Eurocat

European Surveillance of Congenital Anomalies

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EUROCAT FINAL ACTIVITY REPORT
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OBJECTIVES OF EUROCAT

1. To provide essential epidemiologic information on congenital anomalies in Europe

2. To facilitate the early warning of teratogenic exposures.

3. To evaluate the effectiveness of primary prevention.

4. To assess the impact of developments in prenatal screening.

5. To act as an information and resource centre regarding clusters or exposures or risk factors of concern.

6. To provide a ready collaborative network and infrastructure for research related to the causes and prevention of congenital anomalies and the treatment and care of affected children.

7. To act as a catalyst for the setting up of registries through Europe collecting comparable, standardized data.

EXECUTIVE SUMMARY

The EUROCAT network and database

EUROCAT now has 34 full members, 5 associate members and 10 affiliate members operating in 20 countries of Europe. Population coverage is 1.5 million annual births, 26% of EU births, and 25% of births in all European countries represented.

The EUROCAT database documents 150,000 cases of congenital anomaly for the period 2000-2005.

A revision of the common coding and classification system has been implemented from 2005, described in EUROCAT Guide 1.3 "Instructions for the Registration of Congenital Anomalies" (2005). This includes additions to and deletions from the common dataset, changes to coding of variables, changes to minor anomalies listed for exclusion, and changes to the definition of congenital anomaly subgroups to which cases are allocated for routine surveillance. The changes have been incorporated in the common registry software (the EUROCAT Data Management Programme - EDMP). Coding guidelines and software development work was also undertaken to facilitate the identification of syndromes and children with multiple malformations.

Data Quality Indicators suitable for congenital anomaly registers have been designed and implemented.

A survey of the operation of registries in relation to parental consent for registration has shown that while very few parents refuse, the logistical difficulties make the operation of the registry very difficult and costly. Nine countries (in 2004) had enacted legislation or created a supervisory body allowing registries to operate without informed consent, while concentrating on other measures such as confidentiality procedures and informing parents about the use of their data and giving them the option to remove their child's data.

Software, interfacing with the EDMP, has been developed to allow rapid monitoring for temporal clusters and trends in member registries. Annual monitoring by Central Registry is communicated to member registries for investigation.

The utility of EUROCAT for pharmacovigilance has been extensively tested. A database of antiepileptic (AED) drug exposure has been constructed with the participation of 19 registries covering 3.8 million births since 1995, and 495 cases of congenital anomaly exposed to AED, to our knowledge the largest database in the world on this issue. A study of lamotrigine exposure in relation to oral clefts using this database has been completed and submitted for publication.

A meeting on "Methodological Approaches to the Assessment of the Impact of Environmental Pollution on the Risk of Congenital Anomalies" was held, and has led to several collaborative activities.

Prevalence and Prevention

In the period 2000-2004:

- the livebirth prevalence of congenital anomalies was 19.8 per 1,000 livebirths,
- the total prevalence (including fetal deaths and terminations of pregnancy for fetal anomaly) was 23.7 per 1,000 births.
- There were 0.9 stillbirths or first week deaths with congenital anomaly for every 1,000 births.
- There were 4 terminations of pregnancy for fetal anomaly for every 1,000 births.
- Four fifths of cases of congenital anomaly survived the first week of life.
- Fourteen percent of cases had a chromosomal anomaly.

Down Syndrome has been increasing in prevalence across Europe due to increasing tendency to delay childbearing among mothers. In 2000-2004, the total prevalence of Down Syndrome was 1.9 per 1,000 births, and the livebirth prevalence 0.9 per 1,000 births.

The majority of neural tube defects could be prevented by raising periconceptional folic acid status. An updated survey of policies regarding folic acid supplementation and their implementation in European countries, and analysis of EUROCAT data on neural tube defect rates, show very disappointing progress, and little or no decline in neural tube defect rates. In 2000-2004, the total prevalence of Neural Tube Defects was 9.3 per 10,000 births, and the livebirth prevalence 2.7 per 10,000. EUROCAT registries are however ready to monitor the impact of changes in policy in a few countries which are considering folic acid fortification of a staple food. A EUROCAT survey showed a high level of support among spina bifida parent/patient support groups in Europe for fortification.

The abdominal wall anomaly gastroschisis has been increasing in prevalence in most European countries, except Italy. Young mothers are at greatest risk, but the increase in prevalence is occurring across all age groups. In 2000-2004, the total prevalence was 2.2 per 10,000 births, similar to omphalocele (2.1 per 10,000 births).

The prevalence of oral clefts 2000-2004 was 13.3 per 10,000 births. Geographic variation between European countries has been found for both cleft palate and particularly cleft lip, the latter being more common in northern countries. Specific associations with other congenital anomalies have been documented. EUROCAT has contributed data to the WHO International Craniofacial Database on oral clefts.

Cornelia de Lange syndrome has been the first of a list of 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.

A study of the association between loratidine and hypospadias was inconclusive, due to the very low reported exposure rate to loratidine in the European population (one exposed case was found).

A collaborative project with SCPE (Surveillance of Cerebral Palsy in Europe) has found a high rate of congenital anomalies among children with cerebral palsy.

A study of Arthrogryposis Congenital Multiplex is ongoing, so far identifying 800 cases in the EUROCAT database.

Prenatal Screening and Diagnosis, and Termination of Pregnancy for fetal anomaly

A EUROCAT survey showed a wide variation in prenatal screening policies in Europe, as well as variation in laws regarding termination of pregnancy (whether legal or not, and up to what gestational age). In Poland, TOPFA is not encouraged, and done only in case of lethal anomaly. Some countries allow TOPFA at any gestational age (Austria, Belgium, Croatia, England & Wales, France, Germany). Others have an upper gestational age limit (Finland, Italy, Spain, Sweden, Switzerland), and yet others have an upper gestational age limit but allow TOPFA for lethal anomalies beyond this limit (Netherlands, Norway, Portugal, Denmark).

Analysis of data showed that screening policy has a significant impact on prenatal detection rates, but there is still wide variation between countries with similar policy, indicating other cultural and organisational factors intervening. An upper legal gestational age limit for terminations of pregnancy for fetal anomaly did not have an impact on overall termination rates, indicating that services could be organised to allow early prenatal diagnosis.

Overall in Europe, termination of pregnancy has counterbalanced the effects of increasing maternal age on the number of livebirths with Down Syndrome, leading to a fairly stable livebirth prevalence of Down Syndrome. However this situation differs markedly between countries. There are now large differences in livebirth prevalence rates between countries.

Analysis of EUROCAT data on gastrointestinal malformations show that cases which are prenatally diagnosed tend to be born slightly earlier than those postnatally diagnosed, suggesting that early induction of birth may be adding to the risks of morbidity and mortality of the malformation itself.

The highest rates of perinatal mortality associated with congenital anomaly 2000-2004 are recorded in Ireland (2.3 per 1,000) and Malta (2.2 per 1,000). These are both countries where termination for fetal anomaly (TOPFA) is illegal, and thus the perinatal mortality rate includes affected fetuses with a lethal or high mortality anomaly which would have been prenatally diagnosed in other countries leading to termination of pregnancy (and exclusion from mortality statistics). The ratio of TOPFA to births 2000-2004 varies from 0 (Ireland and Malta) to 10.8 (France) per 1,000 births. The highest TOPFA ratio both before and after 20 weeks gestation is recorded in France (5.3 and 5.5 per 1,000 births respectively). Comparison between countries is complicated by different laws and practices regarding the recording of late terminations. Late TOPFA, where legal, may be recorded as stillbirth or as livebirth with neonatal death in some countries, and practice may also vary within countries.

A Report by Workprogramme Item

A1 Provision of essential epidemiologic information on congenital anomalies in Europe

A1.1 Coverage of the European Population

EUROCAT now has 34 full members, 5 associate members and 10 affiliate members operating in 20 countries of Europe. Full Members transmit individual anonymised case data to the EUROCAT Central Registry and Associate members transmit aggregate case numbers (Figure 1). Population coverage is shown in Table 1, a total of 26% of births in the EU-27 population and 25% of births in the European countries represented i.e. a coverage of approximately 1.5 million births.

We were particularly glad to welcome as new Full members Hungary, Wielkopolska (Poland), South-East Ireland, Ukraine, and as Associate Members Ile de la Reunion and Poland. We also welcome Norway as a Full Member registry (previously as Associate Member) and the National Down Syndrome Cytogenetic Register (UK) (NDSCR) as an Affiliate Member.

One full member (Glasgow) passed to affiliate status due to inability to transmit data to the central database for administrative reasons, and five full members passed to affiliate status after an interruption of registration activities of at least three years (Sofia, Galway, Asturias, El Valles, Merseyside). One Associate Member (Central East France) has experienced a change of institution and leadership with temporary interruption of data transmission.

Figure 1: Map of EUROCAT Registries 2007 (Full or Associate Member)

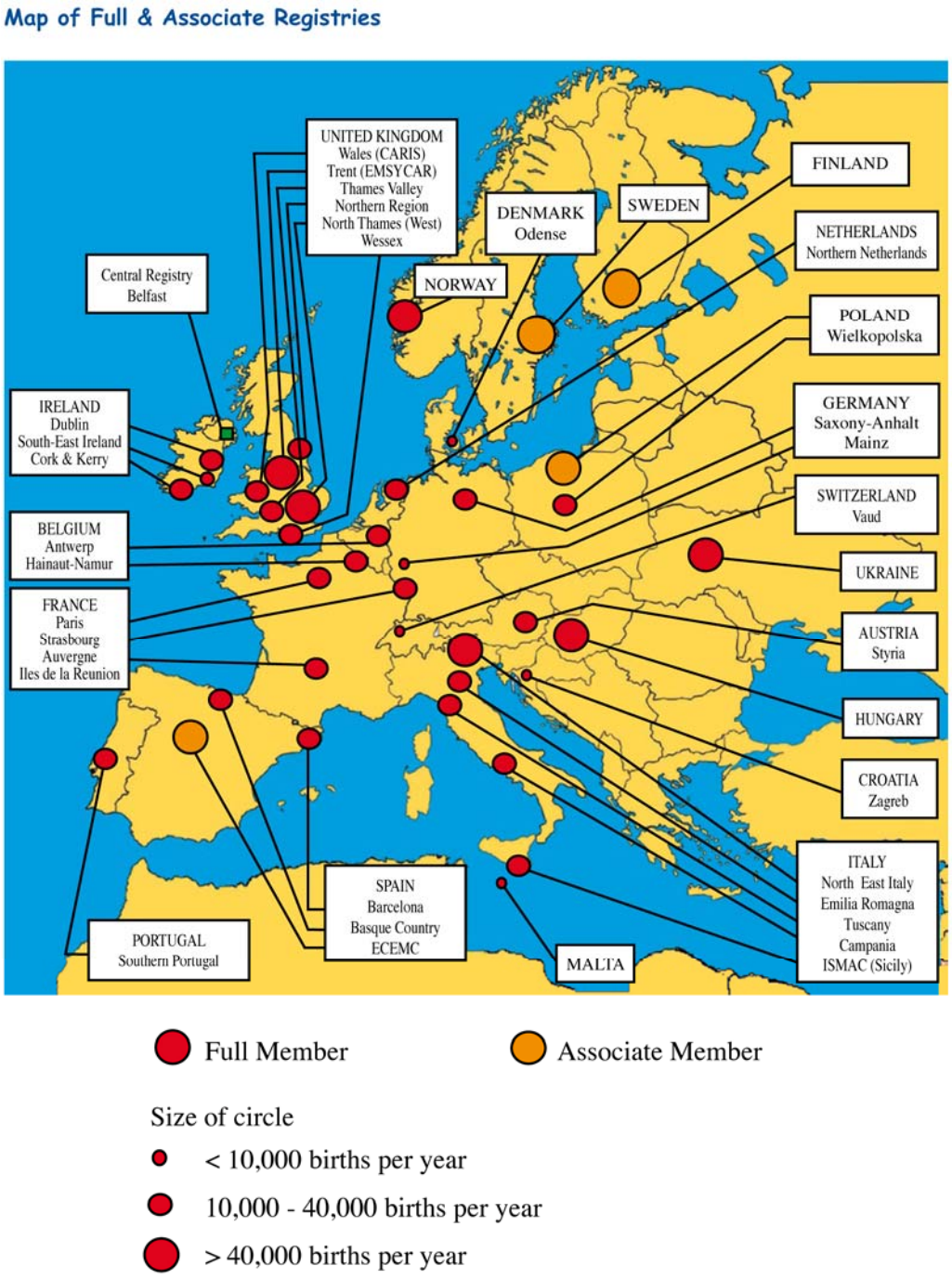


Table 1: Coverage of the European Population by EUROCAT Full or Associate Member Registries

Country	EUROCAT Registry	Year started EUROCAT data transmission	Annual Births 2005, Registry	Annual Births 2005, Country[1]	% Country Covered
EU					
EU (Present EU Member States)				5,123,500	25.6
EU-15 (EU Member Countries since before 2004)				4,114,700	23.4
EU-NMS (Countries acceded in 2004-2007)				1,007,700	35.0
Belgium	Antwerp	1990	19,200		
	Hainaut	1980	12,500		
	Total		31,170	117,400	27.0
Bulgaria				71,300	0.0
Czech Republic[2]				102,100	0.0
Denmark	Odense	1980	5,300	64,200	8.2
Germany	Mainz	1990	3,100		
	Saxony-Anhalt	1987	17,200		
	Total		20,400	686,100	3.0
Estonia				14,400	0.0
Ireland	Cork & Kerry	1996	8,500		
	Dublin	1980	23,400		
	South East	1997	6,300		
	Total		38,200	60,300	63.4
Greece				107,300	0.0
Spain	Barcelona	1992	14,700		
	Basque Country	1990	19,800		
	Madrid[3]	1980	106,700		
	Total		141,200	462,500	30.5
France	Auvergne	2002	13,600		
	Isle de la Reunion[3]	2001	14,500		
	Paris	1981	39,300		
	Strasbourg	1982	12,900		
	Total		80,400	804,700	10.0
Italy	Campania	1996	59,900		
	Emilia Romagna	1981	37,600		
	North East	1981	60,200		
	Sicily	1991	16,000		
	Tuscany	1980	29,400		
	Total		203,200	552,600	36.8
Cyprus				8,200	0.0
Latvia				21,600	0.0
Lithuania				30,600	0.0
Luxembourg				5,300	0.0
Hungary	Hungary	1998	97,600	97,600	100.0
Malta	Malta	1986	3,900	3,900	100.0
Netherlands	Northern	1981	18,400	187,700	9.8
Austria	Styria	1985	10,500	77,900	13.4

Poland	Wielkopolska	1999	33,600		
	Rest of Poland[3]	1999	217,900		
	Total		251,500	364,400	69.0
Portugal	South	1990	18,000	109,200	16.6
Romania				221,300	0.0
Slovenia				18,100	0.0
Slovakia				54,400	0.0
Finland[3]	Finland	1993	57,600	57,600	100.0
Sweden[3]	Sweden	2001	101,100	101,100	100.0
United Kingdom	Northern Region	2000	31,600		
	North West Thames	1991	48,500		
	Oxford	1991	27,300		
	Trent	1998	67,300		
	Wales	1998	32,800		
	Wessex	1994	27,000		
	Total		234,600	720,500	32.6
Non EU					
Candidate countries in EUROCAT					
Croatia		1983	5,900	42,500	14.0
EFTA countries in EUROCAT					
Norway		1980	56500	56,500	100.0
Switzerland		1989	7200	72,700	9.9

[1] Source: Crude birth rate (accessed 29-08-07)
http://ec.europa.eu/health/ph_information/dissemination/echi/echi_02_en.pdf
Total Population (EUROSTAT)
http://epp.eurostat.ec.europa.eu/portal/page?_pageid=1996,45323734&_dad=portal&_schema=PORTAL&screen=welcomeref&open=/&product=Yearlies_new_population&depth=2
Due to rounding, totals may not add up exactly.
[2] National non-EUROCAT congenital anomaly registry
[3] Associate EUROCAT Registries (transmit aggregate data only)

A1.2 Implementation of EUROCAT Data Management Program (EDMP) Software by Registries for Data Entry/Import, Validation and Annual Transmission to Central Registry

EUROCAT makes available standard registry software written in Microsoft Access. It is used for data entry or data import, data validation, data export, production of standard tables, and statistical monitoring. In this way, all resources spent on centralized computing are also made available to member registries. Significant development work has been carried out on EUROCAT's Data Management Program (EDMP) to ensure compatibility with the newly developed Guide 1.3 coding system published in 2005 (Appendix 3. see A1.5), for coding of cases born from 1 January 2005. The EDMP switches between Guide 1.2 and Guide 1.3 coding format, depending on the year of birth.

Further refinements have been made to the EDMP software to incorporate the new EUROCAT subgroups of congenital anomalies (see A1.6), with an option to include or exclude chromosomal anomalies, to identify cases of multiple malformation and syndromes,

and to allow the user to specify their own subgroups based on a range of ICD (International Classification of Disease) codes.

The last version released of the EDMP is Version 4.14 (02/10/2006).

The EDMP has successfully been used by all full member registries for annual data transmission.

A1.3 Uploading of Updated Data to Website to Provide Prevalence Rates of 96 Congenital Anomaly Subgroups

Four years of prevalence data have been collected and published on the website (http://www.eurocat.ulster.ac.uk/pubdata/tables.html). By June 2007, this included data up to 2005 for 21 registries, data up to 2004 for 33 registries, and data up to 2002/3 for 40 registries (Table 2). Data are available for all the revised subgroup definitions published in EUROCAT Guide 1.3, and the data have all been verified by member registries back to 1980 (Table 3).

Website prevalence tables allow the user to specify the registry(s), congenital anomaly subgroup(s) and years of interest.

Table 2: Transmission of Data to EUROCAT: Registry, years (2000-2005), no. births covered, no. cases of congenital anomaly, total prevalence rate per 10,000 births.

Registry	Country	Years	Total cases	Total births	Total prevalence per 10,000 births
Styria	Austria	2000-2005	2162	62667	345.00
Antwerp	Belgium	2000-2005	2772	108365	255.80
Hainaut	Belgium	2000-2005	1983	74102	267.60
Zagreb	Croatia	2000-2004	438	27998	156.44
Odense	Denmark	2000-2004	701	26745	262.11
Finland (A)	Finland	2000-2004	9932	283887	349.86
Auvergne	France	2002	374	13397	279.17
CE France (A)	France	2000-2004	9651	463951	208.02
Isle de la Reunion (A)	France	2002-2004	1099	43749	251.21
Paris	France	2000-2005	7708	220911	348.92
Strasbourg	France	2000-2003	1733	51707	335.16
Mainz	Germany	2000-2005	1051	18695	562.18
Saxony Anhalt	Germany	2000-2005	3540	106257	333.15
Hungary	Hungary	2000-2002	8154	341214	238.97
Cork and Kerry	Ireland	2000-2003	815	32617	249.87
Dublin	Ireland	2000-2005	2702	137013	197.21
SE Ireland	Ireland	2000-2004	597	31520	189.40
Campania	Italy	2000-2004	3383	283377	119.38
Emilia Romagna	Italy	2000-2005	3482	178331	195.25
Sicily	Italy	2000-2002	1263	47426	266.31
North East Italy	Italy	2000-2003	4085	233833	174.70
Tuscany	Italy	2000-2005	3473	165640	209.67
Malta	Malta	2000-2005	735	23668	310.55
N Netherlands	Netherlands	2000-2005	2384	118971	200.38
Norway	Norway	2000-2005	13345	346838	384.76
Poland (A)	Poland	2000-2004	17158	1040249	164.94
Wielkopolska	Poland	2000-2004	3985	170725	233.42
S Portugal	Portugal	2000-2004	934	92879	100.56
Asturias	Spain	2000-2004	1042	34835	299.12
Barcelona	Spain	2000-2003	982	52709	186.31
Basque Country	Spain	2000-2005	2158	112155	192.41
ECEMC (A)	Spain	2000-2005	6278	634016	99.02
Vaud	Switzerland	2000-2005	1631	42874	380.42
NorCAS	UK	2000-2005	4318	181377	238.07
North Thames	UK	2000-2004	3074	235990	130.26
Oxford	UK	2000-2005	1173	80555	145.61
Trent	UK	2000-2005	7914	362415	218.37
Wales	UK	2000-2005	7171	189191	379.03
Wessex	UK	2000-2005	2997	157899	189.80
Ukraine	Ukraine	2005	567	25835	219.47
Total			148944	6856583	217.23

(A) Associate Member

Table 3: Prevalence per 10,000 births of Selected Congenital Anomaly Subgroups* 2000-2004 (All Full Member Registries Combined)

Anomaly Subgroup	LB (prevalence)#	LB+FD+TOPFA (prevalence)
All Anomalies	197.96	236.68
All Anomalies Excluding Chromosomal	183.31	203.26
Nervous system	9.61	20.30
Neural Tube Defects	2.72	9.29
Anencephalus and similar	0.40	3.67
Encephalocele	0.33	1.03
Spina Bifida	1.99	4.59
Hydrocephaly	2.49	4.85
Microcephaly	1.56	1.77
Eye	3.06	3.24
Ear, face and neck	2.03	2.32
Congenital heart disease	60.39	63.71
Transposition of great vessels	2.79	2.97
Ventricular septal defect	26.35	26.88
Atrial septal defect	19.48	19.50
Atrioventricular septal defect	1.11	1.47
Tetralogy of Fallot	2.43	2.64
Pulmonary valve stenosis	3.15	3.18
Aortic valve atresia/stenosis	1.00	1.09
Hypoplastic left heart	1.34	2.34
Coarctation of aorta	2.96	3.06
Respiratory	3.46	4.79
Oro-facial clefts	12.55	13.32
Cleft lip with or without palate	7.65	8.17
Cleft palate	4.90	5.15
Digestive system	12.36	14.12
Oesophageal atresia with or without tracheo-oesophagal fistula	1.88	2.02
Ano-rectal atresia and stenosis	2.22	2.74
Diaphragmatic hernia	1.96	2.38
Abdominal wall defects	3.06	4.55
Gastroschisis	1.84	2.18
Omphalocele	1.16	2.13
Urinary	24.20	27.85
Bilateral renal agenesis including Potter syndrome	0.32	1.20
Cystic kidney disease	4.08	5.29
Congenital hydronephrosis	9.55	9.80
Genital	16.24	16.60
Hypospadias	13.29	13.13
Limb	32.81	35.38
Limb reduction	3.84	5.10
Upper limb reduction	2.76	3.57
Lower limb reduction	1.15	1.72
Club foot - talipes equinovarus	7.52	8.20
Hip dislocation and/or dysplasia	6.10	6.00
Polydactyly	7.23	7.43
Syndactyly	5.03	5.20

Musculo-skeletal	5.22	7.62
Craniosynostosis	1.12	1.17
Other malformations	6.90	8.37
Disorders of skin	4.35	4.46
Genetic syndromes + microdeletions	3.69	4.59
Chromosomal	14.65	33.42
Down Syndrome	9.49	19.15
Patau syndrome/trisomy 13	0.43	1.71
Edward syndrome/trisomy 18	0.89	4.15
Turner's syndrome	0.60	2.17

LB - Live Births
FD - Fetal Deaths / Still Births from 20 weeks gestation
TOPFA - Terminations of pregnancy for fetal anomaly following prenatal diagnosis

* Subgroups with total prevalence of at least 1 per 10,000 births are shown. For the full list of 92 subgroups see http://www.eurocat.ulster.ac.uk/pubdata/tables.html, (accessed 29-08-07)

LB denominators unavailable for Antwerp (Belgium), SE Ireland, NE Italy and Sicily, therefore total births were used as denominator for these 4 registries

A1.4 Provision of Data to Other Organisations

a) Request from UK Department of Health in August 2004 for information on prevalence of Vein of Galen using EUROCAT database. This is a very rare malformation. 52 confirmed cases were found in 21 registries, a prevalence of 0.08 per 10,000 births, and details regarding geographical variation and survival were provided.

b) Information on prevalence of congenital anomalies, as well as text, provided for the WHO European Health Report, 2005 (http://www.euro.who.int/ehr2005)

c) Provision of additional data on congenital anomaly prevalence for Report of WHO/EURO Meeting on Regional policy for prevention of congenital disorders "Folic Acid and the prevention of neural tube defects: from research to public health practice". Report by the Rapporti ISTISAN 04-26 (Istituto Superiore di Sanita), edited by Domenica Taruscio of the Centro Nazional Malattie rare, Dipartimento di Biologia Cellulare e Neuroscienze, ISSN 1123-3117.

d) In June 2004, prevalence information was provided to ORPHANET along with a link to the EUROCAT website prevalence tables, for 14 subgroups of congenital anomalies for which there are appropriate entries in ORPHANET. An expansion of the set of anomalies for which information is linked is underway.

e) In May 2005, EUROCAT provided data on maternal-age stratified rates of congenital anomalies for UK CEMACH (Confidential Enquiry into Maternal and Child Health) cohort study of congenital malformations in diabetic mothers. This resulted in a publications referencing EUROCAT (www.cemach.org.uk/getdoc/7cbb498a-f176-4cb5-ab83-6549bb19a886/Maternal-and-Perinatal-Health.aspx); Macintosh et al (2006), BMJ, Vol 333, pp 177

f) A number of organisations requested data on EUROCAT prevalence rates for various congenital anomalies who were directed to the EUROCAT website tables (http://www.eurocat.ulster.ac.uk/pubdata/tables.html) with instructions on how to access the prevalence information. Requests included:

I UK General Practice Research Database (GPRD). Comparison of GPRD prevalence of all heart defects, ventricular septal defects, coarctation of aorta and tetralogy of fallot with EUROCAT prevalence rates (April 2005).
II UK Evidence Base Medicine Journal. Request for prevalence of chromosomal anomalies (October 2005)
III International PPB Registry, Minnesota, USA. Request for prevalence of lung malformations (December 2005).
IV Spina Bifida and Hyrodcephalus Association of Quebec, Canada. Request for prevalence of Hydrocephalus and Spina Bifida in France (February 2006).
V Stem Cell Innovations, The Netherlands. Request for the top 10 major causes of TOP in EU (November 2006).
VI Yorkhill Hospital, Glasgow. Request for prevalence of colonic atresia, January 2007.
VII Sunday Times. February 2007. Request for prevalence of Down Syndrome In Ireland and the rest of Europe.

g) EUROCAT was invited by the EUGLOREH project "Global Report on Health Status of the European Union" to contribute a chapter on congenital anomalies. This was submitted to EUGLOREH, and will be published in 2008.

A1.5 Revision of Common Dataset for Births from 2004: Revised Coding of Drugs, Prenatal Screening/Diagnosis, Assisted Conception, Survival, New Coding of Folic Acid Supplementation, civil Registration Status, Social Class, Migrant Status. Consultation with EU Health Monitoring Indicator Development for Compatibility

Guide 1.3 "Instructions for the Registration of Congenital Anomalies" was published in 2005 (Appendix 3), for coding of cases born from 1 January 2005. Guide 1.3 includes a number of new variables: specification of twin status, civil registration status, first positive prenatal test, specification of first positive prenatal test, planned or performed surgery, folic acid supplementation, specification of consanguinity, maternal education, socioeconomic status of both parents, and migrant status. In addition to new variables, the coding systems for drugs during pregnancy (now using international ATC codes), consanguinity and assisted conception techniques have been extended/modified. The new variable set is more stream-lined towards surveillance and a number of old variables will no longer be collected centrally, although registries can continue to use these locally or for specific research projects.

The project leader remained in close contact with developments made in the ECHI project, and in PERISTAT, to ensure compatibility, but in general it should be noted that very little European population information exists for births (or women of childbearing age) with regard to the variables of interest here. This means that where comparisons are to be made between babies with and without congenital anomalies, control information must be specifically sought by registries.

A1.6 Expansion of Range of Indicators of Data Quality and Harmonization, including Registry Descriptions, Data Manual and Validations of Prevalence Data

Descriptions of each registry's methodology are updated each year by members and are available on the website under "Member registries". These give a first indication of data quality.

A range of data quality indicators (DQI) were designed for the first time to measure the quality and characteristics of data transmitted from participating registries (Appendix 2). This is a very important development in relation to increasing 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 Coe and Non-Core Variables, Timeliness and Denominator Data Availability. Comparisons can be made between each registry and the EUROCAT average and all other registries. The DQI were first presented at the Registry Leaders Meeting in Poland, June 2005, and have been since updated and presented at all yearly RLMs. It was agreed to make the DQI publicly available. The DQI are accompanied by a document showing the completeness of data on each variable in each registry, updated each year. Additional elements of the data manual include when each registry has started coding in ICD10 and which coding supplements they have used.

Guide 1.3 also includes a number of further important developments agreed by the Coding and Classification Committee:

a) revision of the standard EUROCAT subgroups and subgroup definitions
b) revision of the list of minor anomalies for exclusion
c) development of a multiple malformation algorithm to identify children with more than one major malformation
d) development of coding guidelines addressing specific malformation coding difficulties

The Coding & Classification Committee continued work on the publication of guides for the correct coding of congenital anomalies. The following guides were published on the website:

EUROCAT Guide 6 (2004) "Definition and Coding of Syndromes", *EUROCAT Central Registry, University of Ulster*. (Appendix 4)
www.eurocat.ulster.ac.uk/pdf/Ester/EUROCAT-Guide-6-Version-3.pdf

EUROCAT Guide 3 (2004) (2nd Edition): For the Description and Classification of Congenital Limb Defects", *EUROCAT Central Registry, University of Ulster*. (Appendix 5)
(www.eurocat.ulster.ac.uk/pdf/EUROCAT-Final-Guide-3.pdf)

A2 To co-ordinate the establishment of new registries throughout Europe collecting comparable, standardized data

A2.1 Assistance To and Exchange with New/Applicant Members

Contacts are ongoing with Moscow Region, Lithuania, Latvia, Cyprus, Guadeloupe, Georgia, Czech Republic, Luxembourg, Slovak Republic, Slovenia, Bulgaria and Romania.

A number of interested Registries from Central and Eastern Europe attended the Registry Leaders Meeting in Poznan in June 2005 (See Appendix 4) – they included two teams from the Ukraine (one which has since become a member) as well as Latvia, Moscow Region and Belarus.

The EDMP software and user-guide was sent to Belarus in July 2005.

An application to INTAS was made to fund collaboration with Moscow, Byelorussia and Ukraine but was not successful

Members of the EUROCAT Steering Committee visited Ukraine in 16-19 July 2007.

A2.2 Organisation of One-Day Induction Workshop for New/Applicant Members

Coding workshops were organized for EUROCAT members in Dublin (26 April 2005, 13 participants), London (12 April 2005, 23 participants) Rome (6-7 October 2005, 50 participants). Attendance at coding workshops was funded by member registries.
In addition, "EDMP clinics" were held at the Registry Leaders Meeting in Bergen (2004), Poznan (2005), Styria (2006) and Naples (2007), to teach new and old registries how to use the EDMP software

A2.3 Survey of Confidentiality and Consent Issues in EUROCAT Registries

Registries collecting personal medical data must, under EC Directive 95/46/EC, obtain consent for the processing of such data, unless national law or a national supervisory body allows for an exemption. Member states have not always taken advantage of the ability to exempt health care or disease registries. There has been much debate about the consequent effect on epidemiologic research and surveillance. We conducted a survey of congenital anomaly registries with regard to the requirement for informed consent and its implementation. A questionnaire designed by the EUROCAT Committee on Ethics and Confidentiality was sent to 37 EUROCAT registries in February 2003. 29 registries from a total of 15 EU countries (and 2 registries from 2 non-EU countries subsequently excluded from further analysis) replied. Information was updated in June 2004.

Nine countries have enacted legislation or created a supervisory body which allows registries to operate without informed consent. In three of these, registries effectively operate opt-out consent (every effort is made to ensure families are aware of the registry's activities; parents must explicitly ask for their children to be removed).

Eight registries (from 6 countries) report experience of informed consent. Of five registries relying on clinician notification or access to medical records, four report marked reduction in case reporting after introducing consent and considerable difficulty maintaining high ascertainment levels, largely due to logistic difficulty associated with tracing parents. Less than 1% of parents refuse consent or opt-out of participation.

EUROCAT experience indicates that opt-in consent poses a serious threat to the operation of congenital anomaly registries. The debate about informed consent has eclipsed more relevant consideration of procedures to maintain confidentiality of data.

This survey of EUROCAT registries was published:

> Busby A, Ritvanen A, Dolk H, Armstrong N, De Walle H, Riano-Galan I, Gatt M, McDonnell R, Nelen V and Stone D (2005), "Survey of Informed Consent for Registration of Congenital Anomalies in Europe", *British Medical Journal*, Vol 331, pp 140-41.

The report was also presented to the Network of Competent Authorities, 5-6 July 2005 in Luxembourg and to the Rare Diseases Task Force. The paper was also referred to at an international workshop on developments in e-Health by Walter Deville of the NCA secretariat.

A3 To co-ordinate the detection of and response to clusters and early warning of teratogenic exposures

A3.1 Testing, Training and Implementation of New Statistical Surveillance Software (Compatible with EDMP) for Rapid Monitoring in Member Registries

Statistical monitoring tools integrated to the EDMP (which allow registries to identify trends and time clusters as soon as they have a new period of data to analyse) have been further tested for robustness and accuracy of statistical output. Several important modifications were made:

a) method of specifying start and end of period of analysis using scan statistic
b) relating clusters to date of conception rather than date of birth
c) indicating expected number of cases per year in output
d) analyzing chromosomal and non-chromosomal cases separately
e) producing timeline graphs showing all possible clusters, some which may overlap in time

"EDMP clinics" at the four Registry Leaders' Meetings allowed registries to train in the use of the statistical monitoring tools.

A statistical monitoring protocol, and two annual statistical monitoring reports, have now been produced (Appendix 6a and 6b). They were presented at the Budapest Environment and Congenital Anomalies meeting in 2007 (Appendix 12), with discussant comments by three spatial statisticians: Ben Armstrong, Marco Martuzzi, Andrea Berghold (Appendix 12), resulting in overall approval of the approach but also some directions for further development.

Nevertheless at the moment, registries still tend to rely on the Central Registry to run statistical monitoring, and more work is needed to implement rapid monitoring locally.

A3.2 Annual Central Registry Monitoring of Validated Data to Detect Trends and Clusters

Each year, statistical monitoring of updated data is carried out centrally to detect trends and time clusters. These are communicated to registries for investigation. The timetable for statistical analysis, investigation and reporting is shown in the Statistical Monitoring Protocol (Appendix 6a). Reports of preliminary investigations are discussed at each Registry Leaders Meeting.

The Statistical Monitoring Report 2004 detected 75 upward trends and 156 downward trends over the preceding 5 years. 56 clusters were detected of which 48% were investigated. 5 % were cause for concern; 11% were due to changes in diagnosis, aetiologic heterogeneity and familial/twin recurrence; no explanations were found for 11%; 7% were due to changes and improvements in prenatal detection techniques and 13% were caused by data quality issues. Further details are given in the Statistical Monitoring Report (Appendix 6b).

The latest statistical monitoring to 2005 detected 87 upward trends and 197 downward trends over the preceding 5 years. 14 clusters were detected of which 71% were investigated. 36% were due to changes in diagnosis, aetiologic heterogeneity and familial/twin recurrence; an excess of cases was found in 14%, but further investigation is not proposed other than surveillance and 21% were caused by data quality issues.

Experience has shown that statistical monitoring has a useful secondary benefit for data quality monitoring.

A3.3 Response to Clusters or Public Health Concerns Through Analysis of Central Database, Co-ordination of Extra Data Collection

a) Gastroschisis. Gastroschisis is a rare abdominal wall anomaly which has been increasing in prevalence in Europe and worldwide. It is well established that young maternal age is a strong risk factor for this anomaly. Smoking, recreational drug use and some therapeutic drugs are also risk factors. Analysis of EUROCAT data led to the following publication:

> 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.

The study found that the increase in risk of gastroschisis over time was not restricted to younger mothers only as there was a similar increased risk in mothers of all ages.

b) A project funded by the Department of Health, London investigated congenital anomaly risk in five British regions in relation to air pollution. A report is being prepared for publication. While the study did not find a generally raised risk of chromosomal or non-chromosomal anomalies in relation to SO_2, NO_2 or PM-10, there were some specific associations for one cardiac anomaly which need further investigation.

c) EUROCAT data on maternal age and risk of non-chromosomal anomalies has been analysed, and the report is being prepared for publication. Results were presented at Society for Social Medicine Conference in Cork, 12-14 September 2007. For non-chromosomal anomalies, older maternal age is not associated with a higher risk, but young mothers (<20) are at higher risk.

A3.4 Drug Surveillance Through Analysis of Drug-Malformation Associations and Collaboration with International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS) Madre Project

The past three years have seen a strong push by EUROCAT, through its Drugs Working Group, to meet the potential of the network for pharmacovigilance. This has involved data validation, a major change to the drug coding system, and studies of individual drugs. EUROCAT was represented at an EMEA ENCePP meeting in June 2007 to discuss a new European network for pharmacovigilance. First steps should increase communication between European partners, but there are currently no plans for real investment in a pharmacovigilance infrastructure based on database development. There are two areas where EUROCAT needs to find specific funds: a) to increase the number of sources of information that are accessed for information about drugs during pregnancy at member registry level, including electronic pharmacy databases and maternal interviews b) to collect information about control births as well as malformed births

Other than the EncePP network, EUROCAT has been working with partners in the International Society for Pharmacoepidemioogy towards a specific forum for exchange regarding drugs during pregnancy. A specific working group has been set up, and a meeting with the President of ISPE, Allen Mitchell, in Amsterdam was held in April 2007. Prof Mitchell runs the Slone Birth Defect Drug Surveillance system in Boston, which collects

detailed data on cases and controls, but is much smaller than EUROCAT. We look forward to further collaboration.

a) Improvement of drug exposure data quality.

The first part of this work was done largely under the previous EUROCAT contract, as a survey of all member registries, with final report published during this contract period.

> Meijer W, Cornel MC, Dolk H, de Walle HEK, Armstrong NC, de Jong-van den Berg LTW and a EUROCAT Working Group (2006), "The Potential of the European Network on Congenital Anomaly Registers (EUROCAT) for Drug Safety Surveillance: A Descriptive Study", *Pharmacoepdemiology and Drug Safety*, Vol 15, pp 675-682.

This investigation showed great potential for EUROCAT to work as a pharmacovigilance system for drugs during pregnancy. Recommendations to change to ATC coding of drugs (an international code, with a hierarchical system coding each specific drug) has been implemented (EUROCAT Guide 1.3) for births from 2005. A specific training session in ATC drug coding was conducted at the Registry Leaders Meeting in Graz, Austria (2006).

A further study specifically investigated the potential of the EUROCAT database to yield useful information on drugs for chronic diseases – epilepsy, diabetes and asthma.

> Geurts MME (2006), “Drug Use During Pregnancy: The Use of Chronic Drugs During Pregnancy Using the EUROCAT Database”, *University of Groningen*

This study concluded that ascertainment of antiepileptic drug exposures by those registries collecting drug information was high, that ascertainment of drugs for diabetes was also high but with less specificity as to type of insulin, and that ascertainment of drugs for asthma was lower than for the other chronic diseases, but still acceptable for study given the huge advantage of population size, and the fact that drug exposures are generally recorded in medical notes before the outcome of pregnancy is known, thus reducing the potential for bias.

b) A case-control study was carried out to investigate the relation of loratidine (an antihistamine) and hypospadias, following reports in Sweden of an increased risk. We used data from the central database from 1991 to 2000. Cases were all subjects with hypospadias, with or without any other anomaly; controls were all subjects without hypospadias, regardless of other malformations. The study included 81,603 cases of congenital anomaly in the EUROCAT database, of which 4,623 had hypospadias. The exposure rate to loratidine was much lower than that reported in Sweden. A single case of hypospadias exposed to loratidine was found, an odds ratio of 1.36 with very wide confidence intervals. While the study did not have the power to either confirm or refute an excess of a similar size to that reported in Sweden, it was evident that exposure levels in Europe are estimated to be low, and if an excess risk exists, the number of cases attributable to loratidine is very small.

c) A database has been collated and validated to analyse antiepileptic exposures in relation to the risk of specific congenital anomalies. Antiepileptic drug exposure has been entirely ATC coded within this database. The database covers 3.9 million births since 1995, from 19 registries, with an AED exposure rate among cases of congenital anomaly of 6 per 1,000, equivalent to 495 exposed cases. This is as far as we know the largest existing database of malformations in relation to antiepileptic exposures in the world. A first study has been performed using this database to respond to a recent signal regarding the risk of orofacial cleft in relation to lamotrigine exposure, lamotrigine being a newer generation antiepileptic about which less is known of the potential risks of malformation. The extra work required to conduct this study was funded by Glaxo Smith Kline, although we note that ideally pharmacovigilance studies should be funded through an intermediary to avoid direct funding relationships with the pharmaceutical industry. The database is now ready for other studies of both older generation drugs (e.g. valproic acid, carbamazepine) and newer generation drugs, and a specific working group, the EUROCAT Antiepileptic Drug Working Group, made up of all registries participating in this database has been formed, and met at the Naples Registry Leaders Meeting (May 2007).

d) Initial plans to contribute data to the MADRE project of ICBDMS have been shelved, though future collaboration is possible. MADRE collects data on drug exposed cases of malformation only, with a coding system for drugs and malformations which is not compatible with that of EUROCAT. It would therefore require considerable work to recode EUROCAT data to MADRE requirements. MADRE statistical analysis then detects significantly higher than expected frequency drug-malformation associations, without prior hypothesis as to associations of interest. We have decided in EUROCAT to concentrate our efforts at the moment on testing hypotheses or signals from pregnancy cohort studies, and on analyzing chronic disease drug exposures for which we believe the data is more complete. Several EUROCAT registers which are also ICBDMS members do however contribute data to MADRE independently of EUROCAT Central Registry.

A3.5 Collaboration with ICBDSR for Multiple Malformation Monitoring

ICBDMS (International Clearinghouse for Birth Defect Monitoring Systems) has for many years been carrying out monitoring of multiple malformations, by analyzing reports of babies with more than one multiple malformation each quarter, following a standard protocol. Some EUROCAT registers already participate in this process. The procedural problems to solve were the recoding of data to ICBDMS requirements, timing of data sharing, and arrangements around data confidentiality. A protocol for EUROCAT participation was sent to ICBD Rome in June 2004. No response was received by February 2005, and then the matter was referred to a meeting in Poland (Registry Leaders Meeting June 2005). It was decided that the lack of outcome of previous years of monitoring did not warrant great resources being allocated to recode EUROCAT data. Instead, ICBD proposed to concentrate on specific studies of malformation associations, rather than temporal surveillance, and request EUROCAT data according to a protocol for each such study. At present, the ICBD focus is on orofacial clefts, an area where EUROCAT data has already been extensively analysed (see A 6.4).

Meanwhile, EUROCAT has been conducting descriptive epidemiological work to establish the prevalence of multiple anomalies (babies with more than one major anomaly) in member regions. A computer algorithm was designed, applied, and improved, to identify by computer cases of “possible multiple malformation” by excluding cases with isolated anomalies, sequences, syndromes, or one major anomaly with other minor or unspecified anomalies. These cases were reviewed by a panel of three medical geneticists to further refine the

algorithm. The exercise also proved to be useful to examine differences in malformation coding practice between registers. The experience is being written up for publication, before proceeding to further epidemiological analysis, and before instituting routine multiple malformation surveillance.

A3.6 EUROCAT Network Communications as a Rapid Reaction and Response Facility

EUROCAT network communications are sent out approximately every two weeks and contain information relating to organizational, surveillance and research issues. In addition it is possible to use these communications to respond to issues of concern to local Registries such as a suggestion of a local cluster or an increasing prevalence of a specific congenital anomaly. Registries can communicate details of their cluster/prevalence increase and ask other local Registries to check their data for the same time period, and thus compare the situation in their local area with the wider situation in other European countries. Within the last two years this has been done for two alleged clusters of Down syndrome in two different Registries (different time periods) and an excess of specific upper limb anomalies in a third registry. These alleged clusters were not reported by other registries.

During the contract period, 57 EUROCAT Communications were sent out, by email, to all members.

A3.7 Maintenance and Updating of EUROCAT Cluster Advisory Service on the Web and Translation of Key Parts into Five Languages

All materials developed under the last EUROCAT contract are still fully available on the website [www.eurocat.ulster.ac.uk/clusteradservice.html]. However, it has been decided not to invest our limited resources into translating the material into other languages at this time.

An extension of the EUROCAT Special Report "Review of Environmental Risk Factors" (part of the Cluster Advisory Service) with two chapters, one on maternal obesity and the other on the system in Europe for testing teratogenicity, has been completed (www.eurocat.ulster.ac.uk/pubdata/Envrisk.html)

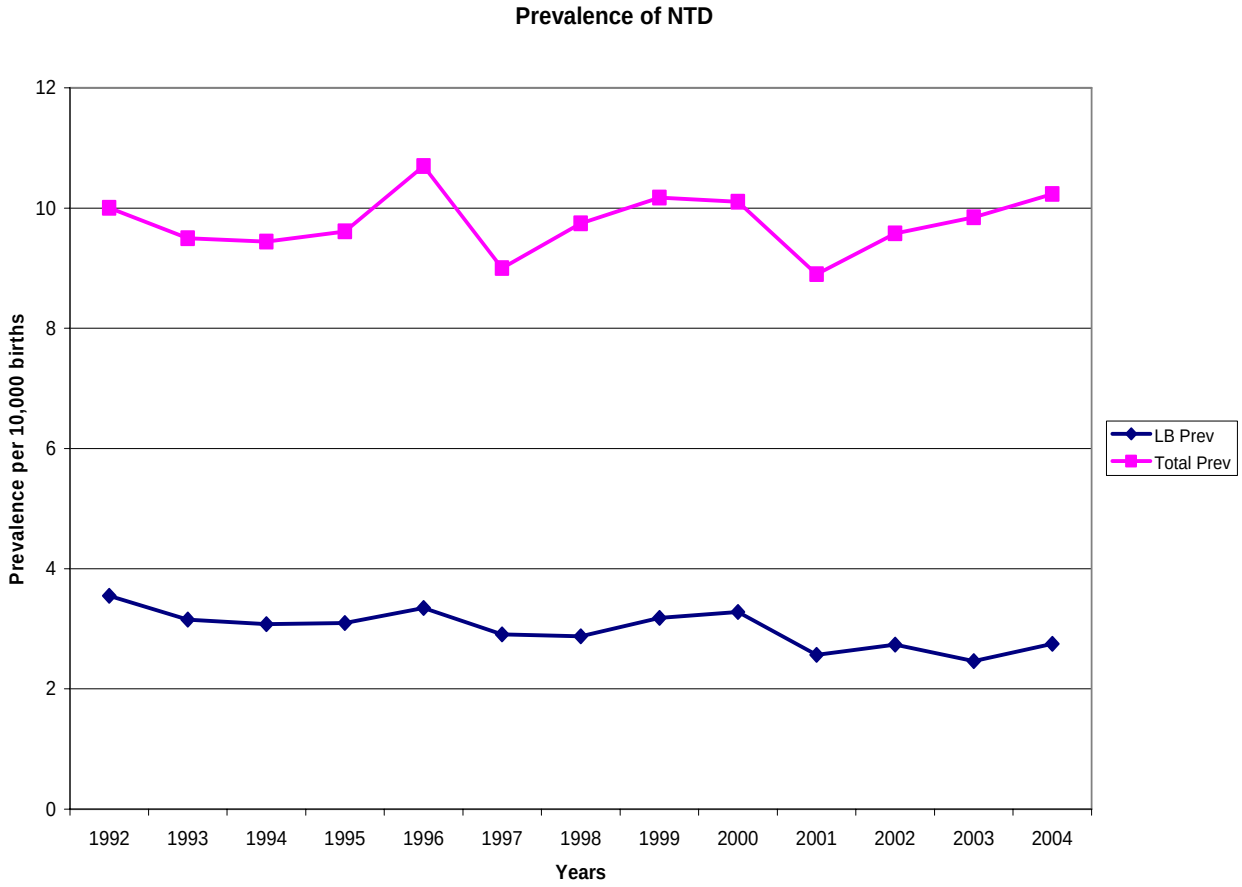
A4 To evaluate the effectiveness of primary prevention

The major issue in the last two decades regarding prevention of congenital anomalies has been the demonstration that raising maternal folic acid status can prevent the majority of cases of neural tube defect, finally demonstrated in randomized controlled trials in the very early 1990s. EUROCAT is in a unique position to track progress in public health implementation of these research findings. The main policy response has been to advise periconceptional folic acid supplementation. This has had limited success however, as the majority of women do not take the supplement early enough, either because the information campaigns do not reach them, or they are unaware of the need to start preconceptionally, or because they do not plan their pregnancy. Thus, we have found very little decline in the prevalence of neural tube defects. Some European countries are now considering fortification of a staple food (e.g. flour), following the example of US and Canada among others. EUROCAT is well placed to follow the impact of any future changes in policy.

A4.1 Annual Production and Website Dissemination of Commentated Yearly Updated Prevalence Rates of Neural Tube Defects (Births and Terminations)

Data for 2002-2005 have been transmitted to Central Registry (Table 2), and are available on the website. Papers and reports have been written as commentary on these data as listed under Section A4.2. Generally, there has been little or no decline since 1990 in the prevalence of neural tube defects across Europe when terminations of pregnancy as well as births are included. Prenatal screening and diagnosis have led to an increasing termination rate and lowering of livebirth rate.

Figure 2: Trends in the Total and LB prevalence per 10,000 births of Neural Tube Defects, 1992-2004.



* all EUROCAT full member registries combined

A4.2 Annual Survey in member Countries of Policy Changes Regarding Periconceptional Folic Acid Supplementation, Health Education Initiatives Undertaken, Available Data of Folic Acid Uptake and Analysis of Available Data on Protective Effect for Other Congenital Anomalies

In 2005 we published the second edition of the Prevention of Neural Tube Defects by Periconceptional Folic Acid Supplementation in Europe (www.eurocat.ulster.ac.uk/pubdata/Folic-Acid.html)

The update includes one more country (Sweden) in addition to the 40 previously included, and two more recent years' NTD prevalence data (births from 2001 and 2002). It documents

policy changes in a few countries, especially Italy, and the extremely slow progress with regard to consideration of fortification of food with folic acid. Although fortification has been advised in a few countries, it has not yet been implemented. This updated report is now on the EUROCAT website. EUROCAT continues to advocate the recommendations from the earlier report (see below).

EUROCAT findings have been and will continue to be widely reported in journals and conferences including (but not limited to):

> Abramsky L, Busby A, Dolk, H, Armstrong B and EUROCAT Working Group, "Prevention of Neural Tube Defects by Folic Acid Supplementation", presented at the 8th European Symposium "Prevention of Congenital Anomalies" in Poznan, Poland, June 2005.
>
> Abramsky L, Busby A, Dolk, H Armstrong B and EUROCAT Working Group, "The Role of Folic Acid in Preventing Congenital Anomalies", presented at 33rd Annual Conference of the European Teratology Society, Haarlem, Netherlands, September 2005,
>
> Busby A, Abramsky L, Dolk, H, Armstrong B and EUROCAT Working Group (2005), "Preventing Neural Tube Defects in Europe – A Missed Opportunity", *Reproductive Toxicology*, Vol 20, pp 393-402.
>
> Abramsky L, Busby A, Dolk, H (2005), "Promotion of Periconceptional Folic Acid Has Had Limited Success" *Journal of the Royal Society for the Promotion of Health*, Vol 125, No 5) (special issue on health promotion during pregnancy).
>
> Busby A, Abramsky L, Dolk H, Armstrong B, and EUROCAT Working Group (2005), "Preventing Neural Tube Defects in Europe: Population Based Study, *BMJ*, Vol 330, pp 574-575.
>
> A summary of the EUROCAT findings were presented to the European Rare Diseases Conference in Luxembourg June 2005, both as a poster and in the context of a lecture on the prevention of rare diseases.

In addition, summaries of the 2003 EUROCAT Special Report have been published in the Journal of the Norwegian Medical Association, Journal of the Danish Medical Association, and Review of Obstetrics and Gynecology in Poland, and have been quoted in papers in Germany, Ireland and Italy.

A variable regarding whether and when folic acid supplementation was taken periconceptionally has been added to the EUROCAT dataset for births from 2005, but few registries have so far been able to find this information successfully for the majority of pregnancies.

In January 2006, we sent a questionnaire to NTD parent/patient support groups in 25 Europe countries asking about their position regarding mandatory fortification of flour with folic acid. This resulted in a short publication – a letter to the Lancet, (Appendix 9), showing a high level of support for folic acid fortification.

> 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.

EUROCAT recommendations regarding prevention of neural tube defects by raising folate status:

a) Countries should review their policies regarding folic acid fortification and supplementation.
b) European countries could prevent most neural tube defects in planned pregnancies by putting in place an official policy recommending periconceptional folic acid supplementation and taking steps to ensure that the population are aware of the benefits of supplementation and the importance of starting supplementation before conception.
c) As many pregnancies are unplanned, European countries could achieve more effective prevention of neural tube defects by additionally introducing fortification of a staple food with folic acid. The particular objectives of this policy would be preventing neural tube defects among women who do not plan their pregnancy, and reducing socio-economic inequalities in neural tube defect prevalence.
d) Health effects of supplementation and fortification should be monitored, and policies should be reviewed periodically in light of the findings.
e) The European population should be covered by high quality congenital malformation registers which collect information about affected pregnancies (livebirths, stillbirths and termination for fetal abnormality). One important use for the information would be to assess the effect of folic acid supplementation and fortification on NTD rates as well as rates of other congenital malformations.

A5 To assess the impact of developments in prenatal screening

A5.1 Annual Updating of Website Regarding the Frequency of Terminations of Pregnancy Following Prenatal Diagnosis

Prenatal diagnosis of congenital anomaly may lead to preparation for the birth of an affected child by the family and health services, or in severe cases to termination of the pregnancy. Prenatal screening services are constantly evolving within Europe and EUROCAT seeks to document this and examine the impact of screening and prenatal diagnosis in terms of the proportion of cases prenatally diagnosed, and the proportion of prenatal diagnoses leading to termination of pregnancy.

Information on the number of terminations of pregnancy following prenatal diagnosis per type of anomaly, registry and year was updated to 2005, available on the EUROCAT website: http://www.biomedicalweb.biz/eurocat/search.cgi. In late 2005 it was decided to give website data on the proportion of cases diagnosed prenatally (irrespective of pregnancy outcome) for selected subgroups of congenital anomalies: anencephalus, spina bifida, transposition of great arteries, hypoplastic left heart, bilateral renal agenesis and Down syndrome. This has required further data validation regarding timing of diagnosis for livebirths, and design of new tables to give the most meaningful data while preserving data confidentiality. The tables are due to be publicly available on the website for December 2007, at the same time as the second yearly upload of prevalence data, all development of these tables having been completed.

A5.2 Analyses of Central Database Regarding Impact of Prenatal Screening and Maternal Age Changes on Geographic Inequalities in Livebirth Prevalence and Perinatal Mortality

a) General prenatal screening and diagnosis policies and impact

Two studies carried out in 2003 using the EUROCAT database with respect to prenatal diagnosis were published in 2004/2005.

> Ester Garne, Maria Loane, Catherine de Vigan, Gioacchino Scarano, Hermien de Walle, Yves Gillerot, Claude Stoll, Marie-Claude Addor, David Stone, Blanca Gener, Maria Feijoo, Carmen Mosquera-Tenreiro, Miriam Gatt, Annette Queisser-Luft, Neus Baena and Helen Dolk (2004), "Prenatal Diagnostic Procedures Used in Pregnancies with Congenital Malformations in 14 Registries in Europe", *Prenatal Diagnosis*, Vol 24, No 11, pp 908-12.
>
> Ester Garne, Maria Loane, Helen Dolk, Catherine de Vigan, Gioacchino Scarano, David Tucker, Claude Stoll, Blanca Gener, Anna Pierini, Vera Nelen, Christine Rösch, Yves Gillerot, Maria Feijoo, Radka Tincheva, Annette Queisser-Luft, Marie-Claude Addor, Carmen Mosquera, Miriam Gatt, Ingeborg Barisic (2005), "Prenatal Diagnosis of Severe Structural Malformations in Europe", *UOG*, Vol 25, No 1, pp 6-11.

These and other analyses pointed out the need for updating the EUROCAT dataset in relation to prenatal screening and diagnosis to keep up with progress in the field. EUROCAT Guide 1.3 (Appendix 3) now includes a variable "first positive prenatal test" to denote which prenatal test was the first positive test leading to the diagnosis of the congenital anomaly. This variable has been recorded from 2005 births.

At the meeting of the Prenatal Diagnosis Working Group in Bergen in June 2004 it was decided to write a EUROCAT Special Report on prenatal screening and diagnosis policies, including policies regarding termination of pregnancy, in the European countries. This report including a chapter for each of eleven countries was published in 2005, and a paper has been accepted for publication in BJOG based on the report and analysis of data on neural tube defects and Down Syndrome. The report and paper show wide variation in prenatal screening policies across Europe, as well as variation in laws regarding termination of pregnancy (whether it is legal at any gestational age, and if legal whether there is a gestational age limit). Analysis of data showed that whereas policy does have an impact on the prenatal detection rates, there is still variation between countries with the same policy suggesting other cultural and organizational factors intervening. Furthermore, gestational age limits for terminations did not have a measurable impact on overall termination rates, implying that it is possible for prenatal care to be organized to deliver early prenatal diagnosis where necessary. Report reference:

> Boyd PA, DeVigan C, Khoshnood B, Loane M, Garne E, Dolk H and the EUROCAT working group (in press), "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", *BJOG*

b) Down Syndrome

An analysis of the counterbalancing effects on livebirth prevalence of Down Syndrome of the increasing maternal age at birth across Europe on the one hand, and the increasing prenatal detection rate followed by termination of pregnancy on the other hand, done under the previous EUROCAT contract, was published (Appendix 12):

> Dolk H, Loane M, Garne E, de Walle, H, Queisser-Luft A, de Vigan C, Addor M-C, Gener B, Haeusler M, Jordan H, Tucker D, Stoll C, Feijoo M, Lillis D, Bianchi F (2005), "Trends and Geographic Inequalities in the Livebirth Prevalence of Down Syndrome in Europe 1980-1999", *Revues Epidem Sante Publique*, Vol 53, pp 2S87-2S95.

EUROCAT data was contributed to a study investigating the risk of Down Syndrome to mothers over 40 years of age. This has confirmed that the risk does not increase further after the age of 42-44, and has important implications for prenatal screening and counseling. The results can be found in:

> Morris, J et al (2005)**,** "Risk of a Down Syndrome Live Birth in Women of 45 Years of Age and Older", *Prenatal Diagnosis*; Vol 25, pp 275-278.

c) Prenatal diagnosis and postnatal outcome.

A study was carried out in seven EUROCAT registries of the impact of prenatal diagnosis of Transposition of Great Arteries on postnatal outcome of livebirths. This study found some evidence of a higher survival rate after prenatal diagnosis, but numbers were very small. The study also showed a higher postnatal mortality than previously reported from tertiary center based studies, but on the other hand a good outcome for those who survived the first year. The general issue of the impact of prenatal diagnosis on livebirth outcome is of increasing importance and will be pursued in the next EUROCAT contract phase.

> Garne E, Loane M, Nelen V, Bakker M, Gener B, Abramsky L, Addor MC and Queisser-Luft A (2007), "Survival and Health in Liveborn Infants with Transposition of Great Arteries – A population Based Study", *Congenital Heart Disease*, Vol 2, pp 165-169.

An analysis of gestational age at live-birth for infants with gastro-intestinal malformations showed that gestational age at birth was significantly lower for infants with a prenatal diagnosis of a gastro-intestinal malformation compared to infants with a postnatal diagnosis, potentially adding risks related to early birth to the risk of mortality and morbidity relating to the malformation itself.

> Garne E, Loane M, Dolk H and a EUROCAT Working Group (2007), "Gastro-Intestinal Malformations: Impact of Prenatal Diagnosis on Gestational Age at Birth, *Journal of Paediatric & Perinatal Epidemiology*, Vol 21, No 4, pp 370-375.

d) Termination of pregnancy and perinatal mortality.

The relationship between termination rate and stillbirth and neonatal mortality is complex. On the one hand, early termination of severe anomalies with high mortality can reduce the perinatal mortality rate. On the other hand, late termination when counted as a stillbirth can inflate stillbirth rates. Moreover, countries differ in their regulations regarding the civil registration of terminations of pregnancy as births. To address these problems more

effectively, a new civil registration variable has been added to the EUROCAT dataset in EUROCAT Guide 1.3 (Appendix 3).

Stillbirth and first week mortality rates for the years 2000-2004 are given in Table 4.

Table 4: Perinatal mortality due to congenital anomalies in EUROCAT full member registries combined, 2000-2004

Anomaly Subgroup*	% contribution of anomaly subgroups to 1st week LB deaths	% contribution of anomaly subgroups to SB	Stillbirths per 1,000 births	First week deaths per 1,000 births	Perinatal mortality per 1,000 births
All Anomalies	100.00	100.00	0.42	0.52	0.94
All Anomalies Excluding Chromosomal	84.27	70.58	0.30	0.44	0.74
Nervous system	20.69	19.64	0.08	0.11	0.19
Neural Tube Defects	11.42	11.56	0.05	0.06	0.11
Anencephalus and similar	6.75	7.20	0.03	0.04	0.07
Hydrocephaly	3.52	5.16	0.02	0.02	0.04
Congenital heart disease	28.59	16.44	0.07	0.15	0.22
Hypoplastic left heart	7.40	1.42	0.01	0.04	0.04
Respiratory	12.21	9.51	0.04	0.06	0.10
Oro-facial clefts	5.24	5.51	0.02	0.03	0.05
Digestive system	14.73	9.24	0.04	0.08	0.12
Diaphragmatic hernia	6.61	1.51	0.01	0.03	0.04
Abdomnal wall defects	3.81	5.60	0.02	0.02	0.04
Urinary	17.74	12.80	0.05	0.09	0.15
Bilateral renal agenesis including Potter syndrome	5.32	2.84	0.01	0.03	0.04
Cystic kidney disease	7.26	2.67	0.01	0.04	0.05
Limb	10.78	14.04	0.06	0.06	0.12
Club foot - talipes equinovarus	3.74	5.60	0.02	0.02	0.04
Musculo-skeletal	8.62	8.44	0.04	0.05	0.08
Other malformations	5.96	5.51	0.02	0.03	0.05
Chromosomal	15.73	29.42	0.08	0.12	0.21
Down Syndrome	2.59	8.36	0.01	0.04	0.05
Edward syndrome/trisomy 18	5.96	8.00	0.03	0.03	0.06

LB - Live Births

SB - Fetal deaths / Still Births from 20 weeks gestation

* Subgroups contributing to at least 5% of first week deaths or SB are shown.

Congenital anomalies are an important contributor to perinatal mortality. The overall recorded rate of stillbirths with congenital anomaly is 0.42 per 1,000 births, and deaths in the first week 0.52 per 1,000 births, giving a total perinatal mortality rate associated with congenital anomaly of 0.94 per 1,000 births (Table 4). The main congenital anomaly subgroups contributing to perinatal mortality are congenital heart disease (23% of perinatal deaths with anomaly), nervous system anomalies (20% of perinatal deaths with anomaly), and chromosomal anomalies (22%) (Table 4). Chromosomal anomalies contribute more to stillbirths than first week deaths, while congenital heart disease contributes more to first week deaths than stillbirths, and nervous system defects contribute equally in both categories (Table 4).

Perinatal mortality due to congenital anomaly varies by country. The lowest rates are recorded in Italy (0.2 per 1,000) but there is a known problem with recording of cause of death for stillbirths and neonatal deaths so this figure is probably considerably underascertained. The highest rates of perinatal mortality associated with congenital anomaly are recorded in Ireland (2.3 per 1,000) and Malta (2.2 per 1,000). These are both countries where TOPFA is illegal, and thus the perinatal mortality rate includes affected fetuses with a lethal or high mortality anomaly which would have been prenatally diagnosed in other countries leading to termination of pregnancy (and exclusion from mortality statistics).

The ratio of TOPFA to births varies from 0 (Ireland and Malta) to 10.8 (France) per 1,000 births. Differing prenatal screening policies and practices, differences in uptake of prenatal screening and diagnosis due to cultural and organisational factors, and differences in TOPFA laws, influence the rate of TOPFA in the population. In Poland, TOPFA is not encouraged, and done only in case of lethal anomaly. Some countries allow TOPFA at any gestational age (Austria, Belgium, Croatia, England & Wales, France, Germany). Others have an upper gestational age limit (Finland, Italy, Spain, Sweden, Switzerland), and yet others have an upper gestational age limit but allow TOPFA for lethal anomalies beyond this limit (Netherlands, Norway, Portugal, Denmark).

Table 5 shows TOPFA before and after 20 weeks gestation. The highest TOPFA ratio both before and after 20 weeks gestation is recorded in France (5.3 and 5.5 per 1,000 births respectively). Comparison between countries is complicated by different laws and practices regarding the recording of late terminations. Late TOPFA, where legal, may be recorded as stillbirth or as livebirth with neonatal death in some countries, and practice may also vary within countries.

TOPFA in most countries far outnumber stillbirths and neonatal deaths with congenital anomaly. Up to 0.8% (Switzerland) of fetuses die due to the presence of a congenital anomaly, whether as a TOPFA, stillbirth or neonatal death (but excluding spontaneous abortions), and 5 countries record a rate above 0.5%. The differences in total mortality (TOPFA + perinatal) between countries probably mainly reflects the frequency with which TOPFA is carried out for non-lethal anomalies, but is also influenced by differences between countries in the prevalence of anomalies such as neural tube defects and Down syndrome and, as previously mentioned, the completeness of ascertainment of stillbirths, neonatal deaths, and TOPFA.

Table 5: Ratio of Terminations of Pregnancy for Fetal Anomaly following prenatal diagnosis (TOPFA) to all births, and Perinatal Mortality per 1,000 births, by country, 2000-2004, EUROCAT full member registries

Country[1]	TOPFA <20 weeks	TOPFA 20+ weeks	Total TOPFA*	Perinatal Mortality**	Perinatal Mortality + TOPFA
Belgium	1.70	1.31	3.24	1.15	4.28
Denmark	2.43	0.86	3.29	1.53	4.82
Germany	2.34	1.71	4.08	0.98	5.06
Ireland[2]	0	0	0	2.34	2.35
Spain	3.60	2.05	6.08	0.45	6.52
France	5.34	5.50	10.84	0.97	7.47
Italy	1.55	1.88	3.61	0.24	3.55
Hungary	1.15	0.71	2.06	-	-
Malta[2]	0	0	0	2.22	2.22
Netherlands	0.91	0.44	1.36	1.71	2.98
Austria	2.16	0.98	3.16	0.84	3.99
Poland[3]	-	-	-	1.41	1.41
Portugal	1.03	1.21	2.27	0.54	2.80
UK	2.40	2.15	4.99	1.27	6.49
Croatia	0.57	0.43	1.04	0.54	1.50
Norway[4]	-	-	2.67	-	-
Switzerland	5.55	1.68	7.32	1.01	8.25
TOTAL	2.07	1.84	4.36	0.94	4.41

[1] EUROCAT Full Member registries only
[2] Termination of pregnancy illegal
[3] TOPFA known to be under-ascertained
[4] No information available on gestational age at TOPFA

* Total TOPFA with gestational age known
** Paris, Auvergne, Barcelona, Oxford and Trent registries are not included in the country perinatal mortality rates due to lack of information on first week deaths (to be revised)

An analysis of survival curves of malformed babies through pregnancy and the first year of life was conducted but left unfinished due to departure of key personnel. Initial results did however show large differences in the prevalence of survivors at one week and one year between countries.

A study of "Monitoring Inequalities in Pregnancy Outcome" funded by the Northern Ireland Research & Development Office has allowed us to analyse stillbirth and infant death (SBID) data (from stillbirth and death registrations) in Northern Ireland with regard to time trends in SBID due to congenital anomalies and socioeconomic differences according to level of deprivation of the area of residence. Northern Ireland currently practices very little termination of pregnancy for fetal anomaly compared to other parts of the United Kingdom. Results show that socioeconomic deprivation increases the risk of SBID due to all congenital anomalies combined and neural tube defects specifically, and that in the period 1991 to 2001 there has been a strong downward trend in SBID due to cardiac anomalies, probably linked to improvements in surgical services. There has been no downward trend in SBID due to neural tube defects.

A6 To provide an information and resource centre and ready collaborative research network to address the causes and prevention of congenital anomalies and the treatment, care and outcome of affected children

A6.1 Organisation of European Workshop on Methodological Approaches to the Assessment of the Impact of Environmental Pollution on the Risk of Congenital Anomalies

A successful meeting was held in March 2007, with 35 participants representing congenital anomaly registers, child health, rare diseases, environmental epidemiologists, spatial statisiticians, toxicologists and environmental exposure experts, WHO Geneva and WHO Euro offices. See Appendix 12 for programme. The proceedings can be found on www.eurocat.ulster.ac.uk/announcements.html. Outcomes of the meeting include a) a group of registries collaborating to investigate the impact of air pollution on congenital anomaly risk b) a group of registries collaborating with human biomonitoring experts to investigate the potential for a case-control biomonitoring network c) a session being organized by the European Teratology Society for September 2008 on biomarkers as a response to the Budapest meeting.

A6.2 Organisation of 8th and 9th European Symposiums on the Prevention of Congenital Anomalies (for Objectives 3, 4, 5 and 6)

The 8th European Symposium on the Prevention of Congenital Anomalies was held in Poznan, Poland in 2005, and the 9th European Symposium on the Prevention of Congenital Anomalies was held in Naples, Italy in 2007 (Appendix 11).

A6.3 Collaboration with international Centre for Birth Defects (ICBD) on WHO World Craniofacial Anomalies Registry and World Study of Risk Factors for Gastroschisis

EUROCAT has contributed three years of data (2001-2003) to the WHO Craniofacial Anomalies database, co-ordinated by the International Centre for Birth Defects in Rome (ICBD), mainly regarding prevalence of cleft lip and cleft palate. Data are available on the WHO Genomic Resource Centre website (www.who.int/genomics/anomalies/idcfa/en/). Most of the data shown are also available on the EUROCAT website.

Registers from around the world, including EUROCAT, contributed to the world study of risk factors for gastroschisis. This material was analysed at ICBD, but nothing very new was found. Instead, ICBD concentrated on an analysis of multiply malformed infants with gastroschisis, to which 10 EUROCAT registers contributed:

> 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.

A6.4 Central Registry Administrative and Database Support for Research and Provision of Anonymised Data Extracts on Request

a) A project was undertaken with part funding by NEPHIRD on the epidemiology of Cornelia de Lange syndrome in Europe. This is a rare syndrome with a prevalence of 1.2 per 100,000 births, and is the first of a list of syndromes to be analysed. The study has been published:

> Barisic I, tokic V, Loane M Bianchi F, Calzolari E, Garne E, Wellesley D, Dolk H and a EUROCAT working Group (in press), "Descriptive Epidemiology of Cornelia de Lange Syndrome in Europe", *American Journal of Medical Genetics.*

b) A collaborative project was undertaken with SCPE (Surveillance of Cerebral palsy in Europe) on the association between cerebral palsy and congenital anomalies. The proportion of cerebral palsy cases with cerebral and non-cerebral anomalies in the SCPE database was compared to EUROCAT prevalence figures. A relatively high rate of anomalies was found among cases of cerebral palsy, especially brain anomalies but also some non-brain anomalies such as oral clefts. The rate was particularly high in children with cerebral palsy born at term, and in cases of non-spastic cerebral palsy. This project has been published.

> Garne E, Dolk H, Krageloh-Mann et al (in press), "Cerebral Palsy and Congenital Malformations", *European Journal of Paediatric Neurology*.

A follow-up to this project was funded by the Fondation Motrice in France, to directly link data from cerebral palsy and congenital anomaly registers existing in the same areas of Europe. Three pairs of registers are taking part (in UK, Denmark and France). The idea of linkage was to assess and improve the data quality on congenital anomalies in cerebral palsy registers. The study is ongoing.

c) Central Registry provided data extracts on orofacial clefts, which led to two publications:

> 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.
>
> Calzolari E, Bianchi F, Rubini M, Ritvanen A, Neville A and a EUROCAT Working Group (2004), "Epidemiology of Cleft Palate in Europe: Implications for Genetic Research Strategy", *The Cleft Palate-Craniofacial Journal*, Vol 41, No 3, pp 244-249.

d) A study Arthrogyrposis Multiplex Congenita (AMC) has been initiated by EUROCAT Norway using the EUROCAT database, funded by Norwegian Research Council under the NeuroNor program to be completed in Spring 2008. Arthrogryposis multiplex congenita (AMC) is a term that encompasses a group of rare but heterogenous disorders in children, where 2 or more joint contractures are present in multiple body areas (Bevan et al. Arthrogryposis Multiplex Congenita: An Orthopaedic Perspective. J Pediatr Orth 2007; 594-600.), either isolated or related to abnormalities in other organs. There are many maternal as well as fetal disorders that

can result in this phenotype, maternal neuromuscular disease (myasthenia gravis) being one of them, as we have previously discussed. (Hoff JM, Daltveit AK, Gilhus NE. Arthrogryposis multiplex congenita – a rare fetal condition caused by maternal myasthenia gravis. Acta Neurol Scand Suppl 2006; 183: 26-27. The aim of the study is to look at the prevalence of AMC in Europe, as well as study different subgroups with respect to maternal age, disease,disorders in siblings etc. Dr Jana Midelfart Hoff, Dept of Neurology, Haukeland Universityhospital, Bergen, Norway is the project leader, closely co-operating with professor Nils Erik Gilhus, University of Bergen. Ass Professor Anne Kjersti Daltveit, Medical Birth Registry of Norway, Bergen and EUROCAT.

800 cases were identified in EUROCAT through the ICD-10 codes Q 68.8 (multiple musculoskeletal deformities, not coded elsewhere) and Q 74.3 (AMC) as well as 754.89 (ICD-9). Of these 800 cases, 541 (67,6%) had the specific code for AMC. These 541 cases were divided into four subgroups:

1. AMC-1 (with affection of limbs only) = 241 cases (30,1%)
2. AMC-2 (additional affection of other organs)= 167 cases (20.9%)
3. AMC-3 (CNS affection)= 108 (13,5%)
4. Trisomy (AMC linked to occurrence of trisomy)= 25 cases (3,1%)

In the AMC-1 group, 13 (5,4%) siblings were born with a congenital malformation. The corresponding numbers for the other subgroups were 11 (6,6%) and 8 (7,4%). There were no siblings with congenital malformations in the trisomy group.

e) A new study on paternal age related risk of Down Syndrome has been initiated in England using the EUROCAT database, but is still ongoing, encountering particular difficulties due to the lack of routinely available information on the father. Data from British EUROCAT registries has also been used to compare maternal age specific risks of Recurrence of Trisomy 21.

A7 Organisation of Annual Registry Leaders' Meeting (to support all above tasks)

The Annual Registry Leaders' Meeting were held in Bergen, Norway in 2004, Poznan, Poland in 2005, Graz, Austria in 2006 and in Naples, Italy in 2007 (see Appendix 4).

A8 Rare Diseases Task Force and Other DG Sanco Related Activities

The project leader of EUROCAT has served as deputy leader of the Rare Diseases Task Force, is on the editorial board of Orphanews, and was on the organizing committee of the European Rare Diseases Conference in Luxembourg (2005) and contributed a presentation "Strategies for Prevention". EUROCAT is represented in the RDTF Working Group on Coding and Classification working with WHO towards a revision of ICD11 suitable for rare diseases.

B Organisation of EUROCAT: Partner Roles

B1 Central Registry

General leadership, co-ordination and central database management. It is administratively based at University of Ulster, but scientific and medical expertise also provided by other Institutions. Most staff are part-time (see Budget for number of hours spent on EUROCAT).

Prof Helen Dolk:
EUROCAT Project Leader, University of Ulster (sabbatical from September 2005 to March 2006)
Prof Hugh McKenna:
Head of School, University of Ulster (left in June 2004)
Dr Carol Curran:
Head of School, University of Ulster (started in July 2004)
Maria Loane:
Database Manager and Research Officer, University of Ulster
Elaine Hand:
Statistician, University of Ulster (left in July 2005)
Ian Bradbury:
Statistician, University of Ulster (left in July 2006)
Ruth Greenlees:
Database and Research Assistant, University of Ulster (started in May 2007)
Barbara Norton:
Administrator, University of Ulster
Barbra Webber:
Administrator, University of Ulster
Suzhuang Hong:
PhD Student, University of Ulster
Dr Araceli Busby:
Epidemiologist, London School of Hygiene & Tropical Medicine (left in August 2005)
Sam Pattenden:
Statistician, London School of Hygiene and Tropical Medicine
Lisa Grisolia:
Administrator, London School of Hygiene & Tropical Medicine
Dr Ester Garne:
Pediatric Epidemiologist, University of Southern Denmark and Chair of Prenatal Diagnosis Working Group and Classification & Coding Committee
Prof Lolkje de Jong van den Berg:
Pharmaco Epidemiologist, University of Groningen and Chair of Drug Exposure During Pregnancy Working Group
Marlies Guerts:
Masters Student in pharmacoepidemiology, University of Groningen (left in June 2006)
Janneke Jentinck:
Masters Student in pharmacoepidemiology, University of Groningen (started in September 2006)
Dr Alan Kelly:
Statistician, Trinity College Dublin (statistical monitoring methods)
Conor Teljeur:
Statistician, Trinity College Dublin (statistical monitoring methods)

Lenore Abramsky:
Chair of NTD and Folic Acid Working Group, Northwick Park Hospital London
Patricia Boyd:
Geneticist, leader of prenatal screening policy study, member of Prenatal Diagnosis Working Group.
Diana Wellesley:
Geneticist, member of Coding and Classification Committtee
Elisa Calzolari:
Geneticist, member of Coding and Classification Committee
Ingeborg Barisic
Geneticist, member of Coding and Classification Committee (External Invitee, Croatia)
Sylvia Wurmitzer:
Administrator for 2006 RLM, Styrian Registry

B2 Project Management Committee and Other Committees and Working Groups

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

Lenore Abramsky (UK) 2003-2006
Ingeborg Barisic (Croatia) 2003-2007
Fabrizio Bianchi (Italy) 2003-2007
Patricia Boyd (UK) 2006-2010*
Araceli Busby (Central Registry Epidemiologist)
Elisa Calzolari (Italy) 2003-2007
Catherine de Vigan (France: President of EUROCAT Association) 2003-2008*
Hermien de Walle (The Netherlands) 2005-2009*
Helen Dolk (Project Leader)*
Ester Garne (Denmark: Chair, Coding Committee and the Prenatal Diagnosis Working Group)*
Martin Haeusler (Austria) 2007-2010*
Lorentz Irgens (Norway) 2007-2010*
Anna Latos-Bielenska (Poland) 2003-2007
David Lillis (Ireland: President of EUROCAT Association) 2003-2006
Vera Nelen (Belgium) 2007-2010*
Annette Queisser-Luft (Germany) 2002-2006

* Current member of Project Management Committee

Members of the Drug Working Group

Marian Bakker (The Netherlands)
Lolkje de Jong van den Berg (Chair) (The Netherlands)
Hermien de Walle (The Netherlands)
Lorentz Irgens (Norway)
Jan Mejnartowics (Poland)
Amanda Neville (Italy)
Annette Queisser-Luft (Germany)
Elisabeth Robert (France)
Margery Morgan (UK)

Members of the Coding & Classification Committee (2006-7)

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

Members of Prenatal Diagnosis Working Group

Marie-Claude Addor (Switzerland)
Ingeborg Barisic (Croatia)
Patricia Boyd (UK)
Elisa Calzolari (Italy)
Marianne Christiansen (Denmark)
Catherine de Vigan (France)
Hermien de Walle (The Netherlands)
Carlos Dias (Portugal)
Helen Dolk (UK)
Ester Garne (Chair) (Denmark)
Miriam Gatt (Malta)
Yves Gillerot (Belgium)
Martin Haeusler (Austria)
Lorentz Irgens (Norway)
Babak Khoshnood (France)
Anna Latos-Bielenska (Poland)
Maria Loane (UK)
Carmen Mosquera-Tenreiro (Spain)
Birgitta Ollars (Sweden)
Isabel Portillo (Spain)
Annette Queisser-Luft (Germany)
Annukka Ritvanen (Finland)

Members of Folic Acid Working Group

Lenore Abramsky (UK)
Marie-Claude Addor (Switzerland)
Ingeborg Barisic (Crotia)
Andrea Berghold (Austria)
Patricia Boyd (UK)
Elisa Calzolari (Italy)
Marianne Christiansen (Denmark)
Guido Cocchi (Italy)
Anne Daltveit (Norway)
Carlos Matias Dias (Portugal)
Hermien de Walle (The Netherlands)
Helen Dolk (UK)
Ester Garne (Denmark)
Miriam Gatt (Malta)
Yves Gillerot (Belgium)
Martin Haeusler (Austria)
Anna Latos-Bielenska (Poland)
Bob McDonnell (Ireland)

Amanda Neville (Italy)
Simone Poetzsch (Germany)
Isabel Portillo (Spain)
Annukka Ritvanen (Finland)

B3 Participating Registries

In EU Countries (see Appendix 1 for addresses)

Austria, Styria	Martin Haeusler
Belgium, Hainaut-Namur	Yves Gillerot
Belgium, Antwerp	Vera Nelen
Denmark, Odense	Ester Garne
France, Auvergne	Christine Francannet
France, Central East	Elisabeth Robert / Emmanuelle Amar
France, Iles de la Reunion	Jean Luc Alessandri
France, Paris	Catherine de Vigan
France, Strasbourg	Claide Stoll / Berenice Doray
Finland	Annukka Ritvanen
Germany, Mainz	Annette Queisser-Luft
Germany, Saxony-Anhalt	Volker Steinbicker / Simone Poetzsch
Hungary	Janos Sandor
Ireland, Cork & Kerry	Mary O'Mahony
Ireland, Dublin	Bob McDonnell
Ireland, Galway	David Lillis
Ireland, South East	Beth Ann Roch
Italy, Campania	Gioacchino Scarano
Italy, Emilia Romagna	Elisa Calzolari
Italy, ISMAC (Sicily)	Sebastiano Bianca
Italy, North East	Romano Tenconi
Italy, Tuscany	Fabrizio Bianchi
Malta	Miriam Gatt
Netherlands, North	Hermien de Walle / Marian Bakker
Poland	Anna Latos-Bielenska
Portugal, South	Maria Feijoo / Carlos Matias Dias
Spain, Asturias	Carmen Mosquera-Tenreiro
Spain, Barcelona	Joaquin Salvador
Spain, Basque Country	Isabel Portillo
Spain, El Valles	Rosa Caballin
Spain, ECEMC (Madrid)	Maria-Luisa Martinez-Frias
Sweden	Birgitta Ollars
Ukraine	Wladimir Wertelecki
UK, Glasgow	David Stone
UK, Northern Region	Martin Ward-Platt
UK, NW Thames	Lenore Abramsky / Hannah Veazey
UK, Oxford	Patricia Boyd
UK, Trent	Liz Draper
UK, CARIS (Wales)	Dave Tucker
UK, Wessex	Diana Wellesley

In Non-EU Countries (see Appendix 1 for addresses)

Croatia	Ingeborg Barisic
Norway	Lorentz Irgens
Switzerland	Marie-Claude Addor
Ukraine	Wladimir Wertelecki

C Meetings, Workshops and Travel

C1 Project Committee Meetings

The EUROCAT Project Management Committee met on:

26 March 2004	London, UK
3 June 2004	Bergen, Norway
29 November 2004	London, UK
11 April 2005	London, UK
29 November 2005	Mainz, Germany
29 March 2006	Dublin, Ireland
9 June 2006	Graz, Austria
20 November 2006	London, UK
21 March 2007	Belfast, UK

C2 Registry Leaders' Meeting

The 19th EUROCAT Registry Leaders' Meeting was held in Bergen, Norway (4-5 June 2004). 31 Registry Leaders attended as well as 16 Central Registry and Local Registry staff and 2 other guests. The attendance list can be found in Appendix 10.

The 20th EUROCAT Registry Leaders' Meeting was held in Poznan, Poland (11 June 2005). 27 Registry Leaders attended as well as 22 Central Registry and Local Registry staff, 5 New Applicant Registry Leaders and their staff and 4 other guests. The attendance list can be found in Appendix 10.

Poznan, Poland was also the venue for the 8th European Symposium on the Prevention of Congenital Anomalies. This meeting took place on 10 June 2005. The programme and abstracts (which were published in the Archives of Perinatal Medicine, September 2005, ISSN 1505-0580) can be found in Appendix 11. This event was hosted by the EUROCAT Registry of Poland

The 21st EUROCAT Registry Leaders' Meeting was held in Graz, Austria (9-10 June 2006). 29 Registry Leaders attended as well as 17 Central Registry and Local Registry staff, 7 New Applicant Registry Leaders and their staff and 2 other guests. The attendance list can be found in Appendix 10.

The 22nd EUROCAT Registry Leaders' Meeting was held in Naples, Italy (8-9 May 2007). 33 Registry Leaders attended as well as 22 Central Registry and Local Registry Staff, 1 New Applicant Registry Leader and 4 other guests. The attendance list can be found in Appendix 10.

Naples, Italy was also the venue for the 9th European Symposium on the Prevention of Congenital Anomalies. This meeting took place on 7 May 2007. The programme and abstracts can be found in Appendix 11. This event was hosted by the Registro Campano Difetti Congeniti.

C3 Workshops

During the 19th Registry Leaders' Meeting the following workshops and committee meetings were held – Coding & Classification, Folic Acid & Neural Tube Defects Working Group, Prenatal Diagnosis Working Group, Drug Safety Surveillance and Ethics & Confidentiality Subgroup.

During the 20th Registry Leaders Meeting the following workshops and committee meetings were held – Coding & Classification, NTD & Folic Acid, Prenatal Diagnosis, Drugs, Genetic Services, Hospital Activity Data and Monitoring of Multiple Malformations.

Three Coding Workshops were held on 12 April 2005 in London (UK), 26 April in Dublin (Ireland) and 6-7 October 2005 in Rome (Italy).

During the 21st Registry Leaders' Meeting the following workshops and committee meetings were held – Hospital Activity Data, EDMP Clinic, Induction Session for New Registries, Drugs and Coding & Classification.

A meeting of Methodological Approaches to the Assessment of Risk of Congenital Anomaly due to Environment Pollution was held in Budapest (Hungary), 6-7 March 2007 (Appendix 12).

During the 22nd Registry Leaders' Meeting the following workshops and committee meetings were held – Foetal Alcohol Syndrome, Hospital Activity Data, Guide 1.3 Coding Issues, EDMP Clinic, Folic Acid, Coding & Classification, Drugs and Prenatal Diagnosis.

C4 Travel and Presentations

Ester Garne, Advanced Research Workshop, Prague (Czech Republic), "Drugs in Pregnancy: Consensus Conference on Teratology Information Service", 16-18 April 2004.

Helen Dolk, Seminar Invitation, University of New South Wales, Sydney (Australia), "EUROCAT: European Surveillance of Congenital Anomalies", 7 July 2004.

Helen Dolk, European Conference of Epidemiology Conference, Porto (Portugal), "Impact of Multiple Births on the Prevalence of Congenital Anomalies in Europe", 8-10 September 2004.

Helen Dolk, Maria Loane and Araceli Busby, BINOCAR Conference, Cardiff (UK), 4-5 October 2004.

Helen Dolk, NorCAS Annual Meeting, Newcastle (UK), "European Surveillance of Congenital Anomalies – EUROCAT", and "Prenatal Diagnosis in Europe", 11 November 2004.

Elisa Calzolari, EUROCAT Representative at the WHO Meeting on International Collaborative Research on Craniofacial Anomalies, Geneva (Switzerland), "The Role of the EUROCAT Network in Research and Epidemiology of Craniofacial Anomalies", 2-4 December 2004.

Helen Dolk and Araceli Busby, The Health Protection Agency, Chemical Hazards & Poisons Division International Conference, Cardiff (UK), "Fetal Exposure: The Role of Surveillance", 7-8 December 2004.

Maria Loane, Newlife Gastroschisis Meeting, London (UK), "Is Increasing Prevalence of Gastroschisis in Europe Restricted to Young Mothers Only?" 1 March 2005.

Araceli Busby, Royal College of Nursing of the UK, The 2005 International Nursing Research Conference, Belfast (UK), "Preventing Neural Tube Defects in Europe – A Missed Opportunity", 8-11 March 2005.

Martine Vrijheid, Arhena Workshop – Environmental Impact on Congenital Diseases, Kos (Greece), "EUROCAT: Surveillance of Environmental Impact", 9-11 June 2005.

Dolk H, European Rare Diseases Conference, Luxembourg, "Building Prevention Strategies for Rare Diseases: The Role of Epidemiology", 21-22 June 2005.

Vera Nelen, Network of Competent Authorities, Luxembourg, "Survey of Informed Consent for Registration of Congenital Anomalies in Europe" 5-6 July 2005.

Alan Kelly, Surveillance of Congenital Anomalies in Wales, Cardiff (UK) "EUROCAT Statistical Monitoring", 5 September 2005.

Dolk H, International Clearinghouse for Birth Defects Surveillance and Research. Scientific Meeting on Evaluation of Medications as Teratogens, Malta, "Components of Pharmacovigilance in relation to Birth Defects", 18-19 September 2005.

Babak Khoshnood, Institut de Veille Sanitarie Working Group on Public Health Indicators for Rare Diseases, Paris (France), 30 January 2006.

Maria Loane, Northern Ireland Food Advisory Committee, Belfast (UK), "Neural Tube Defects and Folic Acid", 22 February 2006.

Simone Poetzsch, Deutsch Selbsthilfe Angeborene Immundefekte e.V., Rare Diseases – Not at all that Rare: Early Diagnosis Saves Lives and Reduces Treatment Costs, Berlin (Germany), 6 April 2006.

Ingeborg Barisic, 38th European Human Genetics Conference (ESHC), Amsterdam (The Netherlands), "The Prevalence Rates of genetic and congenital Diseases in Europe", 8 May 2006.

Hermien de Walle, EURO-PERISTAT II Better Statistics for Better Health Congress, Porto (Portugal), "Prevention of Neural Tube Defects by Periconceptional Folic Acid Supplementation in Europe", 2-3 June 2006.

Catherine de Vigan, 2nd Scientific Symposium and Annual Meeting of ICBDSR, Genetics of Congential Malformations, Uppsala (Sweden), 14-16 September 2006.

Ester Garne, Surveillance of Cerebral Palsy in Europe (SCPE) Plenary Meeting, Vilnius (Lithuania), 5 October 2006.

Helen Dolk, Environmental Public Health tracking, HPA Strategy Group, Didcot (UK), 17 October 2006.

Helen Dolk, European Multi-Centre Research Studies in Childhood Disability, Barcelon (Spain), 18 October 2006

Maria Loane and Suzhuang Hong, Syndrome Study Day, Oxford (UK), 13 November 2006.

Ingeborg Barisic, Task-Force in Europe for Drug Development for the Young (TEDDY), Rome (Italy), "Lessons Learned from European Surveillance of Congenital Anomalies – EUROCAT", 16 February 2007.

Helen Dolk, WHO Workshop on Population Health and Waste Management: Scientific Data and Available Options, Rome (Italy), 29-30 March 2007.

Helen Dolk, Workshop on 7th Framework Programme and European Medicines Association Meeting with Centres on ENCePP, London (UK), 28-29 June 2007.

Maria Loane, Abstract presented at Society for Social Medicine Conference in Cork, 12-14 September 2007 (Appendix 9) "Maternal Age Specific Risk of Non-Chromosomal Anomalies"

C5 Central Registry Co-ordination Travel

Person	Destination	Date
Helen Dolk	Belfast - Luxembourg	January 2004
Helen Dolk	Belfast - Luxembourg	April 2004
Helen Dolk	Belfast - Dublin	April 2004
Helen Dolk	Belfast - Grenoble	May 2004
Ester Garne	Odense - Belfast	May 2004
Araceli Busby	London - Belfast	August 2004
Helen Dolk	Belfast – Porto	September 2004
Ester Garne	Odense - Belfast	September 2004
Araceli Busby	London – Cardiff	October 2004
Helen Dolk	Belfast – Cardiff	October 2004
Helen Dolk	Belfast - Luxembourg	October 2004
Maria Loane	Belfast – Cardiff	October 2004
Helen Dolk	Belfast – Newcastle	November 2004
Elaine Hand	Belfast – London	November 2004
Araceli Busby	London – Cardiff	December 2004
Elisa Calzolari	Bologna – Geneva	December 2004
Helen Dolk	Belfast – Cardiff	December 2004
Isabel Portillo	Bilbao - Belfast	December 2004
James Densem	London - Belfast	January 2005
Ester Garne	Odense - Belfast	January 2005
Helen Dolk	Belfast - London	February 2005
Ian Bradbury	Belfast - Dublin	March 2005
Araceli Busby	London - Belfast	March 2005
James Densem	London - Belfast	March 2005

Helen Dolk	Belfast - Leicester	March 2005
Maria Loane	Belfast - London	March 2005
Ian Bradbury	Coleraine - Belfast	April 2005
Helen Dolk	Belfast - Luxembourg	April 2005
Ester Garne	Odense - Dublin/Belfast	April 2005
Maria Loane	Belfast - London	April 2005
Maria Loane	Belfast - Dublin	April 2005
Helen Dolk	Belfast - Oxford	May 2005
Ester Garne	Odense - Copenhagen	June 2005
Araceli Busby	London - Dublin	June 2005
James Densem	London - Dublin	June 2005
Helen Dolk	Belfast - Luxembourg	June 2005
Maria Loane	Belfast - Dublin	June 2005
Diana Wellesley	London - Belfast	June 2005
Araceli Busby	London - Dublin	July 2005
Ester Garne	Odense - Belfast	August 2005
Helen Dolk	Belfast - Malta	September 2005
Maria Loane	Belfast - Dublin	September 2005
Maria Loane	Belfast - Birmingham	October 2005
Maria Loane	Belfast - Strasbourg	October 2005
Ester Garne	Odense - Belfast	November 2005
Lolkje de Jong van den Berg	Groningen – Belfast	December 2005
Marlies Guerts	Groningen – Belfast	December 2005
Ester Garne	Odense - Belfast	January 2006
Babak Khoshnood	Paris - Paris	January 2006
Helen Dolk	Belfast – London	February 2006
Maria Loane	Belfast – London	March 2006
Maria Loane	Belfast – Dublin	March 2006
Diana Wellesley	London – Dublin	March 2006
Lenore Abramsky	London – Belfast	April 2006
James Densem	London – Belfast	April 2006
Hermien de Walle	Groningen – Belfast	April 2006
Patricia Boyd	London – Belfast	May 2006
Ester Garne	Odense – Belfast	May 2006
Lolkje de Jong van den Berg	Groningen – London	September 2006
Helen Dolk	Belfast – London	September 2006
Ester Garne	Odense – Belfast	September 2006
Maria Loane	Belfast – Bristol	September 2006
Helen Dolk	Belfast – Luxembourg	October 2006
Helen Dolk	Belfast – Barcelona	October 2006
Helen Dolk	Belfast – London	November 2006
Suzhuang Hong	Belfast – Oxford	November 2006
Maria Loane	Belfast – Oxford	November 2006
Barbara Norton	Belfast – Luxembourg	November 2006
Helen Dolk	Belfast – Luxembourg	December 2006
Maria Loane	Belfast – London	December 2006
Lolkje de Jong can den Berg	Groningen – Belfast	January 2007
Hermien de Walle	Groningen – Belfast	January 2007
Sam Pattenden	London – Belfast	January 2007
Ester Garne	Odense – Belfast	February 2007
Helen Dolk	Belfast – Rome	March 2007
Lolkje de Jong van den Berg	Groningen – Belfast	April 2007
Patricia Boyd	London – Odense	June 2007

Lolkje de Jong van den Berg	Groningen – Belfast	June 2007
Helen Dolk	Belfast – Luxembourg	June 2007
Janneke Jentink	Groningen – Belfast	June 2007
Maria Loane	Belfast – Odense	June 2007
Patricia Boyd	London – Ukraine	July 2007
Patricia Boyd	London – Belfast	July 2007
Catherine de Vigan	Paris – Ukraine	July 2007
Lolkje de Jong van den Berg	Groningen – Belfast	August 2007
Ester Garne	Odense – Belfast	August 2007
Janneke Jentink	Groningen – Belfast	August 2007
Dave Tucker	Cardiff – Ferrara	August 2007
Diana Wellesley	London – Ferrara	August 2007
Patricia Boyd	London – Cork	September 2007
Hermien de Walle	Groningen – Cork	September 2007
Helen Dolk	Belfast – Cork	September 2007
Maria Loane	Belfast – Cork	September 2007
Elisa Calzolari	Ferrara – Chianciano Terme	October 2007

D Publications

*** Abstract can be found in Appendix 9**

D1 Collaborative Publications

2004

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EUROCAT (2004) "EUROCAT Special Report: A Review of Environmental Risk Factors for Congenital Anomalies", *EUROCAT Central Registry*, University of Ulster, ISBN 1-85923-187-X. [www.eurocat.ulster.ac.uk/pubdata/Envrisk.html]

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Carbonell Perez JM, Galan Gomez E, Saez Hurtado J, Rodriguez Martinez L, Cardesa Garcia JJ, Martinez-Frias ML (2004), "Duplicacion Parcial de Novo del Segmento Distal del Brazo Largo del Cromosoma 5 (q31-qter)", *An Pediatr*, Vol 60, No 1, pp 80-84.

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Dequino GV, Rodriguez-Pinilla E, Rato Barrio B, Mejias Pavon C, Fernandez Martin P, Martinez-Frias ML (2004), "Servico de Informacion Telefonica sobre Teratogenos Espanol (SITTE) y por el Servicio de Informacion Telefonica para la Embarazada (SITE): Resultado de ano 2003", *Bol ECEMC: Rev Dismor Epidemiol*, Vol 3, pp 84-90.

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