006 and reported a prevalence of 8.5 per 100.000 births. The study found that most cases of AMC had other malformations and a perinatal mortality of 32%. Although information on potential risk factors such as maternal disease or

maternal use of drugs was limited, they did not appear to be associated with the occurrence of AMC. This paper is currently submitted for publication (European Journal of Obstetrics and Gynaecology).

## A7 Work Package No. 7 – Surveillance of Prenatal Screening and Diagnosis of Congenital Anomalies in Europe

The objectives of the work package were:

a) To analyse trends and regional difference in prenatal detection rate, gestational age at prenatal diagnosis and outcome of pregnancy and relate these to screening policies
b) To assess the impact of termination of pregnancy on livebirth prevalence rates
c) To assess the impact of developments in prenatal screening

**Description of the Work**

Trends and Prenatal Detection

Work on analysis of trends and regional difference in prenatal detection rate, gestational age at prenatal diagnosis and outcome of pregnancy is ongoing.

A paper was published showing geographical differences in prevalence of congenital hydronephrosis 1995-2004 using data from 20 EUROCAT registries:

> Garne E, Loane M, Wellesley D, Barisic I and a EUROCAT Working Group **(2009)**, "Congenital Hydronephrosis - Prenatal Diagnosis and Epidemiology in Europe", *Journal of Pediatric Urology*, Vol 5, pp 47-52.

The prevalence of congenital hydronephrosis (excluding chromosomal anomalies) in Europe was 11.5 per 10,000 births (range 2 to 29 per 10,000 births), with 73% of cases diagnosed prenatally. There were large regional differences in the prevalence of prenatally diagnosed cases, but not in postnatally diagnosed cases. The huge difference in prevalence was explained by the availability of prenatal screening in the participating registries.

A study was conducted in 4 EUROCAT registries describing the prevalence, prenatal diagnosis and outcome of pregnancy of congenital hydrocephalus, 1996-2003:

> Garne E, Loane M, Addor MC, Boyd PA, Barisic I and Dolk H (2010). Congenital hydrocephalus – prevalence, prenatal diagnosis and outcome of pregnancy in four European regions. European Journal of Paediatric Neurology 14: 150-155

The prevalence of congenital hydrocephalus was 4.65 per 10,000 births. Eighty per cent of cases were diagnosed prenatally. Almost half of the cases (48%) were terminated following prenatal diagnosis of fetal anomaly; 47% were liveborn and 5% were fetal deaths.

A study assessing prevalence and trends in prenatal diagnosis of Sex Chromosome Trisomies (SCT) in Europe 2000-2005 was published in 2010 using data from 19 population-based registries in 11 European countries. There is wide variation between European countries in prenatal diagnosis and TOPFA rates, related to differences in screening policies as well as organisational and cultural factors.

> Boyd PA, Loane M, Garne E, Khoshnood B, Dolk H, and a EUROCAT working group (2010). Sex Chromosome Trisomies in Europe: Prevalence, prenatal detection and outcome of pregnancy. European Journal of Human Genetics. doi:10.1038/ejhg.2010.148

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Impact of Termination of Pregnancy

A paper describing the prevalence of terminations of pregnancy (TOPFA) after 23 weeks gestation in Europe was published. Late TOPFA is rare in Europe, and varies in prevalence between countries. Compared with earlier TOPFA, late TOPFA (after 23 weeks gestation) is more often performed for a nonchromosomal isolated major structural anomaly and less often for a fetus with a chromosomal syndrome or multiple anomalies.

> Garne E, Khoshnood B, Loane M, Boyd P, Dolk H and EUROCAT Working Group (2010). Terminations of pregnancy for fetal anomaly after 23 weeks of gestation: a European registry-based study. British Journal Obstetrics & Gynaecology 117 (6): 660-666

A paper describing the impact of increasing maternal age, termination of pregnancy for fetal anomaly and prenatal screening on the livebirth prevalence of Down syndrome and other trisomies 1990-2007 is currently in preparation for submission to a journal.

Developments in Prenatal Screening

The paper on prenatal screening policies across Europe in 2004 was published:

> Boyd PA, DeVigan C, Khoshnood B, Loane M, Garne E, Dolk H and the EUROCAT working group **(2008)**, "Survey of Prenatal Screening Policies in Europe for Structural Malformations and Chromosome Anomalies, and Their Impact on Detection and Termination Rates for Neural Tube Defects and Down's Syndrome", *British Journal of Gynaecology,* Vol 115, No 6, pp 689-696.

An updated survey of prenatal screening policies in each participating European country, including organization of services, where/how policy decisions are made, types of tests offered, gestational age at offer, legal situation regarding

termination of pregnancy was published in 2010. This report updates a previous one from 2004 to 2009/10 and outlines National policies regarding screening for Down Syndrome, indications for prenatal cytogenetic testing, screening for structural anomalies by ultrasound scanning and the laws for termination of pregnancy for fetal anomaly in different European countries. Each chapter is written by a EUROCAT representative from the different countries. (see Section ??)

Website

The PRENATAL SCREENING section of the website is now accessible from the home page which allows greater access to this information: http://www.eurocat-network.eu/HomePage. It includes information on prenatal screening policies in European countries, tables showing prenatal detection rates of specific congenital anomalies and any publications related to Prenatal Screening.

# B EUROCAT Partner Roles

## B1 Central Registry (University of Ulster). Leads Workpackages 1, 2, 3 and 4

Prof Helen Dolk:
EUROCAT Project leader, University of Ulster
Dr Carol Curran:
Head of School, University of Ulster
(September 2007 to November 2007)
Dr Owen Barr:
Head of School, University of Ulster (December 2007 onwards)
Maria Loane:
Lecturer/ Research Fellow and Database Manager,
University of Ulster
Ruth Greenlees:
Database Assistant, University of Ulster
Evie Gardner
Statistician, University of Ulster
Breidge Boyle:
Researcher, University of Ulster
Anthony Wemakor:
Researcher, University of Ulster
Michiel Luteijn:
Researcher, University of Ulster
Barbara Norton:
Administrator, University of Ulster
Barbra Webber:
Administrator, University of Ulster

## B2 Project Management Committee

The Project Management Committee consists of the Project Leader, Database Manager, elected Registry Leaders and Working Group Chairs:

Patricia Boyd (UK: President of EUROCAT Association) 2006-2010
Elisa Calzolari (Italy) 2008-2012*
Lolkje de Jong van den Berg (The Netherlands: Chair of
Drug Working Group)*
Catherine de Vigan (France: President of EUROCAT Association)
2003-2008
Hermien de Walle (The Netherlands: Chair of Folic Acid Working Group)
2005-2009*
Helen Dolk (UK: Project Leader)*
Ester Garne (Denmark: Chair of Coding & Classification Committee
and Prenatal Diagnosis Working Group)*

Martin Haeusler (Austria) 2007-2011*
Lorentz Irgens (Norway: President of EUROCAT Association) 2007-2011*
Babak Khoshnood (France) 2009-2013*
Maria Loane (UK: Database Manager)*
Vera Nelen (Belgium) 2007-2011*
Diana Wellesley (UK) 2010-2014*

* Current member of Project Management Committee (11 in total)

## B3 Working Group / Work Package Members

Coding & Classifcation Committee
Ingeborg Barisic (Croatia)
Elisa Calzolari (Italy)
Ester Garne (Chair) (Denmark)
David Tucker (UK)
Diana Wellesley (UK)

Workpackage 5 – Prevention of Congenital Anomalies by Raising Periconceptional Folate Status
Lenore Abramsky (UK, co-Chair)
Marie-Claude Addor (Switzerland)
Ingeborg Barisic (Croatia)
Andrea Berghold (Austria)
Patricia Boyd (UK)
Elisa Calzolari (Italy)
Marianne Christiansen (Denmark)
Guide Cocchi (Italy)
Anne Dalveit (Norway)
Carlos Matias Dias (Portugal)
Hermien de Walle (The Netherlands, co-Chair)
Helen Dolk (UK)
Ester Garne (Denmark)
Miriam Gatt (Malta)
Yves Gillerot (Belgium)
Martin Haeusler (Austria)
Anna Latos-Bielenska (Poland)
Bob McDonnell (Ireland)
Vera Nelen (Belgium)
Amanda Neville (Italy)
Birgitta Ollars (Sweden)
Ksenija Ogrizek Pelkic (Slovenia)
Simone Poetzsch (Germany)
Isabel Portillo (Spain)

Annukka Ritvanen (Finland)
Janos Sandor (Hungary)

Workpackage 6 – Maternal Disease and Drug-Exposure During Pregnancy
Marian Bakker (The Netherlands)
Lolkje de Jong van den Berg (The Netherlands, Chair)
Helen Dolk (UK)
Arno Ebner (Germany)
Lorentz Irgens (Norway)
Janneke Jentink (The Netherlands)
Anna Materna-Kiryluk (Poland)
Jan Mejnartowicz (Poland)
Vera Nelen (Belgium)
Amanda Neville (Italy)
Francesca Riviera (Italy)
David Tucker (UK)
Awi Wiesel (Germany)

Workpackage 7 - Prenatal Diagnosis and Diagnosis of Congenital Anomalies in Europe
Fabrizio Bianchi (Italy)
Patricia Boyd (UK)
Elisa Calzolari (Italy)
Catherine de Vigan (France)
Hermien de Walle (The Netherlands)
Carlos Matias Dias (Portugal)
Helen Dolk (UK)
Ester Garne (Denmark, Chair)
Miriam Gatt (Malta)
Yves Gillerot (Belgium)
Martin Haeusler (Austria)
Lorentz Irgens (Norway)
Babak Khoshnood (France)
Anna Latos-Bielenska (Poland)
Maria Loane (UK)
Joan Morris (UK)
Vera Nelen (Belgium)
Isabel Portillo (Spain)
Annette Queisser-Luft (Germany)
Annukka Ritvanen (Finland)

## B4 Participating Registries

In EU Countries (see Appendix 3 for addresses)

| | |
|---|---|
| Austria, Styria | Martin Haeusler |
| Belgium, Antwerp | Vera Nelen |
| Belgium, Hainaut | Christine Verellen-Dumoulin |
| Czech Republic | Antonin Sipek |
| Denmark, Odense | Ester Garne |
| Finland | Annukka Ritvanen |
| France, Auvergne | Christine Francannet |
| France, Ile de la Reunion | Jean Luc Alessandri |
| France, Paris | Catherine de Vigan / Babak Khoshnood |
| France, Rhone-Alps | Emmanuelle Amar |
| France, Strasbourg | Berenie Doray |
| Germany, Mainz | Annette Queisser-Luft |
| Germany, Saxony-Anhalt | Simone Poetzsch |
| Hungary | Judit Beres |
| Ireland, Cork & Kerry | Mary O'Mahony |
| Ireland, Dublin | Bob McDonnell |
| Ireland, Galway | David Lillis |
| Ireland, South East | Carmel Mullaney |
| Italy, Campania | Gioacchino Scarana |
| Italy, Emilia Romagna | Elisa Calzolari |
| Italy, North East | Romano Tenconi |
| Italy, Tuscany | Fabrizio Biachi |
| Italy, Sicily | Sebastiano Bianca |
| Malta | Miriam Gatt |
| Netherlands, North | Marian Bakker |
| Poland | Anna Latos-Bielenska |
| Portugal | Carlos Matias Dias |
| Spain, Asturias | Carmen Mosquera-Tenreiro |
| Spain, Barcelona | Joaquin Salvador |
| Spain, Basque Country | Isabel Portillo |
| Spain, ECEME Network | Maria-Luisa Martinez-Frias |
| Sweden | Goran Anneren |
| UK, Bristol | Rosie Thompson |
| UK, E Midlands & S Yorkshire | Elizabeth Draper |
| UK, England NCAS | Vera Ruddock |
| UK, Glasgow | David Stone |
| UK, NDSCR | Joan Morris |
| UK, North Thames | Currently not active |
| UK, Northern England | Martin Ward Platt |
| UK, Thames Valley | Patricia Boyd |

| | |
|---|---|
| UK, Wales | David Tucker |
| UK, Wessex | Diana Wellesley |

In Non-EU Countries (see Appendix 3 for addresses)

| | |
|---|---|
| Croatia | Ingeborg Barisic |
| Norway | Lorentz Irgens / Stein Emil Vollset |
| Switzerland | Marie-Claude Addor |
| Ukraine | Wladimir Wertelecki |

# C Meeting, Workshops and Travel

## C1 Project Committee Meetings

| | |
|---|---|
| 26-27 November 2007 | Edinburgh, UK |
| 8 April 2008 | Amsterdam, The Netherlands |
| 5 June 2008 | Helsinki, Finland |
| 30-31 October 2008 | London, UK |
| 18-19 March 2009 | Bologna, Italy |
| 11-12 June 2009 | Bilbao, Spain |
| 26-27 November 2009 | Copenhagen, Denmark |
| 27 April 2010 | Belfast, Northern Ireland, UK |

## C2 Registry Leaders' Meetings and Symposiums

23rd EUROCAT Registry Leaders' Meeting was held in Helsinki, Finland (6-7 June 2008). 28 Registry Leaders attended as well as 23 Central Registry and Local Registry Staff and 5 other guests. The attendance list and agenda can be found in Appendix 4). Total 56 participants.

24th EUROCAT Registry Leaders' Meeting and 10th European Symposium on Prevention of Congenital Anomalies was held in Bilbao, Spain (10-12 June 2009). 27 Registry Leaders attended as well as 26 Central Registry and Local Registry Staff and 6 other guests. The attendance list and agenda can be found in Appendix 4). Total 59 participants.

25th EUROCAT Registry Leaders' Meeting was held in Dublin, Ireland (11-12 June 2010). 31 Registry Leaders attended as well as 30 Central Registry and Local Registry Staff and 7 other guests. The attendance list and agenda can be found in Appendix 4). Total 68 participants.

## C3 Workshops

During the 23rd EUROCAT Registry Leaders' Meeting the following workshops and committee meetings were held – Coding Committee Meeting, Malformation Coding Workshop, ATC Drug Coding Workshop, EDMP Clinic, Antiepileptic Drug Study Working Group, Bio-monitoring Group Meeting, Folic Acid Working Group, Foetal Alcohol Syndrome Meeting, Statistical Surveillance Clinic, Hospital Activity Data Meeting, Antidepressant Study Protocol Development Meeting and Prenatal Diagnosis Working Group

A Coding Workshop was also held prior to the 23rd EUROCAT Registry Leaders' Meeting on 5 June 2008 in Helsinki, Finland.

During the 24th EUROCAT Registry Leaders' Meeting the following workshops and committee meetings were held – Drugs During Pregnancy, ICD11 Meeting, ATC Coding Workshop, Statistical Monitoring Clinic, EDMP Clinic, AED Working Group, Folic Acid Meeting, Guide 1.3 Revisions Committee, Foetal Alcohol Working Group and Cluster Investigation Workshop.

A Coding Committee Meeting was held in Ferrara, Italy on 25 May 2010.

During the 25th EUROCAT Registry Leaders' Meeting the following workshops and committee meetings were held – Electronic and Web-Based Data Capture Workshop, Drugs During Pregnancy, Statistical Monitoring Session, Primary Prevention Meeting, EUROmediCAT Meeting, Air Pollution Meeting and EDMP Clinic.

A Coding Workshop was also held prior to the 25th EUROCAT Registry Leaders' Meeting on 10 June 2010 in Dublin, Ireland.

## C4 Travel for Presentations

9-13 September 2007, Florence, Italy
8th World Congress of Perinatal Medicine
"Congenital Hydronephrosis – Prenatal Diagnosis and Epidemiology in Europe" by Ester Garne

12-14 September 2007 - Cork, Ireland
Society for Social Medicine Conference
"Maternal Age-Specific Risk of Non-Chromosomal Anomalies Using EUROCAT Data" by Maria Loane
"Prenatal Diagnosis" by Patricia Boyd

3-6 October 2007 – Gastein, Austria
European Commission: 10th European Health Forum
Poster Presentation

18-19 October 2007 – Copenhagen, Denmark
8th EPPOSI Workshop on Partnering for Rare Disease Therapy Development
Attended by Ester Garne

20-21 November 2007 – Luxembourg
DG Health & Consumer Protection: Directorate C2 Health Information Children's Workshop
"European Surveillance of Congenital Anomalies" by Ester Garne

5-6 April 2008 – Warsaw, Poland
EUROPERISTAT II, Better Statistics for Better Health for Pregnant Women and their Babies
"Occurrence of Birth Defects in Europe as registered by EURO PERISTAT and EUROCAT: Comparative Aspects" by Lorentz Irgens

25-26 August 2008 – Geneva, Switzerland
A Prioritized Research Agenda for Prevention and Control of Noncommunicable Diseases
Working Group on "Genetics and Chronic Diseases" attended by Patricia Boyd

27-30 August 2008 – Budapest, Hungary
1st Central and Eastern European Summit on Preconception Health and Prevention of Birth Defects
"Birth defects in the Central and Eastern European Region: Morbidity, Epidemiology, Current Activities" by Anna Latos-Bielenska

26 September 2008 – Leicester, UK
BINOCAR, New Developments in the Detection and Treatment of Congenital Anomalies Scientific Conference
Attended by Ruth Greenlees and Maria Loane

16-17 October 2008 – Paris, France
9th EPPOSI Workshop on Partnering for Rare Disease Therapy Development
Attended by Ester Garne

24-28 October 2008 – Nice, France
2nd Congress of the European Academy of Paediatrics (EAP)
"Congenital Hydrocephalus: Prevalence, Prenatal Diagnosis and outcome of Pregnancy in Four European Regions" and
"Infantile Hypertrophic Pyloric Stenosis – A Comparative Study of Incidence and Epidemiology in Seven European Regions"
Poster Presentations by Ester Garne

24-28 October 2008 – Nice, France
2nd Congress of the European Academy of Paediatrics (EAP)
"Congenital Malformations in Children with Cerebral Palsy in European Regions – Prevalence and Clinical Pattern" by Ester Garne

5-7 November 2008 – Ottawa, Canada
Canadian Congenital Anomalies Surveillance Network (CCASN) Planning Meeting
"An International perspective on Data Collection Across Jurisdictions" by Ester Garne

23-25 February 2009 – Rome, Italy
International Conference on Rare Diseases and Orphan Drugs
"EUROCAT – Epidemiological Studies" by Fabrizio Bianchi

10-11 March 2009 – Moldova
Workshop for the Elaboration of the National programe for Monitoring of Congenital Malformations
"Surveillance of Congenital Anomalies in Europe and Use of the Data held by EUROCAT" by Patricia Boyd

27 June to 2 July 2009 – Portoroz, Slovenia
8th World Congress in Fetal Medicine
"European Malformation Registries" by Martin Haeulser

13-14 November 2009 – Portoroz, Slovenia
4th Congress of Slovenia Gynaecology and Obstetrics
"EUROCAT – Epidemiological Surveillance of Congenital Anomalies in Europe" by Ingeborg Barisic
"Congenital Heart Disease in Europe" by Martin Haeusler

17 November 2009 – London, UK
EU H1N1 Vaccines Pharmacovigilance Strategy
Attended by Helen Dolk

18 November 2009 – London, UK
EncePP Meeting
Attended by Helen Dolk

27 January 2010 – Brussels, Belgium
International Federation for Spina Bifida and Hydrocephalus "Act Against Europe's Most Common Birth Defects"
"Latest EUROCAT Data on NTDs" by Hermien de Walle

20-24 June 2010 – Rhodes, Greece
9th World Congress in Fetal Medicine
"Prevention of Neural Tube Defects by Periconceptional Folic Acid Supplementation in Europe" by Hermien de Walle and Martin Haeusler

26-29 May 2010 – Innsbruck, Austria
44th Annual Meeting of the Association for European Paediatric Cardiology
"Congenital Heart Defects in Europe 2000-2005" by Ester Garne

24-28 October 2008 – Nice, France
2nd Congress of the European Academy of Paediatrics (EAP)
"Congenital Hydrocephalus: Prevalence, Prenatal Diagnosis and outcome of Pregnancy in Four European Regions" and
"Infantile Hypertrophic Pyloric Stenosis – A Comparative Study of Incidence and Epidemiology in Seven European Regions"
Poster Presentations by Ester Garne

24-28 October 2008 – Nice, France
2nd Congress of the European Academy of Paediatrics (EAP)
"Congenital Malformations in Children with Cerebral Palsy in European Regions – Prevalence and Clinical Pattern" by Ester Garne

5-7 November 2008 – Ottawa, Canada
Canadian Congenital Anomalies Surveillance Network (CCASN) Planning Meeting
"An International perspective on Data Collection Across Jurisdictions" by Ester Garne

23-25 February 2009 – Rome, Italy
International Conference on Rare Diseases and Orphan Drugs
"EUROCAT – Epidemiological Studies" by Fabrizio Bianchi

## C5 Central Registry Co-ordination Travel

| Person | Travel From / To | Date |
|---|---|---|
| Helen Dolk | Belfast to Cork | September 2007 |
| Barbara Norton | Belfast to Coleraine | September 2007 |
| Helen Dolk | Belfast to Luxembourg | October 2007 |
| Helen Dolk | Belfast to Paris | November 2007 |
| Patricia Boyd | Oxford to Belfast | January 2008 |
| Ester Garne | Odense to Belfast | January 2008 |
| Lolkje de Jong v d Berg | Groningen to Belfast | February 2008 |
| James Densem | London to Belfast | February 2008 |
| Helen Dolk | Belfast to Luxembourg | February 2008 |
| Janneke Jentink | Groningen to Belfast | February 2008 |
| Maria Loane | Belfast to Oxford | February 2008 |
| Maria Loane | Belfast to Dublin | February 2008 |
| Helen Dolk | Belfast to Geneva | April 2008 |
| Ester Garne | Odense to Belfast | April 2008 |
| Conor Teljeur | Dublin to Belfast | May 2008 |
| Patricia Boyd | Oxford to Geneva | August 2008 |
| Patricia Boyd | Oxford to Belfast | September 2008 |
| Ester Garne | Odense to Belfast | September 2008 |
| Ruth Greenlees | Belfast to Leicester | September 2008 |

| | | |
|---|---|---|
| Maria Loane | Belfast to Leicester | September 2008 |
| Patricia Boyd | Oxford to Belfast | January 2009 |
| Lolkje de Jong v d Berg | Groningen to Belfast | January 2009 |
| Diana Wellesley | Southampton to Belfast | January 2009 |
| Helen Dolk | Belfast to Columbia* | February 2009 |
| Ester Garne | Odense to Belfast | February 2009 |
| Patricia Boyd | Oxford to Geneva | April 2009 |
| Helen Dolk | Belfast to Geneva | April 2009 |
| Helen Dolk | Belfast to Luxembourg | April 2009 |
| Barbara Norton | Belfast to Hastings | April 2009 |
| Ester Garne | Odense to Belfast | May 2009 |
| Diana Wellesley | Southampton to Belfast | May 2009 |
| Lolkje de Jong v d Berg | Groningen to Belfast | September 2009 |
| Helen Dolk | Belfast to London | September 2009 |
| Ester Garne | Odense to Belfast | September 2009 |
| James Densem | Hastings to Belfast | October 2009 |
| Lolkje de Jong v d Berg | Groningen to Belfast | November 2009 |
| Helen Dolk | Belfast to Paris | November 2009 |
| Patricia Boyd | Oxford to Luxembourg | December 2009 |
| Patricia Boyd | Oxford to Belfast | December 2009 |
| Helen Dolk | Belfast to Luxembourg | December 2009 |
| Patricia Boyd | Oxford to Belfast | January 2010 |
| Breidge Boyle | Belfast to Dublin | January 2010 |
| Helen Dolk | Belfast to Groningen | January 2010 |
| Ester Garne | Odense to Belfast | January 2010 |
| Ruth Greenlees | Belfast to Dublin | January 2010 |
| Patricia Boyd | Oxford to Luxembourg | February 2010 |
| Helen Dolk | Belfast to Luxembourg | February 2010 |
| Maria Loane | Belfast to Luxembourg | February 2010 |
| Mary O'Mahony | Cork to Luxembourg | February 2010 |
| Patricia Boyd | Oxford to Belfast | March 2010 |
| Maria Loane | Belfast to London | March 2010 |
| Helen Dolk | Belfast to Brussels | April 2010 |
| Michiel Luteijn | Belfast to London | June 2010 |
| Sam Pattenden | London to Belfast | July 2010 |

* Not included in EUROCAT budget

## C6 Visitors to Central Registry

| | |
|---|---|
| Laura Arbor | March 2009 |

# D Publications List

## D1 Collaborative Publications (See also Appendix 7)

### 2007


1. Abramsky L, Dolk H and a EUROCAT Folic Acid Working Group **(2007)**, "Should Europe Fortify a Staple Food with Folic Acid?", *The Lancet*, Vol 369, pp 641-642.
2. Armstrong B, Dolk H, Pattenden H, Vrijheid M, Loane M, Rankin J, Dunn CE, Grundy C, Abramsky L, Boyd PA, Stone D and Wellesley D **(2007)**, "Geographic Variations and Localised Clustering of Congenital Anomalies in Great Britain", *Emerging Themes in Epidemiology*, Vol 4, No 4.
3. Calzolari E, Pierini A, Astolfi G, Bianchi F, Neville AJ, Rivieri F and the EUROCAT Working Group **(2007)** "Associated Anomalies in Multi-Malformed Infants with Cleft Lip and Palate: An Epidemiologic Study of Nearly 6 Million Births in 23 EUROCAT Registries", *American Journal of Medical Genetics Part A*, Vol 143, No 6, pp 528-527.
4. Dolk H **(2007)**, "EUROCAT: Surveillance of Environmental Impact", Nicolopoulou-Stamati et al (Eds), *Congenital Diseases and the Environment*, pp 131-145.
5. EUROCAT **(2007**), "9th European Symposium on the Prevention of Congenital Anomalies, 7-9 May 2007, Naples, Italy", Conference Programme. [http://www.eurocat-network.eu/ABOUTUS/Publications/SymposiaAndWorkshops/NaplesSymposium2007]
6. Garne E, Loane M, Dolk H and a EUROCAT Working Group **(2007)**, "Gastrointestinal Malformations: Impact of Prenatal Diagnosis on Gestational Age at Birth", *Paediatric and Perinatal Epidemiology*, Vol 21, pp 370-375.
7. Garne E, Loane M, Nelen V, Bakker M, Gener B, Abramsky L, Addor M-C and Queisser-Luft A **(2007)**, "Survival and Health in Liveborn Infants with Transposition of Great Arteries - A Population Based Study", *Congenital Heart Diseases*, Vol 2, pp 165-169.
8. Loane M, Dolk H, Bradbury and a EUROCAT Working Group **(2007)**, "Increasing Prevalence of Gastroschisis in Europe 1980-2002: A Phenomenon Restricted to Younger Mothers?", *Paediatric and Perinatal Epidemiology*, Vol 21, pp 363-369.
9. Loane M, Garne E **(2007)**, "Prevalence and Pathogenesis of Congenital Anomalies in Cerebral Palsy - Letter to Editor", *Archives of Disease in Childhood - Fetal and Neonatal Edition*. [http://fn.bmj.com/content/92/6/F489/reply#fetalneonatal_el_1948?sid=5ab248f2-5b87-4f88-aef5-89d697d307e7]

10. Mastrioacovo P, Lisi A, Castilla E, Martinez-Frias M_L, Bermejo E, Marengo L, Kucik J, Siffel C, Halliday J, Gatt M, Anneren G, Bianchi F, Canessa MA, Danderfer R, de Walle H, Harris J, Li Z, Lowry B, McDonnell R, Merlob P, Metneki J, Mutchinick O, Robert-Gnansia E, Scarano G, sipek A, Potzsch S, Szabova E and Yevtushok L **(2007)**, "Gastroschisis and Associated Defects: An International Study", *American Journal of Medical Genetics Part A*, Vol 143A, pp 660-671.
11. Zollino M, Lecce R, Murdolo M, Orteschi D, Marangi G, Selicorni A, Midro A, Sorge G, Zampino G, Memo L, Battaglia D, Petersen M, Pandelia E, Gyftodimou Y, Faravelli F, Tenconi R, Garavelli L, Mazzanti L, Fischetto R, Cavalli P, Savasta S, Rodríguez L, Neri G **(2007)**, "Wolf-Hirschhorn syndrome-associated chromosome changes are not mediated by olfactory receptor gene clusters nor by inversion polymorphism on 4p16", *Hum Genet*, Vol 122, pp 423-430.

**2008**

12. Barisic I, Tokic V, Loane M, Bianchi F, Calzolari E, Garne E, Wellesley D, Dolk H and EUROCAT Working Group **(2008)**, "Descriptive Epidemiology of Cornelia de Lange Syndrome in Europe", *American Journal of Medical Genetics Part A*, Vol 146A, pp 51-59.
13. Boyd PA, de Vigan C, Khsohnood B, Loane M, Garne E, Dolk H and the EUROCAT Working Group **(2008)**, "Survey of Prenatal Screening Policies in Europe for Structure Malformations and Chromosome Anomalies, and Their Impact on Detection and Termination Rates for Neural Tube Defects and Down's Syndrome", *BJOG*, Vol 115, pp 689-696. [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2344123/pdf/bjo0115-0689.pdf/?tool=pmcentrez]
14. Dolk H, Jentink J, Loane M, Morris J, de Jong-van den Berg LTW and the EUROCAT Antiepileptic Drug Working Group **(2008)**, "Does Lamotrigine Use in Pregnancy Increase Orofacial Cleft Risk Relative to Other Malformations", *Neurology*, Vol 71, pp 714-722.
15. EUROCAT **(2008)**, EUROCAT Newsletter October 2008", *EUROCAT Central Registry*, University of Ulster [http://www.eurocat-network.eu/content/EUROCAT-Newsletter-2.pdf]
16. EUROCAT **(2008)**, "EUROCAT Statistical Monitoring Protocol", *EUROCAT Central Registry*, University of Ulster [http://www.eurocat-network.eu/content/EUROCAT-Statistical-Monitoring-Protocol-(April-2008).pdf]
17. EUROCAT **(2008)**, "EUROCAT Statistical Monitoring Report 2005", *EUROCAT Central Registry*, University of Ulster [http://www.eurocat-network.eu/content/EUROCAT-Statistical-Monitoring-Report-2005-(April-2008).pdf]

18. EUROCAT **(2008)**, "EUROCAT Final Activity Report to European Commission March 2004 to August 2007", *EUROCAT Central Registry*, University of Ulster [http://www.eurocat-network.eu/content/EUROCAT-Final-Activity-Report-2004-2007.pdf]
19. EUROCAT **(2008)**, "EUROCAT Newsletter January 2008", *EUROCAT Central Registry*, University of Ulster [http://www.eurocat-network.eu/content/EUROCAT-Newsletter-1.pdf]
20. EUROCAT **(2008)**, "EUROCAT: European Surveillance of Congenital Anomalies", *The Parliament Magazine*, Vol 274, pp 20. [www.eurocat-network.eu/content/EUROCAT-Parliament-Magazine.pdf]
21. EURO-PERISTAT Project, in collaboration with SCPE, EUROCAT, EURONEOSTAT **(2008)**, "European Perinatal Health Report: Better Statistics for Better Health for Pregnant Women and Their Babies", EURO-PERISTAT. [http://www.eurocat-network.eu/content/EUROPERISTAT-Report.pdf]
22. Garne E, Dolk H, Krageloh-Mann I, Holst S, Cans C and the SCPE Collaborative Group **(2008)**, "Cerebral Palsy and Congenital Malformations", *European Journal of Paediatric Neurology*, Vol 12, pp 82-88.
23. Leoncini E, Barabella G, Orioli I, Anneren G, Bakker M, Bianchi F, Bower C, Canfield M, Castilla E, Cocchi G, Correa A, de Vigan C, Doray B, Feldkamp M, Gatt M, Irgens L, Lowry B, Maraschini A, McDonnell R, Morgan M, Mutchinick O, Poetzsch S, Riley M, Ritvanen A, Robert-Gnansia E, Scarano G, Sipek A, Tenconi R, Mastroiacovo P **(2008)**, "Frequency of Holoprosencephaly in the International Clearinghouse Birth Defects Surveillance Systems: Searching for Population Variations", *Birth Defects Research (Part A)*, Vol 82, pp 585-591.
24. Nieuwenhuijsen MJ, Toledano MB, Bennett J, Best N, Hambly P, de Hoogh C, Wellesley D, Boyd PA, Abramsky L, Dattani N, Fawell J, Briggs D, Jarup L, Elliott P **(2008)**, "Chlorination Disinfection By-Products and Risk of Congenital Anomalies in England and Wales", *Environmental Health Perspectives*, Vol 116, No 2, pp 216-222.
25. Pedersen RN, Garne E, Loane M, Korsholm L, Husby S and a EUROCAT Working Group **(2008)**, "Infantile Hypertrophic Pyloric Stenosis: A Comparative Study of Incidence and Other Epidemiological Characteristics in Seven European Regions", *J Matern fetal Neonatal Med*, Vol 21, No 9, pp 599-604.
26. Rittler M, Lopez-Camelo, Castilla E, Bermejo E, Cocchi G, Correa A, Csaky-Szunyogh M, Danderfer R, de Vigan C, de Walle H, da Graca Dutra M, Hirahara F, Martinez-Frias M-L, Merlob P, Mutchinick O, Ritvanen A, Robert-Gnansia E, Scarano G, Siffel C, Stoll C, Mastroiacovo P **(2008)**, "Preferential Associations Between Oral Clefts and Other Major Congenital Anomalies", *Cleft Palate-Craniofacial Journal*, Vol 45, No 5, pp 525-532.

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## E: List of Deliverables

| Deliverable No: | Deliverable Title | Delivery Date | Progress to Date (and where mentioned in Report) |
|---|---|---|---|
| D1 | Four Annual Statistical Monitoring Reports for Birth Years 2005-2008 | M2<br>M14<br>M26<br>M36 | Completed Annual Statistical Monitoring Report 2005 which has been published. Also completed Annual Statistical Monitoring Report 2006 which is in the process of being uploaded to website (see Section A4). |
| D2 | Annually Updated Central Database for Birth Years 2006-2008 | M7 | Data was transmitted to Central Registry in October 2007 (2005 data). February 2008 (2006 data), October 2008 (2006 data) and February 2009 (2007 data) (see Section A4). |
| D3 (i)<br>(ii)<br>(iii) | Three Annual Registry Leaders Meetings | M10<br>M22<br>M34 | 1st Annual Registry Leaders Meeting was held in Helsinki on 5-8 June 2008. The 2nd Annual Registry Leaders Meeting has been organised for Bilbao for 10-12 June 2009 (see Section C2). |
| D4 | Key Public Health Indicators for Congenital Anomalies in Europe | M13 | Work will begin in 2009. |
| D5 | Two Scientific Papers on Prevalence | M18<br>M36 | One paper published and one paper in press (see Section A4). |
| D6 | New Design for EUROCAT Website | M7 | New website design has been created and information is currently being uploaded before official launch (see Section A2). |
| D7 | Annual Updated Interactive Prevalence Tables with registry Descriptions and Data Quality Indicators | M7 | Interactive Prevalence Tables and Registry Descriptions updated December 2007, April 2008 and December 2008. Data Quality Indicators 2001-2005 were created in April 2008 and presented at the Registry Leaders Meeting in Helsinki and published on website (see Section A4). |

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| D8 | 10th European Symposium on prevention of Congenital Anomalies | M22 | Symposium has been organised for Bilbao on 10 June 2009 (see Section C2). |
| D9 | EUROCAT Report 9 Surveillance of Congenital Anomalies 1980-2008 | M33 | Work will begin in 2010. |
| D10 | EUROCAT Special Report on prevention of Congenital Anomalies by Folic Acid (3rd Ed) | M16 | The first part of the report has been published on the website in December 2007 (see Section A5). The second part will be added in early 2009. |
| D11 | One Scientific Paper on Prevention by Folic Acid | M28 | Work is on-going (see Section A5). |
| D12 | One Scientific Paper on Chronic Diseases Drug Exposure | M36 | Scientific paper "Does Lamotrigine Use in Pregnancy Increase Orofacial Cleft Risk Relative to Other Malformations" was published in Neurology in 2008. A follow up paper is currently being prepared (see Section A6). |
| D13 | EUROCAT Special Report on prenatal Screening Policies in Europe (2nd Ed) | M28 | A survey of prenatal screening policies is to be conducted in late 2009 (see Section A7). |
| D14 | Three Scientific Papers on Prenatal Screening and Diagnosis | M36 | Two papers published, two at final draft and two at intial stage (see Section A7). |
| D15 | Scientific Paper on AMC and Myasthemia Gravia | M36 | Preliminary results were presented at the Registry Leaders Meeting 2008 and paper is currently being drafted (see Section A6). |

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| D16 | Coding and Classification Committee Report | M24 | The Coding & Classification Committee continue to work on various coding issues (documentation available on website) and a final report will be published 2009-2010 (see Section A4). |
| D17 | New Versions of EDMP | M12<br>M36 | A new version was made available in June 2008. Work on the next version is on-going (see Section A4). |
| D18 | Interim Technical and financial report to the EAHC | M18 (+2) | Complete and subject to approval. |
| D19 | Final Technical and Financial Report to the EAHC | M36 (+2) | |

* All reports will be sent to DG Sanco and EAHC with their logo in a visible position.