



Supported by the EU-Commission Public Health Directorate Programme of Community Action on Rare Diseases
WHO Collaborating Centre for the Epidemiologic Surveillance of Congenital Anomalies

Special Report: Special Report:

EUROCAT and Orofacial Clefts: The Epidemiology of Orofacial Clefts in 30 European Regions



Italian National Research Council
IFC, Pisa



Università di Ferrara

Authors

| | |
|-------------|---|
| E Calzolari | Medical Genetics Unit, University of Ferrara, Italy |
| M Rubini | Medical Genetics Unit, University of Ferrara, Italy |
| A J Neville | Medical Genetics Unit, University of Ferrara, Italy |
| F Bianchi | CNR Institute of Clinical Physiology, Pisa, Italy |

EUROCAT Working Group consists of:

| | |
|---------------------|-------------------------------|
| M Gatt | Malta |
| R Caballin | El Valles, Spain |
| B Gener | Basque Country, Spain |
| J Salvador | Barcelona, Spain |
| C Mosquera-Tenreiro | Asturias, Spain |
| M Feijoo | Southern Portugal |
| G Scarano | Campania, Italy |
| A Calabro | Umbria, Italy |
| F Bianchi | Tuscany, Italy |
| E Calzolari | Emilia Romagna, Italy |
| R Tenconi | North East Italy |
| I Barisic | Zagreb, Croatia |
| M Haeusler | Styria, Austria |
| M-C Addor | Switzerland |
| V Steinbicker | Saxony-Anhalt, Germany |
| C Stoll | Strasbourg, France |
| Nicole Philippe, | Bouches-du-Rhone, France |
| Segolene Ayme | Bouches-du-Rhone, France |
| C de Vigan | Paris, France |
| Vera Nelen | West Flanders, Belgium |
| Y Gillerot | Hainaut-Namur, Belgium |
| D. Hansen-Koenig | Luxembourg |
| M. Roulleaux | Luxembourg |
| A Hazebroek | South West Netherlands |
| H de Walle | Northern Netherlands |
| A Ritvanen | Finland |
| E Garne | Odense, Denmark |
| G Edwards | Liverpool, UK |
| D Stone | Glasgow, Scotland, UK |
| N Nevin | Belfast, Northern Ireland, UK |
| H Johnson | Dublin, Ireland |
| D Lillis | Galway, Ireland |

Acknowledgements

This report was first presented to the WHO International Collaborative Research on Craniofacial anomalies Meeting in Geneva, 2000.

The authors would like to thank all the physicians, nurses midwives and registry staff for their assistance in collecting and processing the data.

Introduction

EUROCAT is a programme supported by the European Community for the surveillance of congenital anomalies. The main objectives are to detect and investigate trends in the frequency of congenital anomalies that could be due to environmental teratogens or mutagens and to evaluate the effectiveness and efficiency of neonatal and perinatal health services. As congenital anomalies have a relative low prevalence, and good quality exhaustive data is expensive and difficult to collect, a standard European system could allow countries using data from regional registries to pool their data and to exploit their differences by comparing them.

At present EUROCAT involves 36 Registries in 17 European Union and associated countries, with approximately 900,000 births surveyed per year.

A standardised database based on more than 160,000 cases of congenital anomaly among livebirths, stillbirths and terminations of pregnancy since 1980 is located at the host centre.

Epidemiology of Oral Clefts (OC's) in Europe

Objective of the Study

Analysis of OC data:

- To assess their quality ie. completeness, validity and homogeneity amongst Registries.
- To split cases into isolated, associated or recognised conditions.
- To describe the variation of the different types of OC's, with regard to geographical patterns and temporal trend.
- To produce an epidemiological description of the different OC types according to selected variables, such as sex ratio, birth weight, gestational length, and maternal obstetrical history.

Material and Methods

The 1980-1996 EUROCAT database include 9,390 cases with cleft Palate (CP), or Cleft Lip with or without Cleft Palate (CLP) collected by 30 Registries among 6,181,449 live and stillbirths. Induced abortions data were included, in accordance with the EUROCAT guidelines.

Validation and classification procedures have been performed on a sub-file that includes all eligible OC cases provided by the EUROCAT Central Database. This process has been carried out at the Medical Genetics Unit, Department of Experimental and Diagnostic Medicine, University of Ferrara.

Statistical analysis has been performed at the CNR Unit of Epidemiology in Pisa. All participating registries have been involved in the data validation process and in the interpretation as well as discussion of the results. Each individual record was classified into isolated, multiple congenital anomalies (MCA), and recognised conditions (including chromosomal and Mendelian syndromes and dysmorphological sequences.)

Results

Birth prevalence

In the present study birth prevalence of OC's varies significantly in Europe, not only between registries but also within countries, ranging from the lower rate of 6.3 per 10,000 births in El Valles (Spain) to the higher rate of 26.2 per 10,000 in Finland, with a European mean value of 15.2 per 10,000 (95% CI 14.9-15.5) (see Table 1).

When comparing the OC rate 95% confidence interval per each European centre (see Figure 1) with the European mean rate, we observed that:

- Centres over the upper 95% CI are: Finland, Odense, Northern Netherlands, Hainaut-Namur, Glasgow, Strasbourg, Bouches-du-Rhone and Styria.
- Centres below the lower 95% CI are: El Valles, Barcelona, North East Italy, Emilia Romagna, Tuscany, Umbria, Campania, Basque Country, Paris, Luxembourg, West Flanders and Belfast.

showing a clear difference between the north and south of Europe, although with some exceptions worthy of note.

Geographical distribution of OC in Europe is heterogeneous and points out different patterns for CP, CLP:

- CLP exceeded CP in all centres except in Finland, Malta and Glasgow (see Figure 2).
- For CP Finland presented the highest rate for both isolated CP and recognised conditions compared to all the other centres. A significantly higher prevalence compared to the EUROCAT mean was also observed in Dublin, Glasgow, Strasbourg and Bouches-du-Rhone whereas West Flanders, Paris, Luxembourg, Saxony, Tuscany, Umbria, North east Italy, Campania, Barcelona and El Valles showed a significantly lower rate (see Table 2).
- For CLP a significantly higher prevalence compared to the EUROCAT mean was observed in Finland, Odense, Northern Netherlands, Hainaut-Namur, Strasbourg and Styria whilst Belfast, Paris, Luxembourg, Tuscany, Emilia Romagna, Campania, Basque Country, Barcelona, El Valles and Malta showed a significantly lower rate (see Table 3).

Time Trend

No significant time trend was observed for the period 1980-1996.

Impact of Induced Abortions Following Prenatal Diagnosis

The proportion of induced abortions following prenatal diagnosis is small (4.5% for CP; 11.8% for CLP) and generally refers to more severe anomalies associated with OC's (see Table 4). The detection rate diagnosed by ultrasound (Clementi et al, 2000) was 27% for CLP and 7% for CP.

Association of OC's with Other Defects

The prevalence of the isolated conditions confirms, in general, the observations concerning the total cases, especially in the northern registries, both for CP and CLP cases. Among isolated cases 65.8% were CLP.

In 1,720 (18.3%) cases, an OC occurred amongst a recognised condition (see Table 1), OC in chromosomal aberrations were observed in 1,542 cases (16.1%).

In a few centres recognised conditions were observed in excess, both in CP (see Table 2) and CLP cases (see Table 3). The diagnostic ability, particularly in detecting syndromes, must be kept into account.

In 1,530 (16.2%) cases, multiple congenital anomalies of unknown origin was found. In 18% of all cases CP was found to be associated with one or more major anomalies. An association of CP and NTD in a well defined Northern European geographical area was found (see Figure 3).

Sex Ratio

The well-known sex ratio difference between CP and CLP was confirmed (see Figure 4).

Interpretation of the Epidemiological Data

The differential use of multiple sources of ascertainment and diagnostic methods could explain some variations even among EUROCAT Registers with defined inclusion criteria, but it is likely that significant differences in genotype and/or environmental exposures (Romitti et al, 1999; Shaw et al, 1996; Botto and Yang, 2000) may account for some of the geographic differences.

The overall OC data showed a fourfold variation in Europe, a sixfold variation in CP and a fourfold variation in CL(P). Such a large variation remained high also when excluding the maximum and minimum rates observed in Finland and El Valles (Spain) for OC and CP, and in Northern Netherlands and El Valles for CL(P): 2.7 in OC, 2.5 and 3.1 in CL and CL(P) respectively.

Some differences within countries appear worth consideration, such as that between North and South Netherlands, Belgium and Spain. As for France, Strasbourg showed the highest rates compared to Bouches-du-Rhone and Paris. In Italian centres more homogeneous rates were observed. However a slight North-South trend appears for OC overall.

In the British Isles no relevant difference among centres appears, with the exception of Belfast where decreasing rates were observed. In Styria the rate of CL(P) resulted lower only to the higher rates observed in Odense (Denmark) and Northern Netherlands.

Mechanisms that lead to OC's are heterogeneous and the final phenotype is the result of gene products that interact in many ways with one another and the environment to establish phenotypes. Accordingly significant differences in genotype and/or environmental exposures may account for some of the geographic variations. Our interpretation is that genetic diversity accounts for more of the variation in between-register prevalence rates than does differing methods of ascertainment. As a consequence genetic research studies that collect samples from different areas, have to take into account the different gene frequency among the population, different mutations in the same genes and the environment. Knowledge of these factors can be also relevant in the future for genetic testing.

References

1. Botto LD, Yang, Q (2000), "5,10-Methylenetetrahydrofolate Reductase Gene Variants and Congenital Anomalies: A HuGE Review", *American Journal of Epidemiology*, Vol 1, No 151(9), pp 862-877.
2. Clementi M, Tenconi R, Bianchi E, Stoll C and the EUROSCAN Study Group (2000), "Evaluation of Prenatal Diagnosis of Cleft Lip With or Without Cleft Palate and Cleft Palate by Ultrasound: Experience from 20 European Registries", *Prenatal Diagnosis*, Vol 20, No 11, pp 870-875.
3. Romitti PA, Lidral AC, Munger RG, Daack-Hirsch S, Burns TL, Murray JC (1999), "Candidate genes for Nonsyndromic Cleft Lip and Palate and Maternal Cigarette Smoking and Alcohol Consumption: Evaluation of Genotype-Environment Interactions from a Population-Based Case-Control Study of Orofacial Clefts", *Teratology*, Vol 59, No 1, pp 39-50.
4. Shaw GM, Wasserman CR, Lammer EJ, O'Malley CD, Murray JC, Basart AM, Tolarova MM (1996), "Orofacial Clefts, Parental Cigarette Smoking, and Transforming Growth Factor-Alpha Gene Variants", *American Journal of Human Genetics*, Vol 58, No 3, pp 551-561.

Figure 1: Oral Clefts (OC's) in Europe

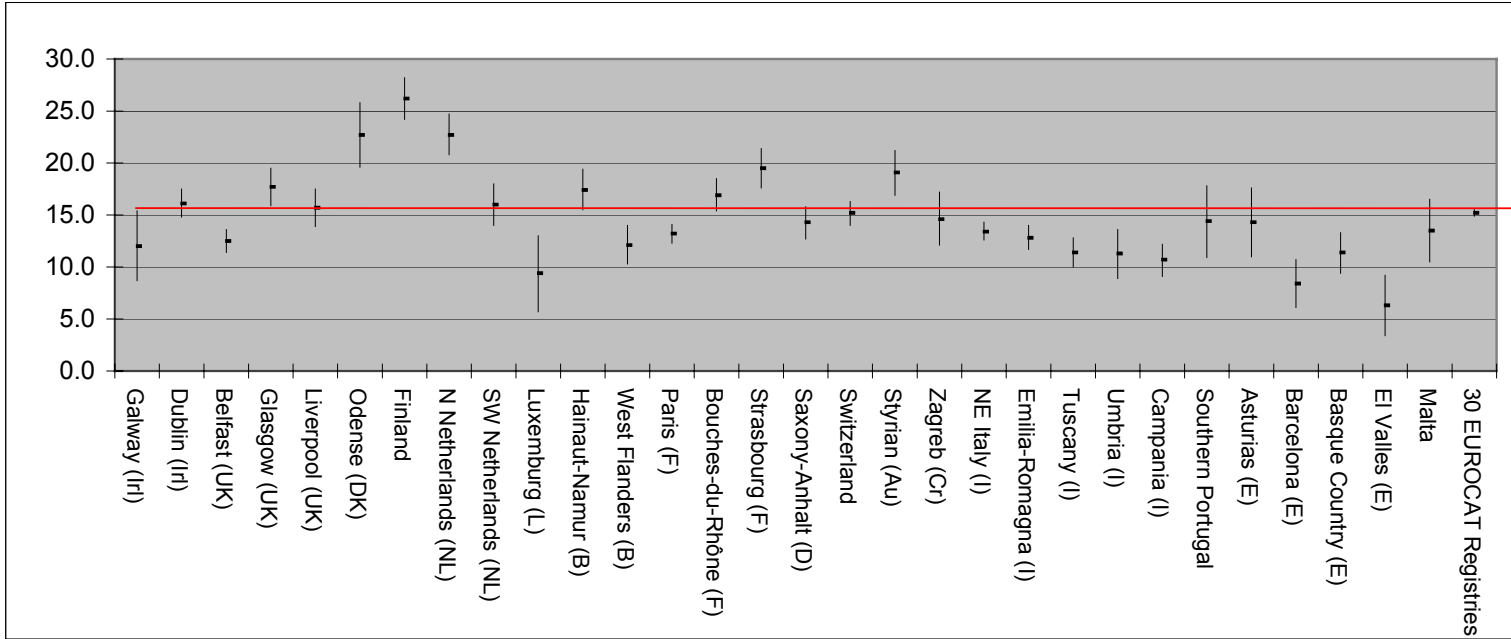


Figure 2: Cleft Palate and Cleft Lip +/- Palate in 30 EUROCAT Centres

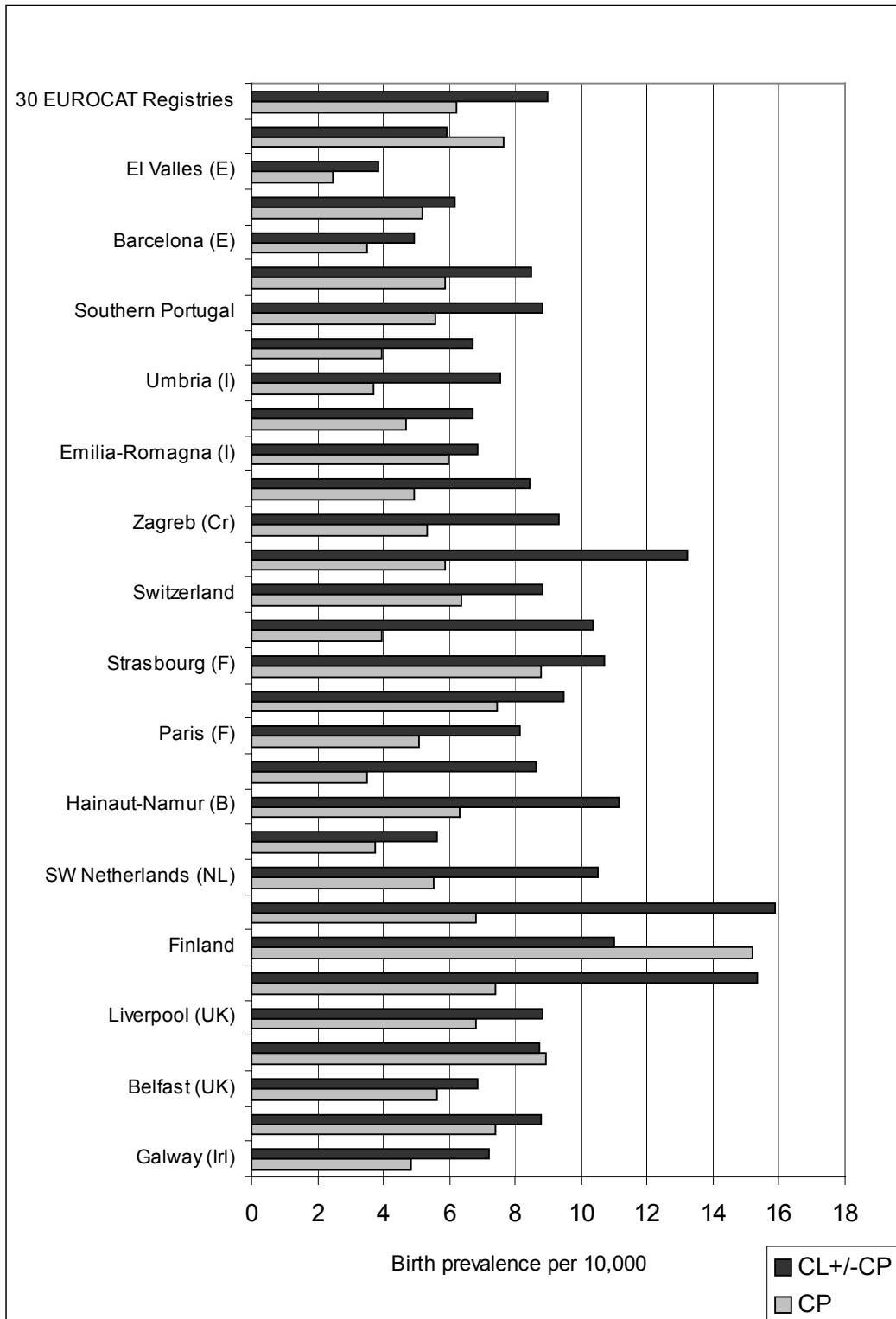


Figure 3: Association of Cleft Palate and Neural Tube Defects in a Well Defined North European Geographic Area

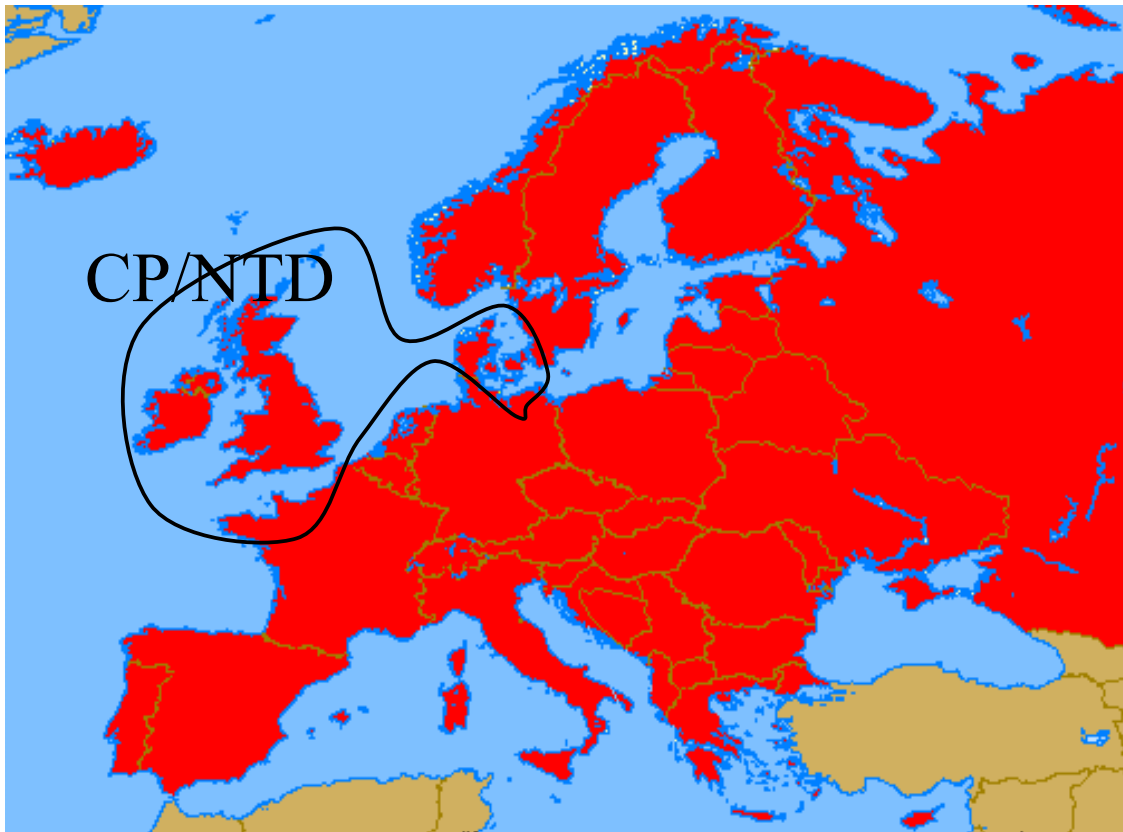


Figure 4: Sex Ratio in Orofacial Clefts

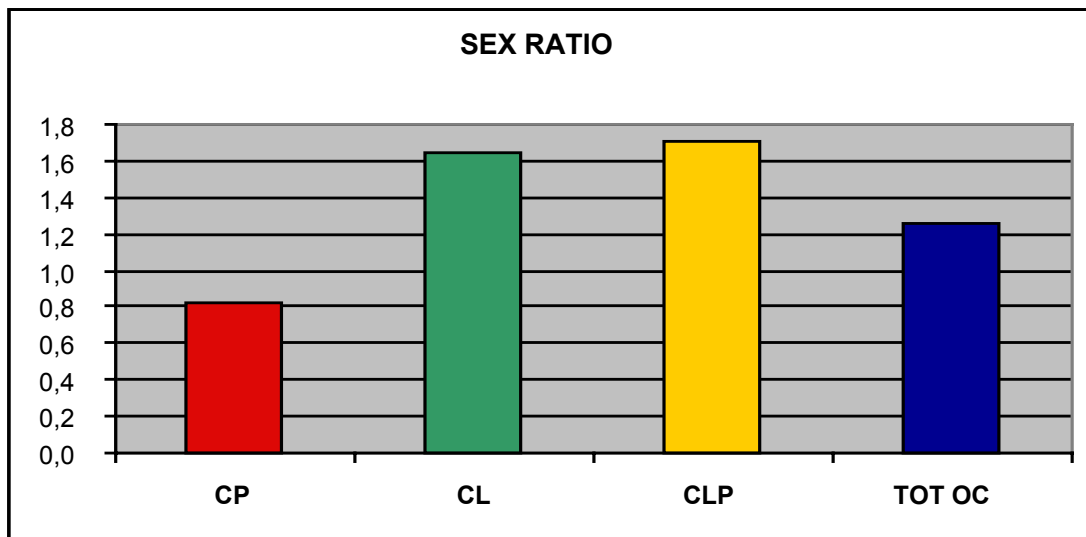


Table 1: Total Oral Clefts in 30 EUROCAT Registries: Number and Prevalence by Association with other Anomalies

| Centres | Period | Total Births | Total | | | Isolated | | | MCA | | | Recognised Conditions | | | | | | |
|------------------------------|---------|------------------|--------------|-------------|-------------|-------------|--------------|-------------|------------|-------------|--------------|-----------------------|------------|------------|--------------|------------|------------|------------|
| | | | No. | Rate | 95% CI | No. | Rate | 95% CI | No. | Rate | 95% CI | No. | Rate | 95% CI | | | | |
| Galway (Ireland) | 1981-94 | 41,549 | 50 | 12.0 | 8.7 - 15.4 | 31 | 7.5 | 4.8 - 10.1 | 6 | 1.4 | 0.3 - 2.6 | 13 | 0.5 | 0.0 - 1.1 | | | | |
| Dublin (Ireland) | 1980-96 | 357,457 | 577 | 16.1 | 14.8 - 17.5 | 430 | 12.0 | 10.9 - 13.2 | 61 | 0.9 | 0.6 - 1.2 | 90 | 0.6 | 0.3 - 0.8 | | | | |
| Belfast (UK) | 1980-94 | 405,352 | 506 | 12.5 | 11.4 - 13.6 | 255 | 6.3 | 5.5 - 7.1 | 136 | 1.8 | 1.4 - 2.2 | 115 | 1.2 | 0.9 - 1.5 | | | | |
| Glasgow (UK) | 1980-96 | 212,677 | 376 | 17.7 | 15.9 - 19.5 | 193 | 9.1 | 7.8 - 10.4 | 81 | 1.9 | 1.3 - 2.5 | 102 | 1.3 | 0.8 - 1.7 | | | | |
| Liverpool (UK) | 1980-87 | 184,530 | 289 | 15.7 | 13.9 - 17.5 | 193 | 10.5 | 9.0 - 11.9 | 62 | 1.5 | 1.0 - 2.1 | 34 | 0.4 | 0.1 - 0.7 | | | | |
| Odense (Denmark) | 1980-96 | 89,349 | 203 | 22.7 | 19.6 - 25.8 | 138 | 15.4 | 12.9 - 18.0 | 42 | 2.8 | 1.7 - 3.9 | 23 | 1.7 | 0.8 - 2.5 | | | | |
| Finland | 1993-96 | 253,847 | 665 | 26.2 | 24.2 - 28.2 | 428 | 16.9 | 15.3 - 18.5 | 67 | 1.4 | 1.0 - 1.9 | 180 | 2.1 | 1.5 - 2.6 | | | | |
| North Netherlands | 1981-96 | 228,599 | 519 | 22.7 | 20.8 - 24.7 | 352 | 15.4 | 13.8 - 17.0 | 90 | 2.1 | 1.5 - 2.7 | 77 | 1.2 | 0.7 - 1.6 | | | | |
| South West Netherlands | 1991-96 | 155,215 | 249 | 16.0 | 14.0 - 18.0 | 194 | 12.5 | 10.7 - 14.3 | 32 | 1.3 | 0.7 - 1.9 | 23 | 0.3 | 0.0 - 0.6 | | | | |
| Luxembourg | 1980-89 | 26,680 | 25 | 9.4 | 5.7 - 13.0 | 20 | 7.5 | 4.2 - 10.8 | 3 | 0.7 | 0.0 - 1.8 | 2 | 0.0 | 0.0 - 0.0 | | | | |
| Hainaut-Namur (Belgium) | 1980-96 | 177,885 | 310 | 17.4 | 15.5 - 19.4 | 203 | 11.4 | 9.8 - 13.0 | 56 | 1.7 | 1.1 - 2.4 | 51 | 1.2 | 0.7 - 1.7 | | | | |
| West Flanders (Belgium) | 1980-90 | 140,061 | 170 | 12.1 | 10.3 - 14.0 | 136 | 9.7 | 8.1 - 11.3 | 22 | 1.3 | 0.7 - 1.9 | 12 | 0.4 | 0.0 - 0.7 | | | | |
| Paris (France) | 1981-96 | 585,049 | 773 | 13.2 | 12.3 - 14.1 | 429 | 7.3 | 6.6 - 8.0 | 171 | 1.7 | 1.4 - 2.1 | 173 | 1.3 | 1.0 - 1.6 | | | | |
| Bouches-du Rhone (France) | 1985-96 | 276,574 | 468 | 16.9 | 15.4 - 18.5 | 288 | 10.4 | 9.2 - 11.6 | 68 | 1.3 | 0.8 - 1.7 | 115 | 2.1 | 1.5 - 2.6 | | | | |
| Strasbourg (France) | 1982-96 | 199,055 | 388 | 19.5 | 17.6 - 21.4 | 251 | 12.6 | 11.0 - 14.2 | 60 | 1.4 | 0.9 - 1.9 | 78 | 1.5 | 0.9 - 2.0 | | | | |
| Saxony-Anhalt (Germany) | 1980-96 | 233,877 | 334 | 14.3 | 12.7 - 15.8 | 251 | 10.7 | 9.4 - 12.1 | 70 | 1.8 | 1.3 - 2.4 | 14 | 0.4 | 0.1 - 0.6 | | | | |
| Switzerland | 1988-96 | 442,197 | 672 | 15.2 | 14.0 - 16.3 | 447 | 10.1 | 9.2 - 11.0 | 74 | 0.8 | 0.5 - 1.1 | 152 | 1.2 | 0.9 - 1.5 | | | | |
| Styrian (Austria) | 1985-96 | 158,754 | 303 | 19.1 | 16.9 - 21.2 | 209 | 13.2 | 11.4 - 14.9 | 50 | 2.0 | 1.3 - 2.6 | 44 | 1.6 | 1.0 - 2.2 | | | | |
| Zagreb (Croatia) | 1983-96 | 84,715 | 124 | 14.6 | 12.1 - 17.2 | 99 | 11.7 | 9.4 - 14.0 | 21 | 1.4 | 0.6 - 2.2 | 4 | 0.1 | 0.0 - 0.3 | | | | |
| North East Italy | 1981-96 | 716,939 | 961 | 13.4 | 12.6 - 14.3 | 643 | 9.0 | 8.3 - 9.7 | 126 | 0.9 | 0.7 - 1.2 | 193 | 1.4 | 1.1 - 1.7 | | | | |
| Emilia Romagna (Italy) | 1981-96 | 371,499 | 477 | 12.8 | 11.7 - 14.0 | 322 | 8.7 | 7.7 - 9.6 | 78 | 0.9 | 0.6 - 1.2 | 77 | 0.5 | 0.3 - 0.7 | | | | |
| Tuscany (Italy) | 1980-96 | 230,455 | 263 | 11.4 | 10.0 - 12.8 | 201 | 8.7 | 7.5 - 9.9 | 38 | 0.9 | 0.5 - 1.2 | 25 | 0.3 | 0.1 - 0.6 | | | | |
| Umbria (Italy) | 1980-89 | 77,957 | 88 | 11.3 | 8.9 - 13.6 | 67 | 8.6 | 6.5 - 10.7 | 14 | 0.9 | 0.2 - 1.6 | 7 | 0.5 | 0.0 - 1.0 | | | | |
| Campania (Italy) | 1993-96 | 174,082 | 186 | 10.7 | 9.1 - 12.2 | 138 | 7.9 | 6.6 - 9.2 | 25 | 1.0 | 0.5 - 1.4 | 30 | 0.5 | 0.1 - 0.8 | | | | |
| South Portugal | 1990-96 | 46,558 | 67 | 14.4 | 10.9 - 17.8 | 44 | 9.5 | 6.7 - 12.2 | 12 | 1.3 | 0.3 - 2.3 | 12 | 0.6 | 0.0 - 1.4 | | | | |
| Asturias (Spain) | 1990-96 | 49,587 | 71 | 14.3 | 11.0 - 17.6 | 40 | 8.1 | 5.6 - 10.6 | 16 | 2.0 | 0.8 - 3.3 | 17 | 1.0 | 0.1 - 1.9 | | | | |
| Barcelona (Spain) | 1992-96 | 63,054 | 53 | 8.4 | 6.1 - 10.7 | 32 | 5.1 | 3.3 - 6.8 | 9 | 1.0 | 0.2 - 1.7 | 12 | 1.0 | 0.2 - 1.7 | | | | |
| Basque Country (Spain) | 1990-96 | 111,750 | 127 | 11.4 | 9.4 - 13.3 | 72 | 6.4 | 5.0 - 7.9 | 20 | 1.1 | 0.5 - 1.7 | 35 | 0.9 | 0.3 - 1.4 | | | | |
| El Valles (Spain) | 1993-96 | 28,506 | 18 | 6.3 | 3.4 - 9.2 | 11 | 3.9 | 1.6 - 6.1 | 6 | 1.4 | 0.0 - 2.8 | 2 | 0.4 | 0.0 - 1.0 | | | | |
| Malta | 1986-96 | 57,640 | 78 | 13.5 | 10.5 - 16.5 | 56 | 9.7 | 7.2 - 12.3 | 14 | 0.7 | 0.0 - 1.4 | 8 | 0.0 | 0.0 - 0.0 | | | | |
| 30 EUROCAT Registries | | 6,181,449 | 9,390 | 15.2 | 14.9 | 15.5 | 6,173 | 10.0 | 5.0 | 15.0 | 1,530 | 2.5 | 0.0 | 5.0 | 1,720 | 9.0 | 8.7 | 9.2 |

Table 2: Cleft Palate in 30 EUROCAT Registries: Number and Prevalence by Association with other Anomalies

| Centres | Period | Total Births | Total | | | Isolated | | | MCA | | | Recognised Conditions | | |
|------------------------------|---------|------------------|--------------|------------|------------------|--------------|------------|------------------|------------|------------|------------------|-----------------------|------------|------------------|
| | | | No. | Rate | 95% CI | No. | Rate | 95% CI | No. | Rate | 95% CI | No. | Rate | 95% CI |
| Galway (Ireland) | 1981-94 | 41,549 | 20 | 4.8 | 2.7 - 6.9 | 9 | 2.2 | 0.8 - 3.6 | 0 | 0.0 | 0.0 - 0.0 | 11 | 2.6 | 1.1 - 4.2 |
| Dublin (Ireland) | 1980-96 | 357,457 | 264 | 7.3 | 6.5 - 8.3 | 169 | 4.7 | 4.0 - 5.4 | 30 | 0.8 | 0.5 - 1.1 | 65 | 1.8 | 1.4 - 2.3 |
| Belfast (UK) | 1980-94 | 405,352 | 228 | 5.6 | 4.9 - 6.4 | 100 | 2.5 | 2.0 - 3.0 | 62 | 1.5 | 1.1 - 1.9 | 66 | 1.6 | 1.2 - 2.0 |
| Glasgow (UK) | 1980-96 | 212,677 | 190 | 8.9 | 7.7 - 10.2 | 75 | 3.5 | 2.7 - 4.3 | 40 | 1.9 | 1.3 - 2.5 | 75 | 3.5 | 2.7 - 4.3 |
| Liverpool (UK) | 1980-87 | 184,530 | 126 | 6.8 | 5.6 - 8.0 | 65 | 3.5 | 2.7 - 4.4 | 34 | 1.8 | 1.2 - 2.5 | 27 | 1.5 | 0.9 - 2.0 |
| Odense (Denmark) | 1980-96 | 89,349 | 66 | 7.4 | 5.6 - 9.2 | 41 | 4.6 | 3.2 - 6.0 | 17 | 1.9 | 1.0 - 2.8 | 8 | 0.9 | 0.3 - 1.5 |
| Finland | 1993-96 | 253,847 | 386 | 15.2 | 13.7 - 16.7 | 237 | 9.3 | 8.1 - 10.5 | 31 | 1.2 | 0.8 - 1.7 | 118 | 4.6 | 3.8 - 5.5 |
| North Netherlands | 1981-96 | 228,599 | 156 | 6.8 | 5.8 - 7.9 | 65 | 2.8 | 2.2 - 3.5 | 41 | 1.8 | 1.2 - 2.3 | 50 | 2.2 | 1.6 - 2.8 |
| South West Netherlands | 1991-96 | 155,215 | 86 | 5.5 | 4.4 - 6.7 | 56 | 3.6 | 2.7 - 4.6 | 12 | 0.8 | 0.3 - 1.2 | 18 | 1.2 | 0.6 - 1.7 |
| Luxembourg | 1980-89 | 26,680 | 10 | 3.7 | 1.4 - 6.1 | 7 | 2.6 | 0.7 - 4.6 | 1 | 0.4 | 0.0 - 1.1 | 2 | 0.7 | 0.0 - 1.8 |
| Hainaut-Namur (Belgium) | 1980-96 | 177,885 | 112 | 6.3 | 5.1 - 7.5 | 57 | 3.2 | 2.4 - 4.0 | 25 | 1.4 | 0.9 - 2.0 | 30 | 1.7 | 1.1 - 2.3 |
| West Flanders (Belgium) | 1980-90 | 140,061 | 49 | 3.5 | 2.5 - 4.5 | 38 | 2.7 | 1.9 - 3.6 | 4 | 0.3 | 0.0 - 0.6 | 7 | 0.5 | 0.1 - 0.9 |
| Paris (France) | 1981-96 | 585,049 | 298 | 5.1 | 4.5 - 5.7 | 132 | 2.3 | 1.9 - 2.6 | 70 | 1.2 | 0.9 - 1.5 | 96 | 1.6 | 1.3 - 2.0 |
| Bouches-du Rhone (France) | 1985-96 | 276,574 | 206 | 7.4 | 6.4 - 8.5 | 117 | 4.2 | 3.5 - 5.0 | 33 | 1.2 | 0.8 - 1.6 | 56 | 2.0 | 1.5 - 2.6 |
| Strasbourg (France) | 1982-96 | 199,055 | 175 | 8.8 | 7.5 - 10.1 | 95 | 4.8 | 3.8 - 5.7 | 32 | 1.6 | 1.1 - 2.2 | 48 | 2.4 | 1.7 - 3.1 |
| Saxony-Anhalt (Germany) | 1980-96 | 233,877 | 92 | 3.9 | 3.1 - 4.7 | 60 | 2.6 | 1.9 - 3.2 | 27 | 1.2 | 0.7 - 1.6 | 5 | 0.2 | 0.0 - 0.4 |
| Switzerland | 1988-96 | 442,197 | 281 | 6.4 | 5.6 - 7.1 | 146 | 3.3 | 2.8 - 3.8 | 38 | 0.9 | 0.6 - 1.1 | 97 | 2.2 | 1.8 - 2.6 |
| Styrian (Austria) | 1985-96 | 158,754 | 93 | 5.9 | 4.7 - 7.0 | 55 | 3.5 | 2.5 - 4.4 | 19 | 1.2 | 0.7 - 1.7 | 19 | 1.2 | 0.7 - 1.7 |
| Zagreb (Croatia) | 1983-96 | 84,715 | 45 | 5.3 | 3.8 - 6.9 | 33 | 3.9 | 2.6 - 5.2 | 9 | 1.1 | 0.4 - 1.8 | 3 | 0.4 | 0.0 - 0.8 |
| North East Italy | 1981-96 | 716,939 | 355 | 5.0 | 4.4 - 5.5 | 204 | 2.8 | 2.5 - 3.2 | 58 | 0.8 | 0.6 - 1.0 | 93 | 1.3 | 1.0 - 1.6 |
| Emilia Romagna (Italy) | 1981-96 | 371,499 | 222 | 6.0 | 5.2 - 6.8 | 120 | 3.2 | 2.7 - 3.8 | 44 | 1.2 | 0.8 - 1.5 | 58 | 1.6 | 1.2 - 2.0 |
| Tuscany (Italy) | 1980-96 | 230,455 | 108 | 4.7 | 3.8 - 5.6 | 74 | 3.2 | 2.5 - 3.9 | 18 | 0.8 | 0.4 - 1.1 | 16 | 0.7 | 0.4 - 1.0 |
| Umbria (Italy) | 1980-89 | 77,957 | 29 | 3.7 | 2.4 - 5.1 | 19 | 2.4 | 1.3 - 3.5 | 7 | 0.9 | 0.2 - 1.6 | 3 | 0.4 | 0.0 - 0.8 |
| Campania (Italy) | 1993-96 | 174,082 | 69 | 4.0 | 3.0 - 4.9 | 45 | 2.6 | 1.8 - 3.3 | 7 | 0.4 | 0.1 - 0.7 | 17 | 1.0 | 0.5 - 1.4 |
| South Portugal | 1990-96 | 46,558 | 26 | 5.6 | 3.4 - 7.7 | 12 | 2.6 | 1.1 - 4.0 | 6 | 1.3 | 0.3 - 2.3 | 8 | 1.7 | 0.5 - 2.9 |
| Asturias (Spain) | 1990-96 | 49,587 | 29 | 5.8 | 3.7 - 8.0 | 13 | 2.6 | 1.2 - 4.0 | 6 | 1.2 | 0.2 - 2.2 | 10 | 2.0 | 0.8 - 3.3 |
| Barcelona (Spain) | 1992-96 | 63,054 | 22 | 3.5 | 2.0 - 4.9 | 13 | 2.1 | 0.9 - 3.2 | 3 | 0.5 | 0.0 - 1.0 | 6 | 1.0 | 0.2 - 1.7 |
| Basque Country (Spain) | 1990-96 | 111,750 | 58 | 5.2 | 3.9 - 6.5 | 25 | 2.2 | 1.4 - 3.1 | 8 | 0.7 | 0.2 - 1.2 | 25 | 2.2 | 1.4 - 3.1 |
| El Valles (Spain) | 1993-96 | 28,506 | 7 | 2.5 | 0.6 - 4.3 | 4 | 1.4 | 0.0 - 2.8 | 2 | 0.7 | 0.0 - 1.7 | 1 | 0.4 | 0.0 - 1.0 |
| Malta | 1986-96 | 57,640 | 44 | 7.6 | 5.4 - 9.9 | 26 | 4.5 | 2.8 - 6.2 | 10 | 1.7 | 0.7 - 2.8 | 8 | 1.4 | 0.4 - 2.3 |
| 30 EUROCAT Registries | | 6,181,449 | 3,852 | 6.2 | 6.0 - 6.4 | 2,112 | 3.4 | 3.3 - 3.6 | 694 | 1.1 | 1.0 - 1.2 | 1,046 | 1.7 | 1.6 - 1.8 |

Table 3: Cleft Lip +/- Palate in 30 EUROCAT Registries: Number and Prevalence by Association with other Anomalies

| Centres | Period | Total Births | Total | | | | Isolated | | | | MCA | | | | Recognised Conditions | | | |
|------------------------------|---------|------------------|--------------|------------|------------|------------|-------------|------------|------------|------------|------------|------------|------------|------------|-----------------------|------------|------------|------------|
| | | | No. | Rate | 95% CI | | No. | Rate | 95% CI | | No. | Rate | 95% CI | | No. | Rate | 95% CI | |
| Galway (Ireland) | 1981-94 | 41,549 | 30 | 7.2 | 4.6 | 9.8 | 22 | 5.3 | 3.1 | 7.5 | 6 | 1.4 | 0.3 | 2.6 | 2 | 0.5 | 0.0 | 1.1 |
| Dublin (Ireland) | 1980-96 | 357,457 | 313 | 8.8 | 7.8 | 9.7 | 261 | 7.3 | 6.4 | 8.2 | 31 | 0.9 | 0.6 | 1.2 | 21 | 0.6 | 0.3 | 0.8 |
| Belfast (UK) | 1980-94 | 405,352 | 278 | 6.9 | 6.1 | 7.7 | 155 | 3.8 | 3.2 | 4.4 | 74 | 1.8 | 1.4 | 2.2 | 49 | 1.2 | 0.9 | 1.5 |
| Glasgow (UK) | 1980-96 | 212,677 | 186 | 8.7 | 7.5 | 10.0 | 118 | 5.5 | 4.5 | 6.5 | 41 | 1.9 | 1.3 | 2.5 | 27 | 1.3 | 0.8 | 1.7 |
| Liverpool (UK) | 1980-87 | 184,530 | 163 | 8.8 | 7.5 | 10.2 | 128 | 6.9 | 5.7 | 8.1 | 28 | 1.5 | 1.0 | 2.1 | 7 | 0.4 | 0.1 | 0.7 |
| Odense (Denmark) | 1980-96 | 89,349 | 137 | 15.3 | 12.8 | 17.9 | 97 | 10.9 | 8.7 | 13.0 | 25 | 2.8 | 1.7 | 3.9 | 15 | 1.7 | 0.8 | 2.5 |
| Finland | 1993-96 | 253,847 | 279 | 11.0 | 9.7 | 12.3 | 190 | 7.5 | 6.4 | 8.5 | 36 | 1.4 | 1.0 | 1.9 | 53 | 2.1 | 1.5 | 2.6 |
| North Netherlands | 1981-96 | 228,599 | 363 | 15.9 | 14.2 | 17.5 | 287 | 12.6 | 11.1 | 14.0 | 49 | 2.1 | 1.5 | 2.7 | 27 | 1.2 | 0.7 | 1.6 |
| South West Netherlands | 1991-96 | 155,215 | 163 | 10.5 | 8.9 | 12.1 | 138 | 8.9 | 7.4 | 10.4 | 20 | 1.3 | 0.7 | 1.9 | 5 | 0.3 | 0.0 | 0.6 |
| Luxembourg | 1980-89 | 26,680 | 15 | 5.6 | 2.8 | 8.5 | 13 | 4.9 | 2.2 | 7.5 | 2 | 0.7 | 0.0 | 1.8 | 0 | 0.0 | 0.0 | 0.0 |
| Hainaut-Namur (Belgium) | 1980-96 | 177,885 | 198 | 11.1 | 9.6 | 12.7 | 146 | 8.2 | 6.9 | 9.5 | 31 | 1.7 | 1.1 | 2.4 | 21 | 1.2 | 0.7 | 1.7 |
| West Flanders (Belgium) | 1980-90 | 140,061 | 121 | 8.6 | 7.1 | 10.2 | 98 | 7.0 | 5.6 | 8.4 | 18 | 1.3 | 0.7 | 1.9 | 5 | 0.4 | 0.0 | 0.7 |
| Paris (France) | 1981-96 | 585,049 | 475 | 8.1 | 7.4 | 8.8 | 297 | 5.1 | 4.5 | 5.7 | 101 | 1.7 | 1.4 | 2.1 | 77 | 1.3 | 1.0 | 1.6 |
| Bouches-du Rhone (France) | 1985-96 | 276,574 | 262 | 9.5 | 8.3 | 10.6 | 170 | 6.1 | 5.2 | 7.1 | 35 | 1.3 | 0.8 | 1.7 | 57 | 2.1 | 1.5 | 2.6 |
| Strasbourg (France) | 1982-96 | 199,055 | 213 | 10.7 | 9.3 | 12.1 | 156 | 7.8 | 6.6 | 9.1 | 28 | 1.4 | 0.9 | 1.9 | 29 | 1.5 | 0.9 | 2.0 |
| Saxony-Anhalt (Germany) | 1980-96 | 233,877 | 242 | 10.3 | 9.0 | 11.7 | 190 | 8.1 | 7.0 | 9.3 | 43 | 1.8 | 1.3 | 2.4 | 9 | 0.4 | 0.1 | 0.6 |
| Switzerland | 1988-96 | 442,197 | 391 | 8.8 | 8.0 | 9.7 | 301 | 6.8 | 6.0 | 7.6 | 36 | 0.8 | 0.5 | 1.1 | 54 | 1.2 | 0.9 | 1.5 |
| Styrian (Austria) | 1985-96 | 158,754 | 210 | 13.2 | 11.4 | 15.0 | 154 | 9.7 | 8.2 | 11.2 | 31 | 2.0 | 1.3 | 2.6 | 25 | 1.6 | 1.0 | 2.2 |
| Zagreb (Croatia) | 1983-96 | 84,715 | 79 | 9.3 | 7.3 | 11.4 | 66 | 7.8 | 5.9 | 9.7 | 12 | 1.4 | 0.6 | 2.2 | 1 | 0.1 | 0.0 | 0.3 |
| North East Italy | 1981-96 | 716,939 | 606 | 8.5 | 7.8 | 9.1 | 439 | 6.1 | 5.6 | 6.7 | 68 | 0.9 | 0.7 | 1.2 | 99 | 1.4 | 1.1 | 1.7 |
| Emilia Romagna (Italy) | 1981-96 | 371,499 | 255 | 6.9 | 6.0 | 7.7 | 202 | 5.4 | 4.7 | 6.2 | 34 | 0.9 | 0.6 | 1.2 | 19 | 0.5 | 0.3 | 0.7 |
| Tuscany (Italy) | 1980-96 | 230,455 | 155 | 6.7 | 5.7 | 7.8 | 127 | 5.5 | 4.6 | 6.5 | 20 | 0.9 | 0.5 | 1.2 | 8 | 0.3 | 0.1 | 0.6 |
| Umbria (Italy) | 1980-89 | 77,957 | 59 | 7.6 | 5.6 | 9.5 | 48 | 6.2 | 4.4 | 7.9 | 7 | 0.9 | 0.2 | 1.6 | 4 | 0.5 | 0.0 | 1.0 |
| Campania (Italy) | 1993-96 | 174,082 | 117 | 6.7 | 5.5 | 7.9 | 92 | 5.3 | 4.2 | 6.4 | 17 | 1.0 | 0.5 | 1.4 | 8 | 0.5 | 0.1 | 0.8 |
| South Portugal | 1990-96 | 46,558 | 41 | 8.8 | 6.1 | 11.5 | 32 | 6.9 | 4.5 | 9.3 | 6 | 1.3 | 0.3 | 2.3 | 3 | 0.6 | 0.0 | 1.4 |
| Asturias (Spain) | 1990-96 | 49,587 | 42 | 8.5 | 5.9 | 11.0 | 27 | 5.4 | 3.4 | 7.5 | 10 | 2.0 | 0.8 | 3.3 | 5 | 1.0 | 0.1 | 1.9 |
| Barcelona (Spain) | 1992-96 | 63,054 | 31 | 4.9 | 3.2 | 6.6 | 19 | 3.0 | 1.7 | 4.4 | 6 | 1.0 | 0.2 | 1.7 | 6 | 1.0 | 0.2 | 1.7 |
| Basque Country (Spain) | 1990-96 | 111,750 | 69 | 6.2 | 4.7 | 7.6 | 47 | 4.2 | 3.0 | 5.4 | 12 | 1.1 | 0.5 | 1.7 | 10 | 0.9 | 0.3 | 1.4 |
| El Valles (Spain) | 1993-96 | 28,506 | 11 | 3.9 | 1.6 | 6.1 | 6 | 2.1 | 0.4 | 3.8 | 4 | 1.4 | 0.0 | 2.8 | 1 | 0.4 | 0.0 | 1.0 |
| Malta | 1986-96 | 57,640 | 34 | 5.9 | 3.9 | 7.9 | 30 | 5.2 | 3.3 | 7.1 | 4 | 0.7 | 0.7 | 2.8 | 0 | 0.0 | 0.0 | 0.0 |
| 30 EUROCAT Registries | | 6,181,449 | 5,538 | 9.0 | 8.7 | 9.2 | 4056 | 6.6 | 6.4 | 6.8 | 835 | 1.4 | 1.3 | 1.4 | 647 | 1.0 | 1.0 | 1.1 |

Table 4: Impact of Induced Abortions Following Prenatal Diagnosis

| | CP | CL | CLP | Total |
|----------------------|------------|-----------|------------|------------|
| Isolated | 4 | 8 | 16 | 29 |
| MCA | 71 | 36 | 85 | 192 |
| Recognised Condition | 100 | 53 | 153 | 305 |
| TOTAL | 175 | 97 | 254 | 526 |
| % | 4.5 | 4.6 | 7.2 | 5.5 |

Table 5: CP and CLP Classified into Isolated, Multiple Congenital Anomalies (MCA) and Recognised Conditions

| | | Isolated | MCA | Recognised Condition | Total |
|--------------|-----------|--------------|--------------|----------------------|---------------|
| CP | No | 2,112 | 694 | 1,046 | 3,852 |
| | % | 54.83 | 18.02 | 27.15 | 100.00 |
| CLP | No | 4,056 | 835 | 647 | 5,538 |
| | % | 73.24 | 15.08 | 11.68 | 100.00 |
| Total | No | 6,068 | 1,529 | 1,693 | 9,390 |
| | % | 65.69 | 16.28 | 18.03 | 100.00 |