

# Eurocat

European Surveillance of Congenital Anomalies

**European Surveillance of Congenital Anomalies**

**Project 2000/RD/10029**

**Of the DG Sanco Rare Diseases Programme**

**FINAL ACTIVITY REPORT**  
**For period November 2000 to April 2002**

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## A. Organisation and Membership

- A1 **Central Registry.** The EUROCAT Project Leader (Prof Dolk) moved to the University of Ulster, now host institution of EUROCAT, on 1 November 2000, coinciding with the start of this funding contract, and following nearly 3 years of a break in funding of EUROCAT by the European Commission. Four staff have been employed in University of Ulster: Michael Rosato as part-time database manager and programmer from January 2001, Barbara Norton as part-time administrator from April 2001, Dr Nicky Armstrong as Research Fellow from January 2002 and Maria Loane as Research Officer from January 2002. Other part-time staff continued to be employed at the London School of Hygiene and Tropical Medicine where the EUROCAT Project was formerly based: Lisa Grisolia (secretary), Martine Vrijheid (epidemiologist – project co-ordinator, from January 2001), Araceli Busby (epidemiologist – project co-ordinator, until August 2001) and Tanya Abramsky (temporary research assistant).
- A2 The **Project Management Committee** consists of the Project Leader and Project Co-ordinator, 4 elected members and 2 chairs of Working Groups (see Appendix 2). Project Management Committee elections were held on 4 June 2001 for four new members and a new President of the EUROCAT Association (Dr Bianchi).
- A3 **EUROCAT member registries.** A full list of EUROCAT member registries is given in Appendix 1 and 2. Reports from individual registries can be found in Annex 4 (Minutes of the 16<sup>th</sup> EUROCAT Registry Leaders' Meeting). Registry descriptions can be found in Appendix 9 (EUROCAT Report 8).

The registry of SW Netherlands (Leader: Dr Alice Hazebroek) has closed due to lack of sufficient funding.

The registry of Sofia-Bulgaria (leader: Prof Simeonov) had funding withdrawn in April 2001 but is in continuing communication with EUROCAT with a view to re-starting.

The EUROCAT registry of the Basque Country (Spain), after a period of suspension, has now restarted operations under a new registry leader, Dr Blanca Gener.

The registry of Auvergne (leader: Dr Christine Francannet) has joined EUROCAT as an associate member sending aggregate data, but may transfer to full member status when it starts transmission of individual data.

The registry of Poland (leader: Dr Anna Latos-Bielenska) joined EUROCAT in June 2001 and transmitted its first data to EUROCAT in March 2002.

The registry of Belarus (leader: Dr Dimitri Nikolaev) has applied for membership, but documentation is not yet complete.

The registries of Moscow (leader: Prof Krasnopolsky), Rumania (leader: Prof Covic), Slovenia (leader: Prof Pelkic) and Hungary (leader: Dr Siffel) have been given documentation and application materials, but have not yet formally applied for membership.

The registry of Cork and Kerry, Ireland (leader Dr O'Mahoney) will begin transmitting data when it reaches coverage of 25,000 births.

The registry of Iles de Reunion (leader : Dr Alain Fourmaintraux) has received EUROCAT documentation and the new EDMP and an application for membership is awaited.

The EUROCAT registry of Northern Ireland has not transmitted data since 1996 and is currently undergoing reorganisation with a view to future data transmission.

A new Registry Leader was appointed to the Paris EUROCAT registry from 1 January 2001: Dr Catherine de Vigan. Dr Janine Goujard, the previous registry leader, continues as a partner as Chair of the EUROCAT Research Working Group.

A new Registry Leader, Dr Bob McDonnell, took over from Dr Howard Johnson as head of the Dublin EUROCAT Registry.

The membership of the registry of Oxford UK (leader: Dr Boyd) was approved in March 2002 but has yet to transmit its first data set.

An application was received from the registry of Wessex, UK (leader: Dr Wellesley) but documentation is not yet complete.

## **B Database, Data Quality and Statistical Surveillance**

- B1** The EUROCAT database was transferred to University of Ulster in January 2001. Since then, extensive validation has been performed, and new data for 1999 transmitted and incorporated into the database. The number of cases currently in the database is shown in Appendix 3. In total, the database includes nearly 170,000 individual records since 1980, and over 10,000 new cases are transmitted each year to Central Registry. In addition, four associate member registries (Finland, Norway, Central-East France, and ECEMC Spain) have sent aggregate data for 1999 and are ready to send data for 2000 when the list of anomaly subgroups has been finalised by the Classification and Coding Committee. A number of registries had transmitted year 2000 data by April 2002, but for the majority, transmission was delayed by the introduction of the EUROCAT Data Management Programme (see Section B2)
- B2** The EUROCAT Data Management Programme (EDMP) (Annex 1) was developed for distribution at the Registry Leaders Meeting in June 2001. A period of testing and revision followed. An updated version of the EDMP was distributed to all EUROCAT registries in February 2002 (Version 06/02/02). The EDMP program, written in Microsoft Access, allows registries to enter or import the standard EUROCAT data, run a range of data validation checks (error checks and logical validation), look for duplicate entries and export files in the format specified by EUROCAT. Future developments will allow interfaces with statistical monitoring and generation of standard reports. The EDMP programme is continually being upgraded as Central Registry becomes aware of common user problems. In the near future, registries will be able to

download the latest version from the website. Instructions for use of the EDMP are included in EUROCAT Guide 1.2 (Annex 2) and further tips for new users are posted on the members area of the EUROCAT website. A EUROCAT Central Database has been created which interfaces with the EDMP. This ensures efficiency and transparency of database management. In a transitional phase, all data up to 1999 has been formatted by Central Registry, and all data from 2000 on is accepted only if it has been processed through the EDMP. This has involved some delays in the transmission of year 2000 data while registries learn the new system.

- B3 A suite of programmes have been written in Visual Basic and Stata in Central Registry to facilitate the production of standard data reports (see Sections G1 and G3). In particular, these programmes have overcome the considerable problems involved in computing classification subgroups using a syndrome code and eight malformation codes per case, in two different coding versions (ICD9 and 10) with variable use of 1 and 2 digit extensions, and with specific exclusions relating to embryologic relationships between anomalies.
- B4 The Committee on Coding and Classification (Chair: Martine Vrijheid, Project Co-ordinator) has been mainly dealing with conversion from International Classification of Disease version 9 to ICD10, exclusion of minor anomalies, and definition of new EUROCAT classification subgroups. The Committee organised a methodological workshop during the Registry Leaders Meeting in Sicily (see Annex 4). EUROCAT Guide 1.2: Instructions for the Registration of Congenital Anomalies (Annex 2), a revision of EUROCAT Guide 1.1, incorporating the new coding and classification instructions, has been published, distributed to all registries, and posted on the public area of the website.
- B5 The Committee on Communication and Ethics (leader: Busby, then Armstrong) has been working on website design (see section G1 and Appendix 8), a new contract for data access, confidentiality procedures and new formats for standard registry descriptions. A new set of registry descriptions have been produced (see Appendix 9) to be published in EUROCAT Report 8 and to be available on the website.
- B6 Dr Alan Kelly, Chair of the Statistics and Surveillance Working Group, was provided with a test data set in order to identify a suitable methodological basis for statistical monitoring. Results of this pilot work and general issues related to statistical monitoring were discussed at the October 2001 meeting of this Working Group in Pisa, Italy (see Section E3). The 1980-99 aggregated dataset was transmitted to Dr Kelly in March 2001 for application of the first set of statistical monitoring techniques. The first set of results are shown in Appendix 9.
- B7 Work is ongoing on the subproject "Capture-Recapture for the estimation of registry underascertainment" (leader Dr Ben Armstrong). This is based on a collaborative project between the London School of Hygiene and Tropical Medicine, the North West Thames EUROCAT Registry and the English Anophthalmia Register (held by Prof Dolk and Araceli Busby) with the assistance of Tanya Abramsky, research assistant. Partial funding was provided by Department of Health, London. A literature review of the use of capture-recapture techniques was undertaken, suitable databases created, and

statistical analyses completed. A final report was submitted to the Department of Health, London in October 2001 and a scientific paper for publication is in preparation. A EUROCAT Special Report (registry methodology) is in preparation using this material as well as contributions by other members of the EUROCAT Statistics and Surveillance Working Group (Lie, Berghold).

- B8 Validation of EUROCAT data on occupation of mother was carried out in connection with the project on hypospadias and occupational exposure to endocrine disruptors (see Section D2). Only 6 registries were found to record occupation for a large proportion of mothers (>45%, not including housewives). Two registries did not use the 1988 version of the International Classification of Occupation. This was presented at the Sicily registry Leaders' Meeting, and coding instructions were updated for EUROCAT Guide 1.2.

## **C Requests to Central Registry for EUROCAT Data**

The Central Registry has supplied data for:

- Second Edition of the World Atlas of Birth Defects, published by WHO and compiled at the International Centre for Birth Defects in Rome (see section G4).
- OECD health statistics regarding limb reduction, Down Syndrome, spina bifida, transposition of great vessels in selected registries.
- WHO for inclusion in Global Burden of Disease Study
- European Pharmacovigilance Working Group and Medicines Control Agency regarding the prevalence of gastroschisis and small intestinal atresias and instances of drugs taken in pregnancy. This followed publication of suspected associations with use of certain over the counter drugs.
- Office for National Statistics (London) for inclusion in "Key Data on Health in Europe" publication (EUROSTAT).

The following requests have been received for EUROCAT Report 7 (published 1997):

BIOMED Project "State of Health in Europe"  
WHO World Health report.  
"Wallonia in the next millennium", Belgium  
Millennium Research Group, Toronto  
The Royal Maternity Hospital, Northern Ireland  
Scientific Institute of Public Health, Belgium  
Institut fur Ernährungswissenschaft, Germany  
Observatoire de la Sante du Hainaut, Belgium  
Transmedia Distributors of Informations, The Netherlands  
University of Birmingham, UK  
"Carol Davila" University of Medicine & Pharmacy, Romania

Shropshire Health Authority, UK  
Office of Orphan Products Development, USA  
Diagnostic Genetic Centre, Greece  
Theraplrix, France

The project “The Effect of Pregnancy Termination on the Perinatal Mortality rate in Europe” , a subproject of the EURONATAL group (leader: Dr Graafmans, Leiden), which were supplied with EUROCAT data in 1998, completed their project, submitted a scientific paper for comment by the EUROCAT Steering Committee, and have had their paper accepted for publication by the journal “Prenatal Diagnosis”.

A request was received from the Medical Genetics Department of Belfast City Hospital regarding the frequency of tibial hemimelia, following the observation of an increased frequency of such cases locally. Further details have been requested

## **D News from Ongoing Subprojects**

- D1 The subproject “Epidemiology of oral clefts in Europe” (leaders: Prof Calzolari and Dr Bianchi) has completed data analysis. A report of the project results were contributed to the WHO meetings on the Prevention of Craniofacial Anomalies in Geneva (Nov 2000), Utah (May 2001) and Bauru (December 2001). A report is included in the WHO Proceedings and is available as a EUROCAT Special Report (Appendix 10). Scientific papers have been submitted for publication. The results show considerable geographic variation in the prevalence of oral clefts across Europe (see Section G5).
- D2 The subproject “Trends in Hypospadias Prevalence in UK and Europe: an assessment and analysis of existing surveillance data in UK and Europe” (leaders: Dolk, Vrijheid, Armstrong) has been completed. This study was partially funded by the Department of Health, London. This project uses data from EUROCAT and from the UK Office for National Statistics (ONS) and consists of two main parts: the validation and analysis of routinely registered hypospadias prevalence data, and the relation between risk of hypospadias and maternal occupation, in particular maternal occupational exposure to endocrine disrupting chemicals. The results of the first part show that implementation of the EUROCAT guideline to exclude distal forms of hypospadias has been inconsistent and that there is significant heterogeneity in the prevalence rates between registries, partly due to registration differences. This has led to a new set of registration guidelines discussed at the Sicily registry Leaders’ Meeting (Annex 4). The results of the maternal occupation study show little evidence of a link between maternal occupation or occupational exposure to endocrine disrupting chemicals and risk of hypospadias. A draft paper for publication is being finalised (Appendix 11).
- D3 The subproject “Folic acid supplementation in Europe” (leader Lenore Abramsky) has nearly completed phase one. Contributors from sixteen countries in Europe have written chapters on the folic acid supplementation position in their country. These chapters report on official and unofficial folic acid supplementation policy, official and unofficial food fortification policy,

health education initiatives about the benefits of periconceptional folic acid, and rates of awareness and uptake of supplementation. The chapter from Poland is still expected. Phase two will be the provision by Central Registry of neural tube defect rates up to and including the year 2000, for registers from all countries in the subproject. In phase three, the information will be collated, and the overall position in Europe (regarding both folic acid supplementation and neural tube defect rates) will be included in a EUROCAT Special Report. It should be completed by November 2002.

- D4 The subproject “A review of environmental causes of congenital anomalies”, is ongoing in collaboration with Prof Nigel Brown, St George’s Hospital Medical School, London. This will include a review of both the human (epidemiological) and experimental (animal) literature. Funding has been obtained from the Department of Health, London to contribute to this project. A complete review of the epidemiologic literature relating to environmental chemicals and birth defects was completed by Martine Vrijheid, and a review of smoking and nutrition as risk factors contributed by Prof Julian Little. Completion of the review is now expected in late 2002. Two further components of this project have been published: a review of risks related to landfills (see Section G6) and a review of risks related to anti-epileptic medication (see Section G7).
- D5 The subproject “A study of the geographical variation in overall rates of congenital abnormalities and the rates of specific abnormalities” (leaders: Prof Dolk, Dr Vrijheid, Dr Armstrong) involves the collaboration of three EUROCAT registers (North West Thames, Glasgow and Oxford) with two other British registers as well as with the National Congenital Anomaly System for England and Wales. The project has created a geocoded database with linkage to ecological data, and statistical analysis is underway. This project aims to characterise the small area geographical variation in congenital anomaly prevalence within UK in relation to socio-economic and demographic determinants, and then to examine the evidence for additional geographic variation which may be related to environmental exposures. The project will employ a time-space surveillance methodology as a pilot for envirovigilance methodology, part of the forthcoming work of the EUROCAT Working Group on Management of Clusters and Environmental Exposure Incidents. The project results will inform a more general EUROCAT strategy for envirovigilance. Funding has been obtained from the Department of Health/Department of the Environment/ Environment Agency, London to contribute to this project.
- D6 The subproject “Epidemiology of Anophthalmia/Microphthalmia in Europe” is ongoing (leaders: Vrijheid, Dolk, Loane). The project has finalised the collection of diagnostic data from local registries on all anophthalmia and microphthalmia cases from 1980-1996 and data analysis and the preparation of a draft paper are underway. The results show significant geographic variation in the prevalence of anophthalmia and microphthalmia across Europe
- D7 Collaboration has been established with the FOCAL Study group in the UK, with the aim of expanding a follow-up study of babies born with congenital anomalies to other European countries. The study, if funded, will assess a broad range of outcomes during childhood, with a primary aim of providing more information on outcomes for genetic or prenatal counselling.



- D8 The EUROCAT Cluster Working Group has been preparing for the next Rare Diseases Programme contract by collating enquiries from different EUROCAT regions regarding the association between birth defects and local environmental exposures. These include an area of dioxin contaminated land in Helsinki, an industrial area of Sicily, and the area around a landfill in Malta. Further results from the EUROHAZCON study (risk of congenital anomaly in relation to residence near hazardous waste landfill sites) have been published as well as a EUROCAT Special Report on this subject (see Section G6).
- D9 A Committee on Drug Exposure during pregnancy was established during the Registry Leaders Meeting in Sicily, and has recommended employment of international ATC drug codes by EUROCAT. Central Registry has started work on validation of drug data held by EUROCAT, and has responded to a request for information on drug exposures from the European Pharmacovigilance Working Group (see Section G12).
- D10 A subproject on “Prenatal diagnosis of cardiac anomalies: does it improve postnatal outcome?” (leader: Dr Ester Garne), agreed at the Sicily Registry Leaders Meeting, is in protocol development phase, and is looking for additional funding. A number of collaborative publications have now appeared on prenatal diagnosis of congenital anomalies using data from EUROCAT registries (see section G).

## **E EUROCAT Meetings, Workshops and Symposia**

- E1 Project Committee Meetings  
The EUROCAT Project Management Committee met on 25 November 2000, 26 March 2001, 1 June 2001, 27-28 October and 2 March.
- E2 Registry Leaders’ Meeting & Symposium  
The EUROCAT Registry Leaders Meeting was held in Catania, Sicily 1-4 June 2001. 28 registry leaders attended as well as 23 Central Registry and local registry staff and 4 other presenters. The programme can be found in Appendix 4.
- The Sixth European Symposium on the Prevention of Congenital Anomalies was held on 2 June 2001, Catania, Sicily. In addition to the registry leaders above, approximately a further 300 participants from Sicily and internationally attended the Symposium. The abstracts of presentations can be found in Annex 3 and programme in Appendix 5.
- The EUROCAT Workshop on ‘Data Quality: Problems and Solutions’ was held on 4 June 2001. A report of the workshop can be found in Appendix 9.
- E3 Workshop of the Statistics and Surveillance Working Group  
The Statistics and Surveillance Working Group met in Pisa, Italy on 27-28 October 2001. The members of this Working Group can be found in Annex 2. Those who attended the meeting were Alan Kelly (Chair), Ben Armstrong, Andrea Berghold, Fabrizio Bianchi, Catherine de Vigan, Helen Dolk, Ester Garne, Blanca Gener, Janine Goujard, Andrew Lawson, Rolv Lie, David Lillis, Marco Martuzzi, Annukka Ritvanen, Aldo Rosano, Martine Vrijheid.

E4 EUROCAT Co-ordination Meetings

Prof Dolk met with Dr Alan Kelly in London on 24 November 2000 and Dublin on 17 May 2001 to discuss statistical monitoring.

Prof Dolk visited the EUROCAT Registry at Mainz on 27 November 2000.

Meeting regarding the EUROCAT Data Management Programme in London included James Densem, Michael Rosato, Helen Dolk, Martine Vrijheid and Araceli Busby on 17 January 2001.

Prof Helen Dolk visited the project co-ordinators in London on 18 January 2001, 27 March 2001 and 24 April 2001.

Araceli Busby (project co-ordinator, London) visited the Central Registry at University of Ulster on 21 May 2001. Martine Vrijheid (Project Co-ordinator, London) visited the Central Registry at the University of Ulster on 29 August 2001, 2 October 2001, 14 November 2001, 7 January 2002, 11 February 2002, 13 March 2002, 26 March 2002 and 24 April 2002.

James Densem (Bio-Medical Computing) visited Central Registry at the University of Ulster on 22 January 2002.

Helen Dolk and Michael Rosato visited Alan Kelly in Dublin Ireland on 30 January 2002 to discuss the progress of Report 8.

Helen Dolk visited the London School of Hygiene and Tropical Medicine on 31 January 2002 for a Geographic Variation Project meeting.

Helen Dolk visited the Department of Public Health Sciences in Edinburgh, Scotland on 13 February 2002 to discuss the results of a case-control study of risk factors for anophthalmia/microphthalmia.

Dr Nicola Armstrong visited North Thames EUROCAT Registry and attended a conference on Multiple Births: Dream or Nightmare? On 22 February 2002.

Dr Martina Cornel visited EUROCAT Central Registry on 29 April 2002 to discuss drug surveillance.

**F Travel and Presentations**

Prof Elisa Calzolari: WHO meeting on International Collaborative Research on Craniofacial Anomalies, Geneva, 5-8 November 2000.

Prof Helen Dolk: Tenth Anniversary Symposium of EUROCAT, Antwerp, 10 November 2000.

Prof Helen Dolk: Northern Region Congenital Abnormality Survey, Newcastle University, meeting with Dr John Scott on validation of Hypospadias registration, speaker at the Maternity Survey Study Day, 16-17 November 2000.

Dr Janine Goujard: Presented EUROCAT to Occupational Reproductive Health Conference, Rome, 4-6 December 2000.

Prof Helen Dolk: Presented EUROCAT to the meeting of the Rare Diseases Committee, Luxembourg, 8 December 2000.

Dr Janine Goujard: Presented EUROCAT to 4<sup>th</sup> US meeting of the National Birth Defects Prevention Network, San Antonio, Texas, 29-31 January 2001.

Prof Helen Dolk: Presented EUROCAT to Fetal Medicine Group, Royal Victoria Hospital, Belfast, 9 February 2001.

Prof Helen Dolk: BINOCAR meeting (British Isles Network of Congenital Anomaly Registries), Edinburgh, 1-2 March 2001.

Prof Helen Dolk: IDA-EUPHIN Rare Diseases Classification Workshop, Brussels, 15-16 March 2001.

Dr Martine Vrijheid: FOCAL study day, Coventry, England, 21 March 2001.

Prof Helen Dolk: Workshop on Determination of Prevalence of Rare Diseases in Orphan Drug Designation Applications, European Agency for the Evaluation of Medicinal Products, London, 11 May 2001.

Dr Ester Garne: Presented EUROCAT to European Conference on Rare Disorders, Copenhagen, 18 May 2001.

Prof Julian Little: WHO meeting on the Prevention of Craniofacial Anomalies, Utah, 24-26 May 2001.

Prof Helen Dolk: IDA-EUPHIN Rare Diseases Validation Meeting, Brussels, 6 June 2001.

Dr Fabrizio Bianchi: NEPHIRD General Meeting, Rome, Italy, 1 July 2001.

Prof Helen Dolk: EUROCAT-ICBDMS Meeting, Rome, Italy, 25-27 January 2002.

Prof Helen Dolk: Presented EUROCAT to European Perinatal Epidemiology Network meeting, Oxford, UK, 14 September 2001.

Prof Elisa Calzolari: WHO Meeting on Medical Genetic Services for Developing Countries, Toronto, Canada, 8-10 April 2002.

## **G Website and Collaborative Publications**

- G1 Website. The EUROCAT website was redesigned in conjunction with a move from London School of Hygiene ([www.lshtm.ac.uk/php/eeu/eurocat](http://www.lshtm.ac.uk/php/eeu/eurocat)) to University of Ulster ([www.eurocat.ulster.ac.uk/](http://www.eurocat.ulster.ac.uk/)). A new logo and design have been implemented (see Appendix 8), as well as a password protected area for internal communication. By the end of April 2002, the major work had been done but testing and corrections remained.

A special section of the open website was designed for “customised tabulations” ([www.eurocat.ulster.ac.uk/pubdata/report8tab](http://www.eurocat.ulster.ac.uk/pubdata/report8tab)). This allows the user to specify the regions/countries, years and congenital anomaly subgroups of interest, in order to obtain a range of data tables giving numbers of cases and prevalence rates for any period of years 1980-1999. Examples of the website pages are given in Appendix 8. The data are identical to those to be published as part of EUROCAT Report 8 (see Section G3), but in future, the website edition will allow updating with each years’ new data, a fast and accessible way of publishing up-to-date data.

- G2 EUROCAT Central Registry (2002), “EUROCAT Guide 1.2: Instructions for the Registration of Congenital Anomalies”, University of Ulster.
- G3 EUROCAT Report 8: Surveillance of Congenital Anomalies in Europe 1980-99. This report will give 20 years of data, focusing also on the most recent five year period. A first draft of tables was produced in January 2002. Inspection of these tables showed the need for extensive corrections to be made to the database, which were implemented during this contract period. A selection of draft tables is shown in Appendix 9. Publication of the Report is due in October 2002.
- G4 ICBDMs/EUROCAT (in press), “World Atlas of Birth Defects”, 2<sup>nd</sup> edition, *World Health Organisation*. Data and text were provided for this collaborative publication and the final draft was agreed in April 2002. (see Annex 5).
- G5 Calzolari E, Bianchi F (in press), “Oral Clefts in EUROCAT Registries During the Period 1980-96” In: “Proceedings from WHO Meeting on, International Collaborative Research on Craniofacial Anomalies, Geneva”, *World Health Organisation*. This publication is also available separately as a EUROCAT Special Report (see Appendix 10).
- G6 Vrijheid M, Dolk H et al. Risk of congenital anomaly in relation to residence near hazardous waste landfill sites. EUROCAT Special Report 2002 (see Annex 6).

Vrijheid M, Dolk H, Armstrong B, Boschi G, Busby A, Jorgensen T, Pointer P and the EUROHAZCON Working Group (in press), “Hazard Potential Ranking of Landfill Sites and Risk of Congenital Anomalies”, *Occupational and Environmental Epidemiology*.

Vrijheid M, Dolk H, Armstrong B, Abramsky L, Bianchi F, Fazarinc I, Garne E, Ide R, Nelen V, Robert E, Scott JES, Stone D, Tenconi R (in press), “Risk of Chromosomal Anomalies in Relation to Residence Near Hazardous Waste Landfill Sites in Europe, *The Lancet*, Vol 359, pp 320-322

Dolk H (in press), “Methodological Issues Related to Epidemiological Assessment of Health Risks of Waste Management”, In: Harrison R (Ed) “Environment Impact of Solid Waste Management Activities”, *Issues in Environmental Science & Technology*, Vol 18.

- G7 Dolk H, McElhatton, P (2002), "Assessing Epidemiological Evidence for the Teratogenic Effects of Anticonvulsant Medications", *Journal of Medical Genetics*, Vol 39, pp 243-244.
- G8 Garne E (2001), "Perinatal Mortality Rates Can no Longer be Used for Comparing Quality of Perinatal Health Services Between Countries", *Pediatric & Perinatal Epidemiology*, Vol 15, No 3, pp 315-316.
- Garne E, Berghold A, Johnson Z, Stoll C (2001), "Different Policies on Prenatal Ultrasound Screening Programmes and Induced Abortions Explain Regional Variations in infant Mortality with Congenital malformations", *Fetal Diagnosis & Therapy*, Vol 16, pp 153-157.
- G9 Cuschieri, A and a EUROCAT Working Group (in press), "Descriptive Epidemiology of Isolated Anal Anomalies: A Survey of 4.5 million Births in Europe", *Journal of Medical Genetics*.
- G10 EUROCAT (2002), "Abstracts of the Sixth European Symposium on the Prevention of Congenital Anomalies", *Reproductive Toxicology*, Vol 16, No 1, pp 81-95.
- G11 Dolk H (2001), "EUROCAT: European Surveillance of Congenital Anomalies", *Chemical Incident Report*, Vol 20, pp 15-18.
- G12 Garne E, and a EUROCAT Working Group (2001), "Prenatal Diagnosis of Six Major Cardiac Malformations in Europe - A Population Based Study", *Acta Obstetrica et Gynecologica Scandinavica*, Vol 80, pp 224-228.
- Garne E, Stoll C, Clementi M and the EUROSCAN Group (2001), "Evaluation of Prenatal Diagnosis of Congenital Health Diseases by Ultrasound: Experience from 20 European Registries", *Ultrasound Obstetrics & Gynaecology*, Vol 17, pp 386-391.
- Stoll C, Garne E, Clementi M, and a EUROSCAN Study Group (2001), "Evaluation of Prenatal Diagnosis of Associated Congenital Heart Diseases by Fetal Ultrasonographic Examination in Europe", *Prenatal Diagnosis*, Vol 21, pp 243-252
- Stoll C, Tenconi R, Clementi M and the EUROSCAN Study Group (2001), *Community Genetics*, Vol 4, pp 225-232.
- G13 Stoll C, Rosano A, Botto L, Erickson D, Khoury M, Olney R, Castilla E, Cocchi G, Cornel M, Goujard J, Bermejo E, Merlob P, Mutchinick O, Ritvanen A, Zampino G, Mastroiacovo P (2001), "On the Symmetry of Limb Deficiencies Among Children with Multiple Congenital Anomalies", *Annales de Génétique*, Vol 44, pp 19-24.

## **H Collaboration with Other Organisations.**

- H1 EUROCAT's status as a WHO Collaborating Centre for the Surveillance of Congenital Anomalies has been renewed for a further four years. EUROCAT was represented (see Section F) at the WHO meetings organised in Geneva,

November 2000 and Utah in May 2001 and Bauru December 2001 on the Prevention of Craniofacial Anomalies. Prof Calzolari attended a WHO meeting on Medical Genetics Service development in developing countries in Toronto, April 2002. EUROCAT collaborative work on risks related to residence near hazardous waste landfill sites (see Section G6) was included in "Children's health and Environment: A Review of the Evidence", A joint report from the European Environment Agency and WHO Regional Office for Europe, WHO Europe, 2002.

- H2 13 EUROCAT registries are also members of ICBDMS (International Clearinghouse for Birth Defects Monitoring Systems). EUROCAT have contributed data to the Second Edition of the World Atlas of Congenital Anomalies, which is a collaborative publication with ICBDMS, published by WHO. The ICBDMS executive committee met during the EUROCAT Registry Leaders' Meeting in Sicily, ICBDMS participated in the Symposium (see Section E2) and Prof Dolk attended the ICBDMS executive committee meeting in Rome, January 2002. A joint programme of work has been agreed which includes statistical surveillance methodology, monitoring of multiple malformations, surveillance of drugs taken during pregnancy, and a possible special study of gastroschisis.
- H3 EUROCAT is a partner in NEPHIRD (Network of Public Health Institutions for Rare Diseases), with members on the Steering Committee of NEPHIRD (Bianchi, Calzolari).
- H4 EUROCAT collaborates with ENTIS (European network on Teratology Information Services) via its liaison with Dr Maurizio Clementi, who is President of ENTIS. A more details collaboration protocol will now be developed by the EUROCAT Committee for Drug Surveillance.
- H5 Surveillance of Cerebral Palsy in Europe (SCPE). Prof Dolk is a member of SCPE, which was successful in obtaining a EC Framework V grant to support its activities. Joint work on specific issues, such as the implications of the rising numbers of multiple pregnancies, is planned.
- H6 ESF/EUROCRAN. EUROCAT is working together with the ESF demonstration project on gene-environment interaction in the aetiology of oral clefts, to design study protocols for the future. The ESF group held the last meeting of its contract in Sicily at the same time as the EUROCAT Registry Leader's Meeting, and a joint session was held at the Symposium on 1 June in Sicily (see Annex 3 and Appendix 5).
- H7 ONS (Office for National Statistics, London). EUROCAT and ONS are in active collaboration, including in specific subprojects (see Section D) above, and with regard to issues such as confidentiality guidelines. The Director of the Congenital Anomaly Monitoring Scheme of ONS attended the EUROCAT Registry Leaders' Meeting in Sicily. Prof Dolk and Prof Stone (EUROCAT Glasgow) are advising on the ONS Child Health Analysis Project with regard to congenital anomalies.

- H8 EUROCAT sent a representative (Prof Dolk) to the Rare Diseases Clarification Workshop and Validation Meeting of the IDA-EUPHIN project (see section F) to explore the feasibility of integrated European information systems on rare diseases.
- H9 EUROCAT participates in the European Perinatal Epidemiology Network and made a presentation at its September 2001 meeting.
- H10 EUROCAT participated in the European Agency for the Evaluation of Medicinal Products Workshop on Determination of Prevalence of Rare Diseases in Orphan Drugs Designation applications (see Section F).
- H11 Dr Yves Gillerot, Registry Leader of EUROCAT Hainaut, is also on the project management committee of the DNA Laboratory index (EDDNAL) funded under the Rare Diseases Programme. EDDNAL was presented to EUROCAT Registry Leaders at the Sicily meeting.
- H12 EUROCAT has established collaboration with the PERISTAT project on perinatal health indicators, based in Paris and funded by the DG Health Health Monitoring Programme.
- H13 EUROCAT collaborated with ESRAR (European Summer School on Risk Assessment for Reproduction) which held its third week long course in Pisa in October 2002. This was organised by Dr Fabrizio Bianchi. Various members of EUROCAT were invited to give lectures and seminars, and a number of EUROCAT registry staff attended the course as students.
- H14 EUROCAT has also established contact with the Institute of Demography in Brussels concerning forming a European network on "Late Childbearing and Reproduction". Dr Wunsch and Dr Gourbin visited the Central Registry in Belfast on 17 December 2001.

## **I PROGRESS IN RELATION TO WORK PROGRAMME, BY WORK PROGRAMME ITEM**

[NB: In Italics are the workprogramme items. In plain type are references to the sections of the main report which deal with these items, as well as any comments on contractual/timetable details. ]

*Full meeting of participants to take place in June 2001 comprising ½ day satellite workshops, ½ day methodological workshops for EUROCAT members, 1 day general meeting, and 1 day EUROCAT Symposium on the Prevention of Congenital Anomalies (see Section E2).*

### ***II Strengthening of EUROCAT capability for early warning of new teratogenic exposures:***

- II.1 *Central level database redesign – subcontracted.* Subcontracted to Biomedical Computing Ltd. See Section B2. The order of work has been changed due to problems in the EUROCAT Data Entry Programme (in DOS) used by local registries since 1996. This DOS programme had not foreseen problems of entering "99" and "00" as years. The redesign of this programme

for Windows with much more sophisticated data entry and validation and reporting facilities had originally been specified for the end of the contract period (stage 5 in the subcontracting agreement), with completion April 2002 but work was brought forward to become the first stage and was completed May 2001. The CD of the “EDMP” – EUROCAT Data Management Programme - (programme written in Microsoft Access) and its explanation can be seen in Annex 1 and 2.

Biomedical Computing Ltd have also redesigned the Central Database, which interfaces with the EDMP, in Microsoft Access (stages 1 and 2 in the subcontract).

- I1.2 *Transmission of data for 1999 and 2000 to Central registry, central level validation and incorporation into database.* See Section B1. The implementation of the EDMP has led to delays in transmission of year 2000 data while registries change their systems to accommodate the new programme. Transmitted data up to 1999 has been checked and reformatted where necessary, extensive correspondence and discussion between individual registries and the Central Registry at University of Ulster have been held, and data have been incorporated into the central database. Year 2000 data has been validated via the EDMP and is directly compatible with the new central database.
- I1.3 *Statistical monitoring incorporating birth years 1999 and 2000. Workshop on methodology for statistical monitoring.* This area of work has been carried out by Alan Kelly, Dublin. Graphs of trends and trend tests were performed for 1980-99. A test set of data has been used to develop other statistical monitoring approaches. Due to delays in transmission of year 2000 data as described above, these data could not yet be incorporated. A Workshop was held in Pisa, October 2001 (see Section B6).
- I1.4 *Validation of EUROCAT data on maternal occupation* (see Section B8).
- I1.5 *Methodological workshop for all EUROCAT members: improvement of coding and data validation, quality audit methods.* This workshop was held as part of the EUROCAT Registry Leaders’ Meeting in Sicily, organised by the Committee on Coding and Classification (see Section B4). See Report in Annex 4.
- I1.6 *Compilation of guidelines for setting up a registry* (see Section B2). EUROCAT Guide 1.2 has been published (Annex 2). A further guide is in preparation on evaluating completeness of ascertainment (see Section B7).
- I1.7 *Pilot new time-space surveillance techniques for envirovigilance in selected registries with geocoded data* (see Section D5). The geocoded database has been constituted but due to various classification and geographical linkage problems (now resolved), statistical analysis was delayed and due to take place May-October 2002.
- I2** ***Publication of three editions of EUROCAT Special Report series, available on website and bound. Two editions will concern the epidemiology and surveillance of specific congenital anomalies, and one will be a review of environmental causes of congenital anomalies.***



- I2.1 Production of tables for “EUROCAT Report 8: Surveillance of Congenital Anomalies in Europe 1980-99” took place during the contract period (see section B3). Rather than simply making this report downloadable from the website, an entirely new and exciting website development was instituted (subcontracted to Biomedical Computing Ltd as an extension of Stage 4 of the subcontract). See Section G1.
- I2.2 Epidemiology of oral clefts in EUROCAT regions (see Section E1 and G5).
- I2.3 Recommendations for the registration and surveillance of hypospadias in relation to endocrine disruptors and other risk factors (see Section D2).
- I2.3 Review of the literature on environmental causes of congenital anomalies (see Section D4 and Annex 6 and 7).

**I3 *Liaison activities :***

- I3.1 *Working with registries newly joining EUROCAT, especially in Central and Eastern Europe* (see Section A3).
- I3.2 *Input into WHO Centre for Environment and Health, Rome “Children and Environment” Report* (see Section H1).
- I3.3 *Collaboration with International Clearinghouse of Birth Defect Monitoring Systems (ICBDMS), NEPHIRD (Rare Diseases Network), European Network of Teratology Information Services, European Network of Cancer Registries, Surveillance of Cerebral Palsy in Europe, in areas of mutual interest* (see Sections H2, H3, H4, H5 and other collaborations under Section H).

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