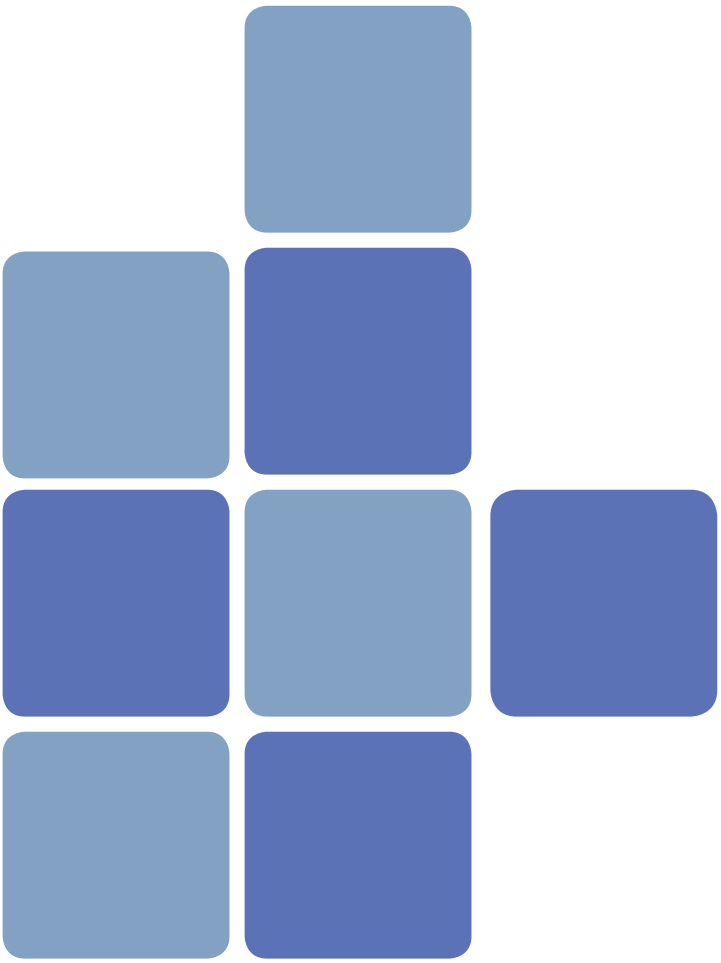
Eurocat

European Surveillance of Congenital Anomalies (EUROCAT)

Final Activity Report 2002-2003



Final report of a project supported by the Community Rare Diseases Programme 2000-2002

Health & Consumer Protection Directorate-General

Eurocat

European Surveillance of Congenital Anomalies

Project 2001/RD/10014

Of the DG Sanco Rare Diseases Programme

FINAL ACTIVITY REPORT
For period December 2001 to December 2003

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1. OBJECTIVES OF EUROCAT:

- To provide essential epidemiologic information on congenital anomalies in Europe
- To facilitate the early warning of teratogenic exposures
- To evaluate the effectiveness of primary prevention
- To assess the impact of developments in prenatal screening
- To act as an information and resource centre regarding clusters or exposures or risk factors of concern
- 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
- To act as a catalyst for the setting up of registries throughout Europe collecting comparable, standardised data

2. PROVISION OF ESSENTIAL EPIDEMIOLOGIC INFORMATION ON CONGENITAL ANOMALIES IN EUROPE

2.1 Coverage of the European population

EUROCAT now has 41 members in 20 countries (see Table 1 over), new members since 2001 including Poland, Hungary, Sweden and 4 UK regions. Of these, 36 are full members transmitting individual level data on congenital anomalies and 5 are associate members transmitting only yearly aggregate numbers. In total, more than one million births per year are surveyed, one quarter of the births in EU member states and more than half of births in seven non-EU countries.

Contacts have been established with new registries developing in Romania, Slovenia, Luxembourg, Iles de Reunion and Canary Islands, and also with existing registries in Moscow Region, Byelorussia and Ukraine.

Table 1. Coverage of the European Population by EUROCAT Registries

Country	Registry	Annual Births per Registry	Annual Births per Country	% Country Covered
EU Countries				
Austria	Styria	10,800	75,800	14.2
Belgium	Antwerp	17,700		
	Hainaut	12,800		
	Total	30,500	116,900	26.1
Denmark	Odense	5,700	65,300	8.7
Finland		56,100	56,100	100.0
France	Auvergne	13,000		
	Paris	38,500		
	Central East	93,700		
	Strasbourg	13,800		
	Total	159,000	772,500	20.6
Germany	Mainz	3,300		
	Saxony-Anhalt	18,100		
	Total	21,400	743,500	2.9
Greece		0	107,000	0.00
Ireland	Cork & Kerry	7,700		
	Dublin	22,000		
	Galway	2,700		
	Total	32,400	56,100	57.8
Italy	Campania	47,400		
	Emilia Romagna	24,800		
	North East	54,400		
	Sicily	17,000		
	Tuscany	26,600		
	Total	170,200	545,000	31.2
Luxembourg		0	5,500	0.0
Netherlands	North	20,500	200,200	10.2
Portugal	South	18,200	114,800	15.9
Spain	Asturias	6,700		
	Barcelona	12,300		
	Basque Country	17,400		
	Madrid (ECEMC)	103,400		
	Total	139,800	407,400	34.3
Sweden		91,800	91,800	100.0
UK	Glasgow	9,700		
	Merseyside	26,600		
	Northern Region	29,100		
	North Thames	45,700		
	Oxford	5,300		
	Trent	62,000		
	Wales (CARIS)	31,400		
	Wessex	26,000		
	Total	235,800	669,000	35.2
	Total	**992,200**	**4,026,900**	**24.6**
Non-EU Countries				
Bulgaria	Sofia	10,200	68,200	15.0
Croatia	Zagreb	5,700	47,500	12.0
Hungary		98,100	98,100	100.0
Malta		3,900	3,900	100.0
Norway		57,000	57,000	100.0
Poland		197,200	363,200	54.3
Switzerland	Vaud	7,300	73,600	9.9
	Total	**379,400**	**711,500**	**53.3**
	GRAND TOTAL	**1,371,600**	**4,738,400**	**28.9**

2.2 The EUROCAT website as a focus for dissemination of information

The EUROCAT Website, under Publications and Data (www.eurocat.ulster.ac.uk/pubdata), gives open access to prevalence data on 85 subgroups of congenital anomalies, with user choice regarding congenital anomaly(s) of interest, years of interest, and registries or countries of interest in order to produce a range of table formats that can be readily printed. Prevalence rates are given as livebirth prevalence rates, birth prevalence rates, and total prevalence rates (the latter including also terminations of pregnancy following prenatal diagnosis). Prevalence data were updated to the birth year 2001. A modification was also made to the website to allow the user to select "basic tables" with default selections for their congenital anomaly of choice, which would also enable ready linkage with other websites giving information on diagnosis and treatment (e.g. Orphanet). The website has now replaced printed data reports as it is considered the most efficient and accessible method of dissemination of information. The last printed report was published in October 2002 (earlier on the website):

EUROCAT Report 8: Surveillance of congenital anomalies in Europe 1980-99. University of Ulster, 2002

The central database holds a total of more than 250,000 cases of congenital anomaly since 1980 including livebirths, stillbirths and terminations of pregnancy following prenatal diagnosis. Average total prevalence rates for 85 congenital anomaly subgroups 1996-2001 are given in Table 2.

Table 2. Number of cases among livebirths, stillbirths and terminations of pregnancy following prenatal diagnosis, and prevalence per 10,000 births, of 85 congenital anomaly subgroups in 34 EUROCAT full member registries, 1996-2001.

Birth year(s) = 1996, 1997, 1998, 1999, 2000, 2001
Total births: 3883879

Centre(s) = Hainaut (B), Odense (DK), Paris (F), Tuscany (I), Dublin (IRL), Galway (IRL), N Netherlands (NL), Glasgow (UK), Emilia Romagna (I), Straszburg (F), Switzerland (CH), Zagreb (YU), Malta (M), North East Italy (I), S Portugal (P), Antwerpen (B), Basque Country (E), Asturias (SP), Saxony Anhalt (D), Mainz (D), Barcelona (SP), El Valles (SP), Styria (AU), Sofia (BG), North Thames (UK), Cork and Kerry (IRL), ISMAC (I), Campania (I), Merseyside & Cheshire (UK), CARIS (UK), Poland (PL), Oxford (UK), Wessex (UK), Trent (UK)

Anomaly	LB (n)	FD (n)	IA (n)	LB+FD+IA (n)	LB+FD+IA (rate)
Nervous system	4014	460	3972	8446	21.75
Neural Tube Defects	1290	258	2347	3895	10.03
Anencephalus and similar	191	152	1081	1424	3.67
Encephalocele	181	26	281	488	1.26
Spina Bifida	918	80	985	1983	5.11
Hydrocephaly	1011	106	894	2011	5.18
Microcephaly	618	25	82	725	1.87
Arhinencephaly/holoprosencephaly	146	30	306	482	1.24

Eye	1537	42	144	1723	4.44
Anophthalmos/microthalmos	348	17	68	433	1.11
Anophthalmos	65	10	23	98	0.25
Microthalmos	283	7	45	335	0.86
Cataract	307	1	12	320	0.82
Ear	1254	81	176	1511	3.89
Anotia/microtia	266	7	28	301	0.77
Anotia	84	2	10	96	0.25
Microtia	182	5	18	205	0.53
Congenital heart disease	20912	455	2250	23617	60.81
Anomalies of cardiac chambers and connections	1844	62	337	2243	5.78
Common arterial truncus	228	13	57	298	0.77
Transposition of great vessels (complete)	977	12	77	1066	2.74
Single ventrical	204	15	73	292	0.75
Malformations of cardiac septa	14832	265	1264	16361	42.13
Ventricular septal defect	9031	138	699	9868	25.41
Atrial septal defect	5685	85	201	5971	15.37
Atrioventricular septal defect	1056	39	354	1449	3.73
Tetralogy of Fallot	989	23	105	1117	2.88
Malformations of valves	3255	83	610	3948	10.17
Tricuspid atresia and stenosis	308	5	73	386	0.99
Ebstein's anomaly	107	6	13	126	0.32
Aortic valve atresia/stenosis	403	10	38	451	1.16
Hypoplastic left heart	561	29	352	942	2.43
Malformations of the great arteries and veins	3990	75	353	4418	11.38
Coarctation of aorta	1119	17	70	1206	3.11
Cleft lip with or without palate	3086	84	368	3538	9.11
Cleft palate	2045	53	170	2268	5.84
Digestive system	5326	202	708	6236	16.06
Tracheo-oesophagal fistula-Oesophageal atresia and stenosis	946	22	84	1052	2.71
Congenital absence, atresia and/or stenosis of the small intestine	762	27	62	851	2.19
Congenital absence, atresia and/or stenosis of the duodenal	381	20	41	442	1.14
Congenital absence, atresia and/or stenosis of other specified parts of small intestine	252	5	15	272	0.7
Ano-rectal atresia and stenosis	900	38	188	1126	2.9
Internal urogenital system-ovaries uterus and renal system	8808	302	1711	10821	27.86
Bilateral renal agenesis	221	73	345	639	1.65
Cystic kidney disease	1413	46	475	1934	4.98
Congenital hydronephrosis	3149	35	234	3418	8.8
Bladder extrophy	86	4	34	124	0.32
External genital system	4825	75	190	5090	13.11
Hypospadias	3634	14	29	3677	9.47
Indeterminate sex	215	20	38	273	0.7
Limb	12422	335	1464	14221	36.62
Limb reduction	1634	91	467	2192	5.64
Upper limb reduction	1153	66	311	1530	3.94
Complete absence of upper limb	18	6	16	40	0.1
Absence of upper arm and forearm with hand present	21	1	9	31	0.08
Absence of both forearm and hand	115	3	28	146	0.38
Absence of hand and fingers	447	29	94	570	1.47
Longitudinal reduction defect/shortening of arm	397	32	152	581	1.5

Lower limb reduction	517	35	198	750	1.93
Complete absence of lower limb	16	0	16	32	0.08
Absence of thigh and lower leg with foot present	8	2	11	21	0.05
Absence of both lower leg and foot	16	3	5	24	0.06
Absence of foot and toe	177	10	41	228	0.59
Longitudinal reduction defect/shortening of leg	203	18	103	324	0.83
Polydactyly	2837	55	288	3180	8.19
Syndactyly	1900	54	164	2118	5.45
Musculoskeletal and connective tissue	6180	385	2047	8612	22.17
Choanal atresia	244	2	12	258	0.66
Craniosynostosis	437	9	28	474	1.22
Pierre Robin Syndrome	279	2	6	287	0.74
Mandibulofacial dystosis (Treacher-Collins and Franceschetti)	28	0	3	31	0.08
Goldenhar's Syndrome	88	1	4	93	0.24
Chondodystrophies and osteodystrophies	430	31	353	814	2.1
Diaphraghmatic hernia	720	39	203	962	2.48
Omphalocele	499	80	467	1046	2.69
Gastroschisis	637	33	115	785	2.02
Prune Belly Syndrome	38	6	53	97	0.25
Chromosomal	5829	433	6219	12481	32.14
Down Syndrome	3857	139	3324	7320	18.85
Patau syndrome (trisomy 13)	169	33	394	596	1.53
Edward syndrome (trisomy 18)	334	110	958	1402	3.61
Other trisomies and partial trisomies of autosomes	281	57	479	817	2.1
Monosomies and deletions from the autosomes	444	12	143	599	1.54
Turner's syndrome	228	56	525	809	2.08
Klinefelters syndrome	156	5	169	330	0.85
Anomalies outside normal range *	2701	163	448	3312	8.53
All Cases**	68357	1954	13374	83685	215.47

LB - Live Births

FD - Fetal deaths / Still Births from 20 weeks gestation

IA - Induced Abortions following prenatal diagnosis

* Any case coded outside the range 740 to 759 of ICD 9 (International Classification of Disease, 9th edition, WHO Geneva 1977) or the Q chapter of ICD 10 (10th edition, WHO Geneva 1992)
** excluding minor anomalies according to the specifications in EUROCAT Guide 1.2.

2.3 Dissemination of data on the prevalence of cleft lip and cleft palate

In 2003, EUROCAT began to provide the WHO Craniofacial Anomalies database with data from European countries. A data extract concerning cases of cleft palate, cleft lip, and cleft lip and palate, was provided to the International Centre for Birth Defects in Rome (ICBD), and the results are available on the WHO Genomic Resource Centre website http://www.who.int/genomics/anomalies/idcfa/en/. A study of EUROCAT data on cleft palate led by Prof Elisa Calzolari is available on the EUROCAT website:

> *EUROCAT Special Report. 2003. The epidemiology of orofacial clefts in 30 European Regions.[online] www.eurocat.ulster.ac.uk/pubdata/*
>
> *Calzolari E, Bianchi F, Rubini M, Ritvanen A, Neville A and a EUROCAT Working Group. Epidemiology of Cleft Palate in Europe: Implications for Genetic Research. The Cleft Palate-Craniofacial Journal (in press).*

2.4 Development of the EUROCAT Data Management Programme

In order to facilitate data transmission to the Central Registry, the EUROCAT Data Management Programme ("EDMP") has been developed in Microsoft Access. This interfaces with the EUROCAT Central Database. New versions are downloadable from the membership area of the EUROCAT website, and a copy is provided to all new members. The EDMP allows a choice between data entry or data import, and runs a standard validation programme on data which is expanded over time to ensure progress toward higher quality data and greater data standardisation. Data can be exported in standard format for transmission to EUROCAT Central Registry. Additional developments during 2003 include the binary (present or absent) coding of EUROCAT congenital anomaly subgroups based on a range of ICD9-BPA and ICD10-BPA codes, a facility to produce standard Excel Tables identical to the tables on the website for these subgroups, and a statistical monitoring facility (see below). The principle of the EDMP is that all computing developments carried out in the Central Registry should be available to local registry members, as an element of the "added value" of European collaboration.

In order to update website prevalence tables, the EUROCAT Central Data Management Programme contains an automatic facility for aggregating data and producing website tables. New tables are first made available on the membership area of the website for checking by member registries and after confirmation by all registries are uploaded to the public access site. Yearly updating can now be done very efficiently.

2.5 Data validation and standardisation activities

The Coding and Classification Committee have been working on developing guides to the coding of limb defects and syndromes, which will be ready in 2004.

An ad-hoc committee was set up to consider revision of EUROCAT Guide 1.2: Instructions for the Registration of Congenital Anomalies. The committee has recommended changes in the common dataset collected by EUROCAT registries, to be finalized by registry leaders at the 2004 Registry Leaders Meeting.

The development of Data Quality Indicators is an important part of EUROCAT activity. Development to date includes: a new Registry Description questionnaire finalized at Lisbon in June 2002 and available on website under 'Applications for Membership'; standardized Registry Descriptions (available on the website under 'Member Registries'); validation checks in the EDMP (see above); missing data summaries (available on the membership only area of the website) and analysis of the ratio of anencephaly to spina bifida to identify underascertainment of pregnancy terminations (included in the EUROCAT report on NTD and folic acid, see below). A methodological report on capture-recapture analysis to analyse completeness of ascertainment was published:

> *EUROCAT Special Report 2003. Using capture-recapture methods to ascertain the completeness of a register: case study and methodological considerations. [online]* www.eurocat.ulster.ac.uk/pubdata/

In recent years, the issue of parent consent for registration of affected individuals has been raised in a number of European countries. A survey was carried out in 2003 of current practice. Ten registries are consent-based or about to become so. However, registries note that the requirement for consent (unless operated on an opt-out basis) is a grave logistic difficulty, with considerable resource implications, and a considerable actual or potential impact on case ascertainment. Experience is that while parents rarely refuse permission, underascertainment comes about through clinicians not asking consent or not completing the paperwork of notification. Since high ascertainment is dependent on multiple sources of notification, systems must be put in place to avoid asking parents repeatedly for their consent. In some countries, there are legal provisions for registration without consent, and the emphasis may instead be on strict data protection.

3. EARLY WARNING OF TERATOGENIC EXPOSURES AND PROVISION OF INFORMATION REGARDING CLUSTERS OR EXPOSURES OR RISK FACTORS OF CONCERN

3.1 Development of the Cluster Advisory Service

In February 2003, a meeting was held of the EUROCAT Working Group on the Management of Clusters and Environmental Exposure Incidents to discuss the development of a web-based cluster advisory service. In preparation for this meeting, the literature regarding clusters of congenital anomalies and cluster investigation protocols was reviewed, and a questionnaire about local practice was sent to EUROCAT members.

Following this meeting, the following documents and tools have been made available on the Cluster Advisory Service section of the EUROCAT website
http://www.eurocat.ulster.ac.uk/clusteradservice.html

How Unusual Is An Observed Cluster Of Anomalies? (commentary and statistical calculator)

Cluster Investigation Protocols (a summary of existing cluster investigation protocols)

Risk Perception And Risk Communication (notes and literature review on the place of risk perception and risk communication within cluster investigation)

A Review Of Environmental Risk Factors For Congenital Anomalies (link to EUROCAT Special Report reviewing the epidemiologic literature on environmental risk factors, see below)

Completed Cluster Investigations: A Database Of References (references of cluster investigations published in the scientific literature or on websites)

The Cluster Working Group meanwhile responded to a number of requests for advice about clusters from EUROCAT members and non-members.

As an example of response to environmental exposure incidents, a preliminary analysis of congenital anomalies data from Belgium in relation to the 1999 dioxin contamination incident has been performed. This will be repeated including more recent data (up to 2002 births) due to the long half-life of dioxin, and including a comparison with other registers. However, the lack of exposure data other than relating to the time period of ingestion of contaminated food, combined with the widespread and low level of contamination, will severely limit the interpretation of data.

The first edition of a literature review of environmental risk factors for congenital anomalies has been completed, jointly funded by the Department of Health (England). It is intended that this should become a regularly updated and expanded resource on environmental risk factors. The first edition is now available on the Cluster Advisory Service area of the website as:

> *EUROCAT Special Report: A Review of Environmental Causes of Congenital Anomalies. 2004 (Edition 1) [online]* www.eurocat.ulster.ac.uk/pubdata/

A study has been conducted in five British regions 1991-99 of Geographical Variation in the prevalence of congenital anomalies, and sociodemographic risk factors, funded by the Department of Health (UK), led by Dolk and Armstrong (UK). Geographical variation and clustering was looked for at the level of region, hospital catchment area, census ward (10,000 households) and enumeration district (1,000 households). Generalised geographical variation was found at the level of region and hospital catchment area, but not below this. The prevalence of non-chromosomal congenital anomalies was positively associated with deprivation of the area of residence, and the prevalence of chromosomal anomalies was negatively associated with deprivation because of the higher average maternal age in more affluent areas. Raised risks persisted near the hazardous waste landfill sites previously included in the EUROHAZCON study. A full report was submitted to the Department of Health (UK) and scientific papers are in preparation or submitted. The same dataset is now being used to look at risks associated with air pollution and drinking water contamination.

3.2 Surveillance of Hypospadias in relation to exposure to endocrine disrupting chemicals

Concern about apparent increases in the prevalence of hypospadias, a congenital male reproductive tract abnormality, in the 1960s to 1980s and the possible connection to increasing exposures to endocrine disrupting chemicals, have underlined the importance of effective surveillance of hypospadias prevalence in the population. We analysed the prevalence of hypospadias from 1980 to 1999 in 20 regions of Europe with EUROCAT population-based congenital anomaly registers, thirteen of which implemented a guideline to exclude glanular hypospadias. Our results do not suggest a continuation of rising trends of hypospadias prevalence in Europe. However, a survey of the registers and a special validation study conducted for the years 1994-96 in nine EUROCAT registers identified a clear need for a change in the guidelines for registration of hypospadias. We recommend that all hypospadias should be included in surveillance, but that information from surgeons must be obtained to verify location of the meatus, and whether surgery was performed, in order to interpret

trends. Investing resources in repeated special surveys may be more cost-effective than continuous population surveillance. We conclude that it is doubtful whether we have had the systems in place worldwide for the effective surveillance of hypospadias in relation to exposure to potential endocrine disrupting chemicals. Work in 2004 will proceed to put a more effective prospective surveillance system in place in Europe.

Two publications in 2003 relate to this study:

EUROCAT Special Report 2003. An assessment and analysis of surveillance data on hypospadias in Europe. www.eurocat.ulster.ac.uk/pdf/hypospadias.pdf

Dolk H, Vrijheid M, Scott JES, Addor M-C, Botting B, de Vigan C, de Walle H, Garne E, Loane M, Pierini A, Garcia-Minaur S, Physick N, Tenconi R, Wiesel A, Calzolari E, Stone D. 2003. Towards the Effective Surveillance of Hypospadias. Environ Health Perspect: doi:10.1289/ehp.6398. [Online 18 November 2003] http://ehpnet1.niehs.nih.gov/docs/2003/6398/abstract.html

3.3 Surveillance of maternal drug exposures

A Working Group on Drug Surveillance chaired by Prof Martina Cornel (Netherlands) and then by Prof Lolkje van den Berg (Netherlands) and co-chaired by Dr Elisabeth Robert (France) and Dr Maurizio Clementi (Italy, President of ENTIS) have advised on the introduction of international ATC coding for drug exposures which will be implemented from 2005. A summary of information in the EUROCAT database relating to drug exposures has also been made, including methods of data collection and numbers of cases by drug category, which will be published in 2004. Twenty registries collect data on drug exposure in the first trimester of pregnancy, with the main source of information being obstetric records. For the 5 years from 1996-2000, nearly two thousand cases were recorded in the EUROCAT database of at least one drug exposure by 14 registries using the 18-category EUROCAT drug code, 12% of all cases in these registers. Despite the difficulties of collecting complete information on drugs, the database represents a considerable resource for further investigations. A pilot project examining evidence for an association between hypospadias and loratidine exposure is underway. After the introduction of ATC coding, EUROCAT will also contribute data to the ICBDMS Madre project, which looks for associations between specific drugs and specific malformations in registry data.

3.4 Statistical monitoring over time

The aim of general statistical monitoring over time is to identify increases or clusters that may be due to changing exposure to teratogens in the environment. In practice, statistical monitoring also operates as a data quality monitoring system.

Statistical monitoring based on the Scan method and chi square test for trend has been integrated into the EUROCAT Data Management Programme and a workshop was held on the new software at the Registry Leaders Meeting in Heidelberg June 2003. Statistical analysis of data to 1999 was discussed at the meeting and subsequently updated to 2000 and disseminated. The results of cluster investigations will be discussed at the Registry Leaders Meeting in 2004. At present, statistical monitoring is applied to the standard EUROCAT congenital anomaly subgroups. Work has been underway also to routinely identify multiply malformed cases in the EUROCAT database for additional monitoring. Due to the volume of data in the EUROCAT database, a computing algorithm has been instituted to identify possible cases of multiple malformations for manual review by medical geneticists. Statistical analysis will be done in collaboration with the International Clearinghouse for Birth Defects Monitoring Systems, who have developed a methodology for multiple malformation monitoring.

3.5 Other risk factors

The risks of congenital anomaly related to assisted conception and the rise in multiple births resulting from assisted conception is of high interest at present. A session of the European Symposium on Prevention of Congenital Anomalies in Heidelberg June 2003 was devoted to this issue, followed by a meeting during the Registry Leaders Meeting to plan the analysis of available EUROCAT data. Following a presentation to the Symposium by Prof Peter Pharoah, on the evidence that the risk of congenital anomalies and cerebral palsy is increased by in utero death of a co-twin, it has been agreed to provide EUROCAT data to investigate this hypothesis further. Data on rare syndromes following assisted conception will be analysed by a group led by Dr Annette Queisser Luft. Discussions have been held with SCPE (Surveillance of Cerebral Palsy in Europe) and PERISTAT to develop a joint assessment of the impact of the rise in multiple births on perinatal health in Europe.

Observations worldwide of a rise in the prevalence of gastroschisis, a high relative risk among young mothers, and an association with socioeconomic deprivation, have also led to increased research activity into this anomaly. EUROCAT data have been provided for a case-control study of gastroschisis using available registry data concerning risk factors led by ICBD (in collaboration with

Dr Fabrizio Bianchi, Italy). Further analysis of maternal age-specific trends in prevalence in EUROCAT data is being undertaken in Central Registry.

4. EVALUATION OF THE EFFECTIVENESS OF PRIMARY PREVENTION AND ASSESSMENT OF THE IMPACT OF DEVELOPMENTS IN PRENATAL SCREENING

4.1 Prevention of neural tube defects by folic acid supplementation

Approximately 4000 pregnancies every year in Europe result in a livebirth, stillbirth or termination of pregnancy of a baby/fetus affected by Neural Tube Defects (NTD), mainly anencephaly and spina bifida. Periconceptional folic acid supplementation has been shown over a decade ago to be an effective method of preventing potentially two thirds of cases. A study was conducted by the EUROCAT Working Group on NTD and Folic Acid, led by Lenore Abramsky (UK), to review progress in the last decade in European countries in terms of developing and implementing public health policies to raise periconceptional folate status, and analyse data on the prevalence of neural tube defects from 36 congenital anomaly registries in 17 countries to determine the extent to which neural tube defects have been prevented up to the year 2000. Representatives from seventeen countries participating in EUROCAT provided information about policy, health education campaigns and surveys of folic acid supplement uptake in their country. At the beginning of 2002, an official governmental recommendation that women planning a pregnancy should take 0.4 mg of folic acid supplementation daily was in operation in nine of the seventeen countries. The earliest countries to introduce an official supplementation policy were the UK, Ireland and Netherlands in 1992-3 and the latest were Spain and France in 2000-2001. In the remaining eight participating countries, no official government recommendation about supplementation was in place, however, professional bodies within a subset had in fact recommended supplementation, and two countries had an official policy of encouraging women to increase their dietary intake of folate periconceptionally. Only seven countries had official health education initiatives: UK, Ireland, France, Poland, Netherlands, Norway and Denmark. Despite all measures taken to date, the majority of women in all countries surveyed are not taking folic acid supplements periconceptionally. The situation regarding low uptake of supplementation advice is reflected in the lack of a clear decline in the prevalence of neural tube defects across Europe. Nevertheless, there was some evidence that in countries with a supplementation policy, a small decline in prevalence had taken place. In the UK and Ireland, it was difficult to distinguish any effect of supplementation policy against the background of a strongly declining NTD prevalence throughout the 1980s, predating folic acid advice.

We conclude that the potential for preventing NTDs by periconceptional folic acid supplementation is still far from being fulfilled in Europe. Only a public health policy including folic acid fortification of

staple foods is likely to avoid widening socio-economic inequalities in NTD prevalence and result in large scale prevention of NTDs.

In view of the findings that there has been a lack of substantial decline in neural tube defect prevalence in Europe in the last decade and even countries which have pursued supplementation policies relatively actively have found a limited preventive impact, EUROCAT has issued the following recommendations:

i) Countries should review their policies regarding folic acid fortification and supplementation, taking account of WHO Europe recommendations.

ii) 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.

iii) 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.

iv) Health effects of supplementation and fortification should be monitored, and policies should be reviewed periodically in light of the findings.

v) The European population should be covered by high quality congenital malformation registers which collect information about affected pregnancies (livebirths, stillbirths and terminations 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.

A full report of this work is available on the EUROCAT website:

EUROCAT Working Group. EUROCAT Special Report: Prevention of Neural Tube Defects by Periconceptional Folic Acid Supplementation in Europe. May 2003. [online] *http://www.eurocat.ulster.ac.uk/pubdata/folic%20acid.html*

A session of the European Symposium on Prevention of Congenital Anomalies in Heidelberg June 2003 was devoted to presentations by EUROCAT registries of studies on periconceptional folic acid supplement uptake in their areas.

EUROCAT participated at the WHO Euro meeting "Folic Acid: from Research to Public Health Practice" Rome, Italy 2 November 2002 and is contributing to the Report of that meeting due to be published in 2004.

The EUROCAT Special Report and website were referenced in a News Roundup item in the British Medical Journal "Inertia on folic acid has caused thousands of unnecessary deaths" BMJ 2003; 326: 1054-6.

4.2 Prenatal diagnosis of congenital anomalies

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. Information on the number of terminations of pregnancy following prenatal diagnosis is available on the EUROCAT website, and can also be seen in Table 2.

Two studies were conducted in 2003 using the EUROCAT database with respect to prenatal diagnosis, led by Dr Ester Garne (Denmark), with papers now submitted for publication. The first of these analysed data from 17 registries 1995-99, to establish the frequency at a population level of prenatal diagnosis of severe congenital malformations that can be detected by ultrasound investigation. The analysis concerned all livebirths, fetal deaths and terminations of pregnancy diagnosed with one or more of the following malformations: anencephalus, encephalocele, spina bifida, hydrocephalus, transposition of great arteries, hypoplastic left heart, limb reduction defect, bilateral renal agenesis, diaphragmatic hernia, omphalocele and gastroschisis. The 17 registries reported 4366 cases diagnosed with the 11 severe malformations and of these 2300 were livebirths (53%) and 1863 terminations of pregnancy (43%). Overall prenatal detection rate was 64% (range 25-88% between regions). The proportion of terminations of pregnancy varied from 15%-59% of all cases. Gestational age at discovery for prenatally diagnosed cases was less than 24 weeks for 68 % (range 36-88%). There was a significant relation between high prenatal detection rate and early diagnosis. For the individual malformations prenatal detection rate was highest for anencephalus (94%) and lowest for transposition of great arteries (27%). Termination of pregnancy was performed in more than half of the prenatal diagnosed cases except for transposition of great arteries, diaphragmatic hernia and gastroschisis where 30-40% of the pregnancies with a prenatal diagnosis

were terminated. We concluded that European countries currently vary widely in the provision and uptake of prenatal screening and its quality, as well as the "culture" in terms of decision to carry on the pregnancy. This inevitably contributes to variation between countries in perinatal and infant mortality, in childhood prevalence and in cost to health services of congenital anomalies.

The second study analysed data in the EUROCAT database from fourteen registries from 1995-99 to investigate outcomes of ultrasound investigations (US) and invasive diagnostic procedures in cases of congenital malformations (CM), and to compare the use of invasive prenatal test techniques (amniocentesis (AC) versus chorionic villus sampling (CVS)) among European populations. 25,400 cases of CM recorded by 14 EUROCAT registries covering a total population of 1,013,352 births 1995-99. US were performed in 91% of cases, and positively detected CM in 35% of cases. AC was performed in 24% of the cases and CVS procedures in 3% of cases. Thirty-eight percent of invasive tests performed gave positive results. Fifty-two percent of cases with maternal age ≥ 35 years had an invasive test performed compared to 20% of cases with younger mothers. Considerable variation was found between registries in the uptake rate of invasive tests in cases with older maternal age and on the use of invasive tests, with only four regions employing CVS techniques in at least a third of cases with invasive tests performed. For chromosomal anomalies US gave positive results in 46% of cases with maternal age <35 years with US performed and in 36% of cases with maternal age ≥35 years with US performed. The study highlighted the counselling implications of the large number of children being born with congenital anomalies after negative prenatal investigations, the large regional variation in the uptake and type of invasive tests performed, the relatively infrequent use of CVS compared to amniocentesis, and the now extremely important role of ultrasound in diagnosing both chromosomal and non-chromosomal anomalies.

A presentation of these and other data on prenatal diagnosis was made to the EURORDIS conference in Paris, October 2003, by Prof Martina Cornel (Netherlands).

Dr Ester Garne (Denmark) is leading a study in a small number of EUROCAT registries of the impact of prenatal diagnosis of Transposition of Great Arteries on postnatal outcome. Extra data collection is nearly finished for this study.

A presentation of EUROCAT data on the combined impact of maternal age and prenatal diagnosis and termination of pregnancy on the livebirth prevalence of Down Syndrome was made by Prof Helen Dolk to the INSEE/INSERM/EAPS meeting on Health Implications of Late Parenthood in Paris, May 2003. Down Syndrome constitutes approximately 8% of cases of registered congenital anomaly in Europe, with over 7,000 affected pregnancies in the 15 current member states of the European Union

each year. A descriptive analysis of data from 24 EUROCAT registries, covering 8.3 million births 1980-99 was presented. Cases include livebirths, stillbirths and terminations of pregnancy following prenatal diagnosis. Since 1980, the proportion of births to mothers of 35 years of age and over has risen quite dramatically. By 1995-99, the proportion of "older"mothers varied between regions from 10% to 25%, and the total prevalence (including terminations of pregnancy) of Down Syndrome varied from 1 to 3 per 1,000 births. Some European regions have shown a more than twofold increase in total prevalence of Down Syndrome since 1980. The proportion of cases of Down Syndrome which were prenatally diagnosed followed by termination of pregnancy in 1995-99 varied from 0% in the three regions of Ireland and Malta where termination of pregnancy is illegal, to less than 50% in 14 further regions, to 77% in Paris. The extent to which terminations of pregnancy were concentrated among older mothers varied between regions. The livebirth prevalence has since 1980 increasingly diverged from the rising total prevalence, in some areas remaining approximately stable, in others decreasing over time. In conclusion, the rise in average maternal age in Europe has brought with it an increase in the number of pregnancies affected by Down Syndrome. The widespread practice of prenatal screening and termination of pregnancy has in most of the regions covered by EUROCAT counteracted the effect of maternal age in its effect on livebirth prevalence. The joint influences of maternal age and prenatal screening have led to significant and changing geographic inequalities in Down Syndrome livebirth prevalence in Europe. These data will be published in Proceedings of the meeting in a special issue of Rev Epidemiol Sante Publique.

Following a presentation by Dr Joan Morris (UK) to the European Symposium on Prevention of Congenital Anomalies in Heidelberg June 2003, EUROCAT has supplied data with which to independently confirm (or refute) the findings of the England and Wales Down Syndrome register that the maternal age specific rates of Down Syndrome for women of 44 years and over level off, rather than continuing to increase steeply with age as previously assumed. This has implications for prenatal screening among these mothers. The results will be available in 2004.

Provision of data by EUROCAT to the EURONATAL group has led to a publication on the impact of termination of pregnancy for congenital anomaly on perinatal mortality rates in Europe.

Van der Pal-de Bouin KM, Graafmans W, Biermans MC, Richardus JH, Zijlstra AG, Reefhuis J, Mackenbach JP, Verloove-Vanhorick SP (2002) The influence of prenatal screening and terminations of pregnancy on perinatal mortality rates. Prenatal Diagn, 22, 966-972

APPENDIX 1

LIST OF PARTNERS WITH CONTACT DETAILS

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APPENDIX 2

TECHNICAL DESCRIPTION OF WORK PROGRAMME

Appendix 2 Technical Description of Workprogramme

A complementary work programme 2000/RD/10029 has been funded from November 2000 to April 2002 (i.e. ending in month 5 of the current programme). New tasks that will be started in the first five months of the new contract (Dec 2001 to Nov 2003) are shown with ***. All other tasks will be carried out in months 6 to 24.
Two meetings of all partners will be held in month 6 (May 2002, Portugal) and month 18 (May 2003, Germany). The second meeting will include the 7th European Symposium on the Prevention of Congenital Anomalies (open to non-partners) and a Statistical Workshop.

1. ***Establishment of EUROCAT Information and Advisory Service for the management of Clusters of congenital anomalies and of Environmental exposure incidents (IASCE) (months 1-24).
1.1 ***Phase 1: development phase, (months 1-12): Establishment of 1) library of existing cluster investigation protocols and literature, including risk communication, from Europe and US; 2) "roadmap" to the library for use by local health authorities in designing local cluster investigation protocols; 3) standard database of cluster investigations (origin, methods and results) in Europe; 4) database of experts in Europe able to assist in specialist fields in cluster investigations. 5) internet access to library/databases at EUROCAT website.
1.2 Phase 2: implementation of service (months 13-24): Creation of a EUROCAT IASCE Team to provide advice to local health authorities; updating of databases and website maintenance;
1.3. ***Analysis of impact of Belgian Dioxin Contamination Incident (1999) and implications for response to exposure incidents, and other dioxin exposure concerns: (report m18).

2. Strengthening of EUROCAT capability for early warning of new teratogenic exposures (m6-24)
2.1 Revision of guidelines for statistical monitoring methods and existing software, report month 24.
2.2 Methodological workshop for EUROCAT members (month 18): improving statistical methods for monitoring: theory and practice
2.3 Design and production of quarterly Monitoring Bulletin (months 6-24).
2.4. ***Revision of EUROCAT Data Management Programme for local registries and its interface to the Central Database to incorporate denominator data, encryption and other features (subcontracted).
2.4 Central level data validation activities and statistical monitoring incorporating birth year 2001 (months 6-24). Validation of EUROCAT data on maternal drug use.
2.5 ***Development and implementation of monitoring of multiple malformations (months 1-24).

3. Improvement of EUROCAT website as a focus for essential epidemiological information on congenital anomalies (m6-24).
3.1. Production of standard epidemiological information and commentary on (initially) 34 congenital anomaly subgroups for website, covering period 1980-2001 (m6-24)
3.2. Development of interactive interface for user-specified tables of epidemiologic information (m6-24).

4. Publication of EUROCAT Special Reports (m6-24) on issues of importance and current interest related to selected anomalies and exposures, including
4.1 Surveillance of neural tube defects in relation to primary prevention (report m 12)
4.2 Down syndrome : trends in prevalence (report m 24).

5. Liaison activities (m 6-24): 4.1. Working with registries newly joining EUROCAT, especially in Central and Eastern Europe 4.2. Collaboration with WHO, International Clearinghouse of Birth Defect Monitoring Systems, European Network of Teratology Information Services, European Network of Cancer Registries, Surveillance of Cerebral Palsy in Europe, in areas of mutual interest. 4.3. Establishment of contact with parent organisations to increase the capacity of EUROCAT to meet information needs

APPENDIX 3

CURRENT EUROCAT ACTIVITIES AND COMMITTEE MEMBERSHIP

Appendix 3 EUROCAT Committee & Working Group Membership

EUROCAT Project Management Committee:

Ingeborg Barisic (EUROCAT SC 2003-2007)
Fabrizio Bianchi (EUROCAT SC 1998-2003, President of EUROCAT Association 2002-2003)
Araceli Busby
Elisa Calzolari (EUROCAT SC 2003-2007)
Helen Dolk
Ester Garne (EUROCAT SC 2001-2004)
Blanca Gener (EUROCAT SC 2001-2003)
Janine Goujard (Working Group leader, until June 2003)
Alan Kelly (Working Group leader, until June 2003)
Anna Latos Bielenska (EUROCAT SC 2003-2007)
David Lilllis (EUROCAT SC 2001-2004)
Annette Queisser Luft (EUROCAT SC 2002-2006)
Annukka Ritvanen (EUROCAT SC 1999-June 2003)
Catherine de Vigan (EUROCAT SC 2003-2007)

The **CENTRAL REGISTRY**:

Management and updating of central database
Production and dissemination of standard prevalence data
Development and maintenance of website
Provision of data extracts on request
Development and maintenance of EUROCAT Data Management Programme
Production of Data Quality Indicators
Revision of common dataset (development of Guide 1.3).
Statistical monitoring
Co-ordination of committees and working groups
Budgetary management
Organisation of meetings
Research projects using EUROCAT database

At University of Ulster: Helen Dolk (Project Leader), Maria Loane (Database Manager and Research Associate), Barbara Norton (Administrator), Nicky Armstrong (Research Fellow until May 2003), Michael Rosato (Database manager/computer programmer to April 2002).
At London School of Hygiene and Tropical Medicine: Araceli Busby (Epidemiologist), Lisa Grisolia (Secretary).
At University of Southern Denmark: Ester Garne (Paediatric epidemiologist)
At Trinity College Dublin: Alan Kelly and Conor Teljeur (statisticians)
At VU Medical Centre Amsterdam: Martina Cornel (medical geneticist)
At University of Groningen: Lolkje van den Berg (pharmaco-epidemiologist) and Wilhelmijn Meijer (research associate)
Subcontractors: Biomedical Computing Ltd (James Densem), SOS statistical Services (Evelyn McCrum)

COMMITTEES AND WORKING GROUPS

Committee on Classification and Coding of malformations (Chair: Dr Ester Garne, co-chair Dr Ingeborg Barisic)

- improves standardised coding and classification of malformations in EUROCAT, in particular create a coding guide to syndromes, cardiac anomalies and limb anomalies
- reviews the list of standard EUROCAT anomaly subgroups for dissemination of prevalence data
- develops and implements the monitoring of multiple malformations, in collaboration with the International Clearinghouse
- disseminates information on the prevalence of multiple malformations and syndromes

Members: Marie-Claude Addor, Switzerland
Ingeborg Barisic, Croatia*
Elisa Calzolari, Italy*
Ester Garne, Denmark*
Pierpaolo Mastriacovo, Italy (ICBD liaison)
Annette Queisser-Luft, Germany
Annukka Ritvanen, Finland
Claude Stoll, France*
Romano Tenconi, Italy*
David Tucker, UK
Diana Wellesley, England*

(* multiple malformations sub-committee)

Committee on Ethics (Chair: Dr Annukka Ritvanen, co-chair: Dr Araceli Busby)

- Surveys practice in EUROCAT registries regarding confidentiality, consent, and steering committees.

Members: Araceli Busby, UK
Hermien De Walle, Netherlands
Isolina Galan, Spain
Miriam Gatt, Malta
Bob McDonnell, Ireland
Vera Nelen, Belgium
Annukka Ritvanen, Finland
David Stone, UK

Committee for Registry Liaison (Chair: Dr Fabrizio Bianchi, co-chair Dr David Lillis)

- Liaises with new and applicant registries, and with registries undergoing organisational changes

Working Group on Clusters and Environmental Exposures (Chair: Prof Helen Dolk, co-chair Dr Alan Kelly)

- Proposes and tests statistical methods to be used for statistical monitoring by EUROCAT registries
- Develops proposals for incorporation of statistical methods into EDMP
- Develops web-based EUROCAT Cluster Advisory Service to allow registries and local health authorities to readily access current European and American knowledge on the management of clusters of congenital anomalies
- Co-ordinates response to clusters detected within and outside EUROCAT member regions

Members:

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Fabrizio Bianchi, Italy
Araceli Busby, UK
Helen Dolk, UK
Marion Drijver, N'lands (external expert)
Judith Greenacre , UK
Alan Kelly, Ireland
Rolv Lie, Norway
Marco Marchi, Italy
Marco Martuzzi, Italy
Vera Nelen, Belgium
Elisabeth Robert, France
Aldo Rosano, Italy
Janos Sandor, Hungary
Paul Wilkinson, UK

Working Group on Prenatal Diagnosis (Chair: Dr Ester Garne, co-chair Dr Catherine de Vigan)

- Advises on and co-ordinates the analysis and dissemination of information on prenatal screening and diagnosis in relation to sensitivity of screening, frequency of termination of pregnancy, inequalities in screening,
- Proposes measures to improve the quality and standardisation of data on prenatal screening and diagnosis

Members:

Lenore Abramsky, UK
Marie-Claude Addor, Switzerland
Marian Bakker, Netherlands
Ingeborg Barisic, Croatia
Fabrizio Bianchi, Italy
Patricia Boyd, UK
Paula Braz, Portugal
Anne Daltveit, Norway
Catherine de Vigan, France
Helen Dolk, UK
Maria Feijoo, Portugal
Christine Francannet, France
Ester Garne, Denmark
Blanca Gener, Spain
Yves Gillerot, Belgium
Martin Haeusler, Austria
Christine Herman-Roy, France
Anna Latos-Bielenska, Poland
David Lillis, Ireland
Maria Loane, UK
Anne Materna-Kiryluk, Poland
Jan Mejnartowicz, Poland
Anna Pierini, Italy
Francesca Rivieria, Italy
Christine Roesch, Germany
Janos Sandor, Hungary
Maria Soares, Portugal
Volker Steinbicker, Germany
Claude Stoll, France
Romano Tenconi, Italy
Radka Tincheva, Bulgaria
Diana Wellesley, UK

Working Group on Periconceptional Folic Acid Supplementation and the Prevention of NTD and other congenital anomalies (Chair: Dr Lenore Abramsky, co-chair Dr Araceli Busby/Dr Nicola Armstrong)

- Conducts annual survey of policy and practice with regard to folic acid supplementation and fortification in Europe
- Conducts annual updating of surveillance of neural tube defect prevalence in relation to folic acid policy and practice

Members:

Lenore Abramsky, UK
Marie-Claude Addor, Switzerland
Nicola Armstrong, UK
Ingeborg Barisic, Croatia
Andrea Berghold, Austria
Patricia Boyd, UK
Paula Braz, Portugal
Elisa Calzolari, Italy
Marianne Christiansen
Guide Cocchi, Italy
Anne Kjersti Daltveit, Norway
Hermien de Walle, Netherlands
Miriam Gatt, Malta
Romana Gjergja, Croatia
Yves Gillerot, Belgium
Janine Goujard, France
Martin Haeusler, Austria
Anna Latos-Bielenska, Poland
Bob McDonnell, Ireland
Amanda Neville, Italy
Annukka Ritvanen, Finland
Christine Roesch, Germany
Volker Steinbicker, Germany

Committee on Drugs during Pregnancy (Chair: Prof Lolkje van den Berg/Prof Martina Cornel, co-chairs Dr Elisabeth Robert & Dr Maurizio Clementi)

- Analyses the EUROCAT database in relation to concerns about specific drugs
- Proposes improvements to the quality and standardisation of EUROCAT data on drugs
- Co-ordinates collaboration with the ICBDMS MADRE project

Members:

Maurizio Clementi, Italy (ENTIS liaison)
Hermien de Walle, Netherlands
Lorentz Irgens, Norway
Willemijn Meijer, Netherlands
Jan Mejnartowicz, Poland
Amanda Neville, Italy
Annette Queisser Luft, Germany
Elisabeth Robert, France
Lolkje van den Berg, Netherlands

RESEARCH AND SURVEILLANCE PROJECTS USING DATA FROM THE EUROCAT DATABASE:

Maternal age-specific rates of Down Syndrome after age 40 (Principal investigator: Dr Joan Morris)

Twinning and congenital anomalies (PI: Prof Peter Pharoah)

WHO World Craniofacial Anomalies Registry (PI: Prof Pierpaolo Mastrioacovo)

Gastroschisis case-control study (PIs: Prof Pierpaolo Mastrioacovo, Dr Fabrizio Bianchi)

Maternal age and non-chromosomal congenital anomalies (PIs: Maria Loane, Helen Dolk)

Congenital Hydrocephalus: a population-based study of prevalence and outcome (PI: Dr Ester Garne)

Down Syndrome: Trends in Livebirth prevalence in relation to maternal age and prenatal screening trends (PI: Prof H Dolk)

Trisomy 18 epidemiology in Europe (PI: Dr Marianne Christiansen)

Impact of Prenatal Diagnosis on outcome for TGA (PI: Dr Ester Garne)

Assisted Conception and rare syndromes (Dr Annette Queisser Luft)

Surveillance of hypospadias in Europe in relation to exposure to endocrine disrupting chemicals (PI: Prof Helen Dolk)

Epidemiology of Multiple malformations: patterns of association and risk among siblings (PI: Prof Elisa Calzolari)

Epidemiology of Pyloric Stenosis (PI: Dr Ester Garne)

Epidemiology of renal anomalies (PI: Dr Ester Garne)

Recurrence risk of Down Syndrome (PI: Dr Joan Morris)

Multiple births and congenital anomalies (PI: Prof Helen Dolk, in collaboration with SCPE and PERISTAT)

ASSOCIATED RESEARCH PROJECTS COLLECTING INDEPENDENT DATA

Euroserscan (Prof Claude Stoll)

Geographic Variation in Congenital Anomalies in Great Britain (Prof Helen Dolk & Dr Ben Armstrong)

Capture-Recapture Analysis to estimate case ascertainment (Dr Ben Armstrong and Dr Lenore Abramsky)

Socioeconomic Inequalities in Pregnancy Outcome in Northern Ireland (Prof Helen Dolk)

APPENDIX 4

MEETINGS AND CONFERENCES

Appendix 4 Meetings and Conferences

1. Project Management Committee Meetings

The EUROCAT Project Management Committee met on 27-28 October 2001, 2 March 2002, 6 June 2002, 7 December 2002, 31 March 2003 and 3 November 2003. Telephone conference calls were held on 3 October 2002, 21 January 2003 and 7 May 2003.

2. Registry Leaders' Meetings

The EUROCAT 17th Registry Leaders' Meeting was held in Lisbon, Portugal 7-9 June 2002. 28 Registry Leaders attended as well as 17 Central Registry and local registry staff and 9 other guests. The programme and attendance list can be found in Appendix 6.

Heidelberg, Germany was the venue for the 2003 EUROCAT 18th Registry Leaders' Meeting together with the 7th European Symposium on the Prevention of Congenital Anomalies. The meeting took place between 29 May and 1 June 2003. 36 Registry Leaders attended as well as 19 Central Registry and local registry staff and 7 other guests. The programme and attendance list can be found in Appendix 7. These events were hosted by the EUROCAT Registries of Mainz and Saxony.

3. Workshops & Working Group Meetings

In 2002, the following workshops and committee meetings were held at the 17th Registry Leaders' Meeting:

Classification & Coding
NTD & Folic Acid
Cluster Management
Data Quality
Prenatal Diagnosis
Gastroschisis
Drug Surveillance
Communication
Ethics
A Cardiac Defects Coding Clinic was also held.

In 2003, the following workshops and committee meetings were held at the 18th Registry Leaders' Meeting:

Ethics
Prenatal Diagnosis
Drug Surveillance
Cluster Management
Classification & Coding
Workshop on Statistical Methods
NTD & Folic Acid
EDMP Clinic
Assisted Conception
EUROCAT Guide 1.3

In February 2003, a meeting of the EUROCAT Working Group on the Management of Clusters and Environmental Exposure Incidents was held in London with eleven participants.

EUROCAT WORKING GROUP ON THE MANAGEMENT OF CLUSTERS AND ENVIRONMENTAL EXPOSURE INCIDENTS

London, 17 February 2003
Programme: (Chair Paul Wilkinson)

1.00 Welcome and coffee and sandwiches

1.30 Overview of the aims of the EUROCAT Cluster Advisory Service – Helen Dolk

1.45 Risk Communication: Local environmental health concerns: public health perspectives – Marion Drijver

2.15 Risk Communication: Sociological Perspectives – Ortwin Renn (cancelled)

2.45 Risk communication in practice: Salim Vohra

3.00- 3.30 Coffee/Tea

3.30 Acting on Clusters Arising from Routine Surveillance- Elizabeth Robert

4.0 Acting on concerns regarding environmental exposures- Virginia Murray/Giovanni Leonardi

4.20 Acting on clusters arising outside routine surveillance- Paul Wilkinson

4.40 Investigating environmental exposures: a case study – Fabrizio Bianchi (to be confirmed)

5.00 Discussion: classification and definition of clusters

A meeting was held in London to revise EUROCAT Guide 1.2 (to Guide 1.3) in November 2003with six participants.

A meeting was held of a sub-committee of the Committee on Coding & Classification on the monitoring of multiple malformations and the coding of syndromes in November 2003 with five participants.

4. Presentations and Conferences

Prof Helen Dolk: Focus 2002, Glasgow, Scotland, 22 May 2002. "Risk of congenital anomalies near hazardous waste landfill sites".

Dr Ester Garne: XVIII European Congress of Perinatal Medicine, Oslo, Norway, 19-22 June 2002.

Dr Hermien de Walle (EUROCAT N Netherlands) presented folic acid and neural tube defects EUROCAT data to the European Teratology Society in Hannover, 8-10 September 2002.

Dr Janine Goujard (Leader, Working Group on Research) presented the first analysis of EUROCAT data included in EUROCAT Report 8, "Trends in the prevalence of Down Syndrome in EUROCAT regions in relation to maternal age and prenatal screening" to the International Clearinghouse for Birth Defect Monitoring Systems, Atlanta, USA, 17-19 Sept 2002.

Prof Helen Dolk and Dr Nicola Armstrong: BINOCAR Meeting, Oxford, UK, 30 September 2002.

Professor Dolk presented the EUROCAT data on folic acid and neural tube defects to the WHO/EURO Meeting on the Regional Policy for Prevention of Congenital Anomalies, Rome, Italy, 11-12 November 2002.

Prof Helen Dolk: 14-17 March 2003, presented EUROCAT data on anophthalmia to the European Science Foundation Workshop, Sorrento, Italy

Prof Dolk presented EUROCAT data on Down Syndrome at an INSEE/INSERM/EAPS meeting on Health implications of Late Parenthood in Paris, May 2003

Dr Araceli Busby: 11 June 2003, presentation on folic acid and neural tube defects at the Research in Midwifery and Perinatal Health Conference, University of Aston, Birmingham

Prof Helen Dolk, Dr Araceli Busby and Maria Loane: 8-9 September 2003, presentation of EUROCAT at the BINOCAR Conference, Trinity College, Dublin, Ireland

Prof Helen Dolk: 18-20 September 2003, presentation of EUROCAT at the ICBDMS Annual Meeting, Clermont Ferrand, France

Prof Helen Dolk: 3 October 2003, presentation of EUROCAT at the European Perinatal Epidemiology Meeting, Oxford, UK

Dr Fabrizio Bianchi: 16 October 2003, presentation of EUROCAT at the Portuguese Congenital Anomaly meeting in Lisbon, Portugal

EUROCAT data relating to 'Attitudes towards, and availability of, antenatal and preimplantation diagnosis in Europe' were presented by Dr Martina Cornel at the Paris 2003 European Conference on Rare Disorders and Disabilities (EURORDIS) on 16 October.

5. Other Travel

Maria Loane: Perinatal Public Health Conference, London, UK, 16 May 2002.

Prof Helen Dolk: Geographic Variation of congenital anomalies meeting, London, UK, 27 May 2002, 26 July 2002 and 27 March 2003

Prof Helen Dolk: Meeting with Alan Kelly, Dublin, Ireland, 9 July 2002.

Dr Martina Cornel: 14 November 2002, co-ordination meeting, Belfast, UK. Phone conference link with Dr Maurizio Clementi, Padua

Prof Helen Dolk: 20 December 2002, Disease Registries Commissioning Group and Geographic Variation of Congenital Anomalies Meeting, London, UK

Dr Nicola Armstrong: 21 November 2002, presenting poster at Chancellor's visit to Coleraine Campus of the University of Ulster, UK

James Demsen, Conor Teljeur: 12 December 2002, meeting on EUROCAT Statistical Monitoring, Belfast

Dr Araceli Busby: 21 January 2003 and 20 June 2003, visits to Central Registry

Dr Nicola Armstrong: 22 January 2003, meeting with clinical collaborators at RVH, Belfast

Prof Helen Dolk: 17-18 March 2003, Maternity Alliance Conference, London, UK

Prof Helen Dolk: 21 March 2003, EU Meeting, Luxembourg

Prof Helen Dolk: 3-5 April 2003, SCPE-EUROCAT meeting in Tubingen, Germany

Dr Ester Garne: 30 April – 2 May 2003, 16-18 June 2003, 22-24 September 2003 and 25-27 November 2003, visits to Central Registry, Belfast

Prof Helen Dolk: 6 May 2003, City University, London, UK

Prof Helen Dolk: 1 July 2003, Visit to Central Services Agency, Dublin, Ireland

Martina Cornel, Willemijn Meijer & Lolkje de Jong van den Berg: 12-13 August 2003, Visit to Central Registry, Belfast

Maria Loane: 30 September – 3 October 2003, Data Management at Clermont Ferrand, France

Willemijn Meijer: 20-24 October 2003, visit to Central Registry, Belfast

Prof Helen Dolk: 21 October 2003, EUROCAT meeting, London

James Demsen: 4 November 2003, meeting in London

Dr Fabrizio Bianchi & Maria Loane: 15 December 2003, EUROCAT meeting and data management, Barcelona

APPENDIX 5

LIAISON ACTIVITIES

APPENDIX 5 Liaison Activities

Dr Fabrizio Bianchi (Italy) visited the registries of Barcelona and Lisbon and Maria Loane (UK) visited the registries of Auvergne and Barcelona. News about EUROCAT was mailed to all contacts in Eastern Europe, and we are seeking funds to support travel exchanges with Eastern European partners.

For communication within EUROCAT, internal newsletters in the form of email communications are sent out regularly to all Registry Leaders and other partners. These are available also on the membership only area of the website, along with minutes of meetings and other documents.

Liaison with other organizations

EUROCAT Central Registry is a WHO Collaborating Centre for the Epidemiologic Surveillance of Congenital Anomalies, in regular contact with the Human Genetics Programme of WHO. EUROCAT has actively engaged in the WHO Craniofacial Anomalies project (see 2.3) EUROCAT also took part in a WHO Euro meeting on periconceptional folic acid (see 4.1).

EUROCAT works with the International Clearinghouse for Birth Defect Monitoring Systems and its executive office the International Centre for Birth Defects on the world craniofacial anomalies database (see 2.3), monitoring of multiple malformations (see 3.4), a study of risk factors for gastroschisis (see 3.5) and the MADRE surveillance of teratogenic drug exposures (see 3.3). 13 EUROCAT registries are also ICBMDS members.

EUROCAT is in contact with ENTIS (European Network of Teratology Information Services) who are represented on the EUROCAT Committee on Drugs in Pregnancy. ENTIS gave a presentation at the EUROCAT Registry Leaders Meeting in Lisbon 2002.

PERISTAT gave a presentation at the EUROCAT Registry Leaders Meeting in Lisbon 2002, and EUROCAT members gave advice on the choice of indicators concerning congenital anomalies for the PERISTAT project.

EUROCAT gave a presentation at a meeting organized by the European Association of Population Studies Working Group on Late Parenthood in conjunction with INSERM and INSEE, Paris, May 2003, and will contribute a paper on Down Syndrome epidemiology in Europe to the published proceedings of that meeting (see 4.2).

EUROCAT and ORPHANET have worked towards website linkages so enhance the complementarity of information given (epidemiologic data from EUROCAT and diagnostic and treatment data from Orphanet).

EUROCAT is in contact with NEPHIRD (Network of Public Health Institutions for Rare Diseases) and several EUROCAT members are also NEPHIRD members. NEPHIRD has submitted a list of priority syndromes for which EUROCAT could analyse and disseminate prevalence information in addition to the current standard list. NEPHIRD gave a presentation to the EUROCAT annual meetings in Lisbon and Heidelberg.

A presentation of EUROCAT was made at the EURORDIS annual conference in Paris October 2003

EUROCAT is represented on the management committee of SCPE (Surveillance of Cerebral Palsy in Europe) and discussions have been held regarding joint work on the impact of multiple birth increases on cerebral palsy and congenital anomalies, socio-economic inequalities, congenital anomalies associated with cerebral palsy. SCPE gave a presentation to the EUROCAT Registry Leaders Meeting in Heidelberg 2003, and EUROCAT gave a presentation to the SCPE annual meeting in Tubingen 2003.

EUROCAT is represented on the DG Sanco Rare Diseases Task Force.

APPENDIX 6

PROGRAMME & PARTICIPANT LIST OF LISBON REGISTRY LEADERS MEETING 2002

Appendix 6 Programme and participant list of Lisbon Registry Leaders Meeting 2002

Programme for 17th Registry Leaders' Meeting
Lisbon, Portugal
7-8 June 2002

Friday 7 June

8.30 Registration

Session 1 9.00 – 12.00 (Chair: Martin Haeusler) Progress Since Sicily

9.00 Welcome (Maria Feijoo)

9.10 Apologies and Minutes of Sicily Registry Leaders' Meeting

9.15 Project Leader's Report

9.40 Reports from Working Groups/Committees:
What have we achieved this year and what do we need to achieve at this RLM?
Statistics & Surveillance (Kelly)
Research (Goujard)
Clusters (Dolk)
Classification & Coding (Garne)
Data Quality (Dolk)
Communication & Ethics (Armstrong)

10.40 News from Local Registries – Romania, Cork & Kerry and Hungary

11.40 Subgroup Meetings I
Classification and Coding Committee I (Garne)
NTD & Folic Acid Project (Abramsky)
Cluster Management (Dolk)

Session 2 14.30 – 18.00 Subgroup Meetings

14.30 Subgroup Meetings II
Data Quality Indicators & revision of Guide 1.2 – Data Quality Committee (Dolk)
Prenatal Diagnosis Committee (Garne)

16.30 Subgroup Meetings III
Gastroschisis Case-Control Protocol (Bianchi)
Cardiac Defects Coding Clinic (Garne)
Drug Surveillance (Cornel/Clementi/Armstrong)
Ethics Subgroup

Saturday 8 June

Session 3 9.00 – 12.00 (Chair: Bob McDonnell) Data Management & Standard Reports

9.00 World Atlas II (Gian Luca Di Tanna)

9.10 Report 8 & State of the Database (Dolk)

9.25 Ethics & Confidentiality (Armstrong/Ritvanen/Botting)

9.40 Web Access to Customised Tables (Densem)

10.15 EDMP: Now & the Future (Densem/Loane)

10.45 Discussion

11.30 Subgroup Meetings IV
EDMP Clinic I (Densem/Loane)
Classification & Coding Committee II (Garne)
Other Subgroups & discussions of draft papers (by request)

14.15 – 18.00 (Chair: Fabrizio Bianchi) Future Registry Leaders' Meetings, Reports from Subgroup Meeting and News from Other Networks

14.15 Registry Leaders' Meeting & Symposium 2003, 2004 and 2005

14.30 Reports from Subgroup Meetings or EDMP Clinic II
Classification and Coding
Data Quality
Prenatal Diagnosis
Gastroschisis
Drug Surveillance
NTD & Folic Acid

16.30 EUROCAT Association Meeting

17.30 News from ICBDMS (Robert)
News from ENTIS (Clementi)
News from PERISTAT (Wildman)
Framework 6 Brainstorming session

18.30 Close

Minutes: Nicky Armstrong & Maria Loane

Lisbon, 2002 Participant List

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APPENDIX 7

PROGRAMME & PARTICIPANT LIST OF HEIDELBERG REGISTRY LEADERS MEETING 2003

Appendix 7 Programme and participant list of Heidelberg Registry Leaders' Meeting 2003

Programme for 18th Registry Leaders' Meeting
Heidelberg, Germany
29 May – 1 June 2003

Thursday 29 May

13.00	Registration	
Session 1	14.00-18.00 News Since Lisbon (Chair: Fabrizio Bianchi)	
14.00	Welcome (Volker Steinbicker and Annette Queisser-Luft)	
14.10	Apologies and Minutes of Lisbon Registry Leaders' Meeting	
14.15	Project Leader's Report	
14.45	State of the Database (Loane)	
15.00	News for Local Registries - Trent, Bulgaria, Wessex, Oxford	
15.45	Coffee	
16.15	Subgroup Meetings I	(Ethics or Prenatal Diagnosis)
17.15	Subgroup Meetings II	(Drugs or Prenatal Diagnosis)

Friday 30 May

Symposium

Saturday 31 May

Session II	09.00 – 13.00 Statistical and Software Development (Chair: Blanca Gener)
09.00	New version of EDMP (Densem)
10.00	Presentation of new Statistical Surveillance Software for EDMP (Kelly, Teljeur, Densem)
10.35	Calculation of Prevalence Rates (de Vigan)
10.45	Coffee
11.15	Workshop on New Statistical Surveillance Software: "Hands on Experience for Registry Leaders"
Or	
	EDMP and Data Quality Clinic
12.30	The EUROCAT Cluster Advisory Service (Busby)
12.45	Investigation of Two Clusters of Down Syndrome in Emilia Romagna (Riveria)
13.00	Lunch

Saturday 31 May (Cont'd)

Session III	14.00 – 18.00 (Chair: Annukka Ritvanen)
14.00	Subgroup Meetings III (Cluster Subgroup or EUROCAT Guide 1.3 or NTD and Folic Acid)
14.45	Categorising Birth Defects (Wellesley)
15.00	Coding Heterogeneity and New Coding Subgroups (Garne)
15.45	Coffee
16.15	New project Proposals/Brainstorming Session: WHO Cleft Registry (Mastrioacovo) Gastroschisis Case-Control Study (Mastrioacovo) Perinatal Mortality (Garne) Ongoing Project Lists and Small Grants Available for New Projects (Dolk) NTD and Folic Acid (Abramsky) Hypospadias Survey (Dolk) Proposals from Local Registries
17.00	Proportion of Local Budget Spent on co-ordinated EUROCAT activities (Calzolari)
17.15	EUROCAT Association Meeting

Sunday 1 June

Session IV	(Chair: David Lillis)
08.30	Subgroup Meetings IV (Classification and Coding or Assisted Conception or Free-time for further subgroups)
10.00	Results of Ethics Survey (Ritvanen)
10.15	Results of Drugs Survey (Robert)
10.30	Coffee
11.00	Registry Leaders' Meeting and Symposium 2004, 2005, 2006
11.15	Liaison with Other Organisations/Projects International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS) (Borman) Surveillance of Cerebral Palsy in Europe (SCPE) (Cans) Network of Public Health Institutions on Rare Diseases (NEPHIRD) (Bianchi) US Birth Defects Prevention Network (USBDPN) (Sever) ENCR (to be confirmed) PERISTAT (to be confirmed) ENTIS (to be confirmed) EURORDIS (to be confirmed)
12.00	The Year Ahead
12.20	Final Words and Farewell

Heidelberg, 2003 Participant List

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APPENDIX 8

PUBLICATIONS LIST

from 2002

Appendix 8 Publications List from 2002

Collaborative Publications Between Registries and EUROCAT Central Registry

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 (in press)

Dolk H, Vrijheid, Scott JES, Addor MC, Botting B, de Vigan C, de Walle H, Garne E, Loane M, Pierini A, Garcia-Minaur S, Physick N, Tenconi R, Wiesel A, Calzolari E & Stone D **(2004)** Towards the effective surveillance of hypospadias. Environmental Health Perspectives, 112, 3, 398-402

EUROCAT **(2004)** EUROCAT Special Report: A Review of Environmental Risk Factors for Congenital Anomalies. *EUROCAT Central Registry*, University of Ulster

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Cordier S, Chevrier C, Robert-Gnansia E, Lorente C, Brula P & Hours M **(2004)** Risk of congenital anomalies in the vicinity of solid waste incinerators. Occup Environ Med, 61: 8-15

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