Eurocat

European Surveillance of Congenital Anomalies

EUROCAT Statistical Monitoring Protocol

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EUROCAT PROTOCOL FOR STATISTICAL MONITORING AND INVESTIGATION OF TRENDS AND CLUSTERS

CONTENTS

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1. Background: monitoring strategy and timetable

Statistical Monitoring relates to two of EUROCAT's objectives:

- to provide essential epidemiologic information on congenital anomalies in Europe
- to co-ordinate the detection of, and response, to clusters and early warning of teratogenic exposures

EUROCAT was established in 1979 in the wake of the thalidomide epidemic, and statistical monitoring still aims at early detection of any new teratogenic drug. Since then, interest has also widened to other environmental chemicals as potential teratogens (see EUROCAT Special Report: a Review of Environmental Risk Factors for Congenital Anomaly 2004 www.eurocat.ulster.ac.uk/pubdata/envrisk.html). Statistical monitoring is only one part of surveillance of teratogenic exposures, to identify potential cause for concern where there is no specific prior hypothesis about the exposure. It is essentially a screening method to scrutinise data regularly and systematically, to detect any previously unrecognised increases in frequency. Where there are specified hypotheses about new teratogens (e.g. which drug, when, where), other direct approaches for analysis should be undertaken which are not the subject of this protocol.

The EUROCAT Coding and Classification Committee select EUROCAT congenital anomaly subgroups for statistical monitoring. All subgroups are defined in EUROCAT Guide 1.3 http://www.eurocat.ulster.ac.uk/pdf/EUROCAT-Guide-1.3.pdf .

Currently, statistical monitoring is conducted to detect changes in time within each registry. Analysing data across registries and incorporating the spatial dimension are envisaged in future developments.

Statistical methods have been chosen to be relatively straightforward for public health authorities to understand and communicate, and which can be supplied in the EUROCAT software (EDMP) to member registries for use by non-statisticians.

The elements of the current monitoring strategy are:

- Common user-friendly statistical software for use centrally and locally (EDMP)
- Annual statistical monitoring for trends and clusters at central level, 15 months after last date of birth (e.g. year 2006 births included in monitoring in March 2008).
- More frequent and/or earlier statistical monitoring locally (by member registries)
- Use of EUROCAT communications and special data analyses to respond to news about clusters identified locally or outside the monitoring system
- A clear and prompt system of investigation and reporting of results
- Use of statistical monitoring additionally as a data quality control system

All full member registries able to meet the annual February data transmission deadline (e.g. Feb 2008 for 2006 births) participate in cluster detection monitoring. All full member registries who have submitted new data since the previous Statistical Monitoring

Report are included in trend analysis. Associate members can also request to be included in trend analysis. Associate member registries are invited to use EDMP locally for cluster detection and report their results to Central Registry.

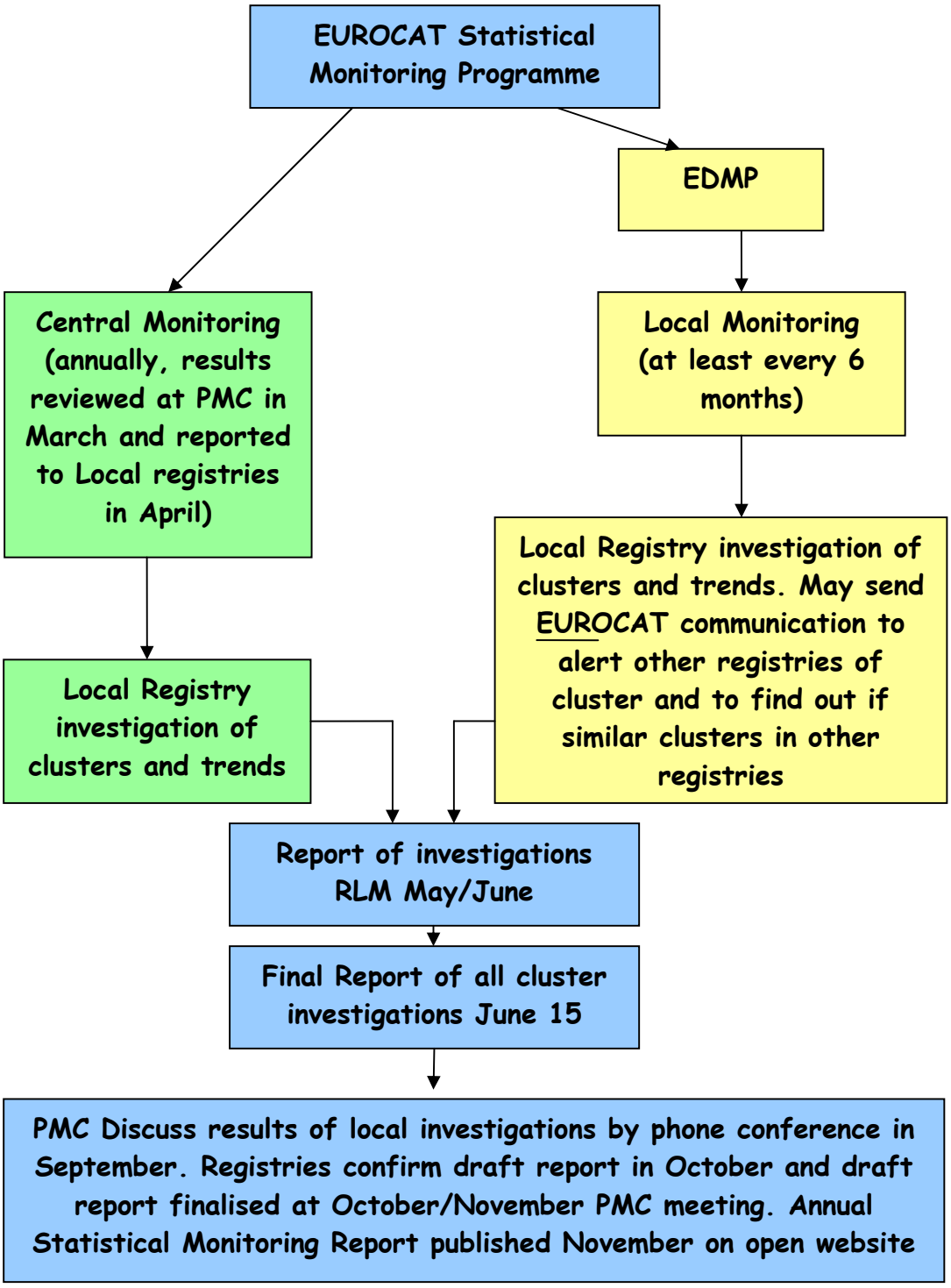


Figure 1: Monitoring and reporting centrally and locally.

2. Statistical Methods

2.1 Statistical methods for the detection of trends

A trend test is performed for each anomaly subgroup (see Appendix 2) for each registry. A chi squared test for heterogeneity and trend uses the number of cases per year of birth and the number of births per year. The output shows the direction (upward or downward) and slope of any linear trend and the statistical significance (p value). Change over time identified as "heterogeneous" in the output indicates significant non-linear heterogeneity (i.e. the prevalence changes from year to year, but overall does not tend to increase or decrease over time). When non-linear heterogeneity is significant, the trend component of Chi square is not shown. Since the Chi squared test is based on conventional probabilistic statistics, 5% of the output will be statistically significant by chance. Currently, Central Registry performs a trend test for the most recent five years of data, based on the number of cases per year, as well as a trend test for the most recent 10 years (or 6 or 8 years if 10 years are not available), grouping each two year interval. A trend test is not performed if the average expected number of cases per year (or two year interval) is less than 5.

2.2. Statistical methods for the detection of clusters

Cluster detection is based on a moving window test described by Naus and Nagarwalla[1] (see Appendix 1 for statistical details). The method uses a moving window of a given number of cases (window size), measuring the length of time between the first and last case. The method detects whether the given number of cases has occurred in a shorter time than would be expected by chance. The method is not robust with a window size of less than 5 cases. A minimum of 7 cases over the study period of interest is needed to run the analysis. All window sizes from a minimum of 5 to a maximum of the total number of cases minus 2 are tested.

Each registry and anomaly subgroup is tested independently and the analysis takes into account the number of tests with different window sizes being performed within each registry/anomaly combination to allocate a likelihood to each cluster. The method gives each cluster identified a scan statistic called "lambda", from which a p-value for significance is derived (see Appendix 1).

Many clusters may overlap in time, the inclusion or exclusion of individual cases changing their significance. All significant clusters are identified. The "most significant" cluster (lowest p-value) is then identified. All other significant clusters ($p<0.05$) for which at least 75% of cases overlap with the "most significant" cluster are considered to belong to the same cluster group. The method then looks for the second most significant cluster not already allocated to a cluster group and proceeds similarly identifying the

[1] Naus, J.I. (1965). The distribution of the size of the maximum cluster of points on a line. Journal of the American Statistical Association 60, 532-538

Nagarwalla, N. (1996). A scan statistic with a variable window. Statistics in Medicine 15, 845-850

second cluster group. The output identifies the most significant cluster in each cluster group, and the first and last case in time belonging to any cluster within the cluster group.

Following identification of all cluster groups over the time period of analysis, cluster groups overlapping with the last two years of data, and in which the most significant cluster is less than 18 months in length, are chosen for output and investigation. An option is also provided in the software for Central Registry to scan the most significant cluster in all years of data scanned, rather than just the last two years, for research purposes. Similarly, options are available to reset the percentage acceptable for missing gestational age, and cluster lengths greater than 18 months.

Currently Central Registry performs annual cluster analysis using the most recent 5 years of data. More than 5 years may tend to identify trends rather than clusters, and will be computationally slower. Less than 5 years may fail to detect if the most recent years are unusual compared to preceding years.

Since it is exposure during early pregnancy (organogenesis) that is relevant, it is preferable to use estimated date of conception rather than date of birth, Thus cases of different gestational ages (and terminations of pregnancy of low gestational age) are related to a common time when they passed through organogenesis. Cluster detection uses date of conception where gestational age is recorded for more than 90% of cases (for any one anomaly subgroup and registry) allowing its estimation. Where gestational age is missing, it is estimated on the basis of the average gestational age in the registry, by year, anomaly subgroup, and outcome of pregnancy. Gestational age is not estimated if it is missing for more than 10% of cases for the registry and anomaly subgroup, in which case cluster detection is based on date of birth.

Where date of conception is used as a basis for cluster detection, the conception period for statistical monitoring must end 9 months before the last birth month where data collection is complete. Where full years of data are used for surveillance, this means ending the period of the scan at 31 March (date of conception) of the last year of data collected. After this date, some conceptions may result in births in the next year which are not yet included in the dataset. Similarly, the start of the monitoring period must include a complete cohort of conceptions. For simplicity, and to be sure to cover early terminations of pregnancy, the monitoring period is set to start with estimated dates of conceptions from 1 January of the beginning of the five year period.

The Scan method identifies both significant excesses and deficits of cases. Excesses are marked in the output as “clusters”, deficits as “deficits”.

The Scan method is based on case counts, and results would not be valid if there is large underlying change in population (births) size. There are two types of population change: change in geographical area that the registry covers, and large change in birth rate within the same geographical area. When basing cluster detection on conception cohorts, the latter could be easily taken into account by statistical modifications. However, it is the former type of population change that is more frequent, and a decision was therefore

made to exclude registries where population (no. births) change is more than 10% between any two years within the five year period. This is under review.

The data requirements are:

- Full individual dataset including full date of birth (day, month, year), outcome of pregnancy (live/still/TOP), gestational age, malformation codes and their derived anomaly subgroups (see EUROCAT Guide 1.3).
- Population change (no. births) must less than 10% between any two years.

Each dataset used for monitoring should be archived, both by Central Registry and by local registries, as the database is dynamic. Registries should archive a copy of the file transmitted to Central Registry in February of the year of monitoring, and to rename the file eg edmpdata_statmon06. With this file, registries should be able to reproduce Central Registry statistical monitoring results using the EDMP.

2.3 History of changes to the statistical software

- The Adobe files showing graphical representation of clusters now includes a case list showing estimated date of conception, and ordered by date of conception (year 2006 onwards).
- Chromosomal anomalies excluded from the statistical monitoring of non-chromosomal subgroups (year 2005 monitoring onwards)
- Cluster detection run by estimated date of conception, instead of date of birth/delivery, unless date of conception is unavailable. See EUROCAT Statistical Monitoring Protocol http://www.eurocat.ulster.ac.uk/pubdata/Stat-Mon.html. (year 2005 monitoring onwards)
- Instead of just showing the most significant cluster in each anomaly subgroup, we now show all significant clusters, which may overlap in time (year 2005 monitoring onwards)
- Trend detection is now run using 10 years of data (where available), as opposed to 5 years of data. (year 2005 monitoring onwards)
- The output of the trend analysis shows observed cases grouped in 2 year intervals, e.g. 1996-97, 1998-99, 2000-01, 2002-03 and 2004-05. A minimum of 5 EXPECTED cases in each 2 year period is needed to be included in the trend analysis. (year 2005 monitoring onwards)
- The cluster output now includes a summary of trend test results run on the same five years of the cluster monitoring, to establish if a cluster could also be described as a trend. (year 2005 monitoring onwards)
- Heterogeneous large subgroups (e.g. digestive system) are not analysed for clusters. (year 2004 monitoring onwards)
- We only report clusters within or overlapping the last two years of data sent by your registry (i.e. “new” clusters), and only clusters of less than 18 months length.(year 2004 monitoring onwards)

3. Use of the EDMP by local registries

Trend tests.
Registries may wish to use the EDMP to expand the trend tests run centrally e.g. use a different period of years (e.g. since beginning of registry or including a more recent year), or congenital anomaly subgroups outside the selected subgroups for monitoring (these "user defined subgroups" can be defined within the EDMP)

Cluster detection
Local monitoring for clusters can be run more frequently using the most recently ascertained data. As a guide, local registries should run the EDMP statistical monitoring program at least every 6 months and as early as possible after data collection is complete (apart from late diagnosed cases).

Local registries can run cluster detection in geographical sub-areas of their registry area, by using the EDMP "user defined LOCATION subgroup", located under the REPORTS function. Registries must also enter the total births for the user defined registry sub-area.

Local registries can also choose to run cluster monitoring on non-standard anomaly subgroups of interest to them ("user defined subgroups" can be defined within the EDMP).

The time period of the scan is important and may affect the results. The reasons Central Registry has chosen a five year period are given above. Registries scanning more recent data every 6 months are recommended to add the extra months available to the basic 5 year period. Remember that dates of conception end 9 months before the last birth month available. Which clusters are detected and their statistical significance will depend on the number of years scanned, which is an a priori protocol decision to be made before running the software (i.e. do not make the cluster "disappear" or "appear" by trying many different time periods, as this is statistically invalid).

Clusters and trends identified locally should be investigated in the same way as those identified by central monitoring (see section 4), and reported at the following Registry Leaders Meeting and in the Annual Statistical Monitoring Report.

Following preliminary investigations, plausible clusters and trends not resulting from data quality errors can be reported to central registry for communication to all local registries for further investigation. In this way the situation across Europe may be monitored for early detection of possible new teratogens.

4. How to investigate trends and clusters identified by statistical monitoring

See Appendix 4 for examples of the output available describing the results of the statistical monitoring.

The results of all cluster investigations in local registries will be part of our report to the EC and will be available on the open website http://www.eurocat.ulster.ac.uk/pubdata/Stat-Mon.html

Note that clusters arising from statistical monitoring are a special situation. Guidelines for investigating clusters more generally (e.g. those reported to you from the community or health professionals) are part of the EUROCAT Cluster Advisory Service (http://www.eurocat.ulster.ac.uk/clusteradservice.html).

4.1 Guidelines for the preliminary investigation of trends

Concentrate your investigations on the increasing trends. However, reasons for significant non-linear heterogeneity (i.e significant change over time but no overall increase or decrease) can also be of interest, especially in terms of data quality monitoring.

Consider the following, consulting with clinicians or others where appropriate:

- Case verification
  - Confirmed and accurate diagnoses?
  - Duplicates?
  - Resident within region? (truly population-based?)
- Print out a graph of the yearly prevalence (see Appendix 4) - is the trend gradual or a steep change? When does the trend appear to begin?
- Has there been a change in definition or diagnosis, or diagnostic methods e.g. increasing use of prenatal or postnatal ultrasound?
- Have there been changes in how cases are reported to the register?
- Is the trend found across all reporting hospitals?
- Is there a similar trend for any other anomalies?
- Is the trend found in isolated or multiply malformed cases?
- Have there been changes in register population?
- Are there any known changes in the risk factors for this anomaly?
- Have any other registers experienced a similar trend for this anomaly?

4.2 Guidelines for the preliminary investigation of clusters (see also Appendix 3)

- Case verification
  - Confirmed and accurate diagnoses?
  - Duplicates?
  - Resident within region? (truly population-based?)
- Diagnostic dimension:

  - How heterogeneous are the diagnoses? Are cases isolated, multiply malformed, syndromes? Any family history recorded?
  - Do any other anomalies have clusters at the same time?
- Space dimension:
  - Are they clustered near each other within region?
  - Do they come from a single hospital?
  - Do other regions have a cluster at a similar time? (use EUROCAT communication to query other registries).
  - NB. The aim is to describe the cluster in terms of its spatial characteristics, giving clues as to possible causes. For example, a new drug on the market may not show spatial concentration, whereas a local chemical pollution accident would be expected to show spatial concentration.
- Time dimension:
  - Is the cluster part of a longer term trend identified by the trend analysis? (if so, investigate as trend rather than as cluster)
  - When does the increased risk appear to start and end – a longer period than the dates of the most statistically significant cluster itself? Look at other clusters in the cluster group to get an idea of the extent of the cluster.
  - If cluster is based on date of birth rather than date of conception, is it likely, making assumptions about gestational age of cases within and outside the cluster, that the cluster would also appear if analysed by date of conception?
- Aetiological factors:
  - Which factors have been investigated?– choice of factors to investigate depends on type of anomaly
  - Which factors have been looked at within the registry database (list variables) and outside the registry database and do any of these appear to explain the cluster?
- Local context:
  - Was there local awareness of the cluster before it was found by central statistical monitoring, either by local EDMP monitoring or other means?
  - Are there any local concerns about environmental exposures which may need investigation?

If investigation of clusters identifies data errors (e.g. incorrect diagnoses, incorrect dates of birth) these errors should be corrected and updated data included in the next data transmission to Central Registry. A record of these errors should be included in the local cluster report sent to Central Registry (MA.Loane@ulster.ac.uk).

4.3 Reporting

Your report on the preliminary investigation of a trend or cluster should include:

1) The methods and results of case verification.

2) A description of the diagnostic, spatial and time dimensions, answering the questions given above

3) the methods and results of any investigations as to whether changes in diagnostic or reporting practice might have contributed to the cluster;

3) an account of local concerns about exposures and how they came to your attention, and methods and results of any investigations of exposures carried out;

4) whether anyone in your region (e.g. local community or health professional) had previously been aware of the cluster;

5) the basis for your decisions to conduct the investigation in the way you did.

6) What is the next step? Do you consider the trend/cluster "explained" by your preliminary investigation? Does it require a further period of surveillance to verify cause for concern, or do you intend to proceed to an aetiologic or other investigation? Note that guidance on further cluster investigation can be found on www.eurocat.ulster.ac.uk/clusteradservice.html

7)_If your preliminary investigation suggests that the cluster is not explained by data quality diagnostic or ascertainment issues and therefore needs further investigation or surveillance, which appropriate public health authorities have been/or will be notified?

When received by Central Registry, results of preliminary investigations will be summarised in tables as follows:

Classification of preliminary investigations into trends:

- A: Changes in case ascertainment and/or coding
- B: Changes in prenatal detection
- C: Changes in referral to clinics/areas not covered by registry
- D: Changes in definition or inclusion criteria
- E: Changes in use of postnatal echocardiography or ultrasound
- F: Heterogeneous subgroups
- G: Most recent years lower prevalence due to non-inclusion of late diagnosed or late notified cases
- H: Apparent trend, further investigation ongoing, or further surveillance indicated
- I: Continuing trend previously detected and investigated/under investigation
- J: Trend not apparent when more recent years included
- N: No report of preliminary investigations sent to Central Registry

Classification of preliminary investigations into clusters:

- A: Apparent cluster with cause for concern, further investigation ongoing
- B: Not 'true' cluster as associated with aetiologic heterogeneity, changes in diagnosis, familial or twin recurrence

- C: Excess of cases confirmed, but no further investigation proposed other than further surveillance
- D: Increase in cases, due to increasing use of invasive prenatal diagnostic procedures or improvements in prenatal ultrasound detection rates
- E: Data quality issues found to explain cluster
- N: No report of preliminary investigations sent to Central Registry

APPENDIX 1.

Scan statistic – procedure for calculation

Scan statistic formula based on the formula defined by Nagarwalla (1996).

Data
The date for each case is provided. A start and end date are specified and each case date is represented as a fraction of the period of interest.

$$fraction_{case} = \frac{date_{case} - date_{start}}{date_{end} - date_{start}}$$

Methods

Calculation of lambda
For a given subset of cases, it is possible to calculate the test statistic lambda as follows:

$$\lambda = \left(\frac{n}{r}\right)^{n}\left(\frac{r-n}{n}\right)^{r-n}\left(\frac{1}{d}\right)^{n}\left(\frac{1}{1-d}\right)^{r-n}$$

Where r is the total number of cases, n is the number of cases in the subset, also called the scanning window, and d is the date fraction spanned by the subset of cases. Typically a minimum scanning window of 5 is used. Lambda is calculated for every possible subset of n consecutive cases for $n = 5,\ldots, r$

The first step is to generate simulated datasets with random numbers. For each simulation, the lambda for each subset is calculated and the largest lambda is recorded. After, for example, 999 iterations the lambdas are ordered by size from smallest to largest and the 95th percentile is noted as λ_{sig}. In order to save computing time, and to give accurate p-values based on sufficient iterations, a look-up table was created for all r between 7 and 700 cases, using 100,000 iterations for r under 200 cases and 50,000 iterations for r over 200 cases. For r of more than 700 cases, Monte Carlo simulations (999 iterations) are used to create an array of lambdas.

For the real dataset, the lambda for each subset of cases is calculated. If the lambda is greater than or equal to λ_{sig} then the cases are designated as a significant cluster and the details of the cluster, such as start date and duration, are recorded. The p-value is recorded as the position of lambda within the simulated lambdas.

As a first step, a 'quick' check is performed to test whether the most significant cluster is significant at p<=0.1. If no significant cluster, then move on to next anomaly subgroup. If significant cluster is found then a full check is performed for all clusters with a p-value less than 0.06.

Group allocation
The final step is to allocate clusters to groups based on their overlap. The cluster with the largest lambda is identified and is allocated to the first group. Each ungrouped cluster is then tested for overlap with the first cluster. Overlap is calculated as the number of cases appearing in both

clusters divided by the number of cases appearing in either cluster. If the overlap is greater than or equal to 0.75 then both are given the same group label. If any clusters remain ungrouped then the cluster with the largest lambda is identified and given a new group label and the procedure is repeated until all clusters are grouped.

Nagarwalla, N. (1996). A scan statistic with a variable window. Statistics in Medicine 15, 845-850

APPENDIX 2.

List of congenital anomaly subgroups for monitoring.

The EUROCAT congenital anomaly subgroups are defined in EUROCAT Guide 1.3, Chapter 3.3 (http://www.eurocat.ulster.ac.uk/pdf/EUROCAT-Guide-1.3.pdf). The following list shows which subgroups are to be analysed in the following ways:

1. Prevalence by outcome of pregnancy, by registry and year (or combined registries/years). All cases, and all cases excluding chromosomal cases.
2. Analysis of trends, all outcomes of pregnancy combined. Chromosomal cases excluded from all subgroups except chromosomal subgroups.
3. Detection of clusters, all outcomes of pregnancy combined. Chromosomal cases excluded from all subgroups except chromosomal subgroups.

	Prevalence by pregnancy outcome, registry, year	Included in cluster analysis	Included in trend analysis
All anomalies	X		X
Nervous system	X		X
Neural Tube Defects	X	X	X
Anencephalus and similar	X	X	X
Encephalocele	X	X	X
Spina Bifida	X	X	X
Hydrocephaly	X	X	X
Microcephaly	X	X	X
Arhinencephaly/ holoprosencephaly	X	X	X
Eye	X		X
Anophthalmos/ micropthalmos	X	X	X
Anophthalmos	X	X	X
Congenital cataract	X	X	X
Congenital glaucoma	X	X	X
Ear, face and neck	X		X
Anotia	X	X	X
Congenital heart disease	X		X
Common arterial truncus	X	X	X
Transposition of great vessels	X	X	X
Single ventrical	X	X	X
Ventricular septal defect (VSD)	X	X	X
Atrial septal defect (ASD)	X	X	X
Atrioventricular septal defect (AVSD)	X	X	X
Tetralogy of Fallot	X	X	X
Tricuspid atresia and stenosis	X	X	X
Ebstein's anomaly	X	X	X
Pulmonary valve stenosis	X	X	X
Pulmonary valve atresia	X	X	X
Aortic valve atresia/stenosis	X	X	X
Hypoplastic left heart	X	X	X
Hypoplastic right heart	X	X	X
Coarctation of aorta	X	X	X
Total anomalous pulmonary venous return	X	X	X
Respiratory	X		X

Choanal atresia	X	X	X
Cystic adenomatous malf of lung	X	X	X
Oro-facial clefts	X		X
Cleft lip with or without palate	X	X	X
Cleft palate	X	X	X
Digestive system	X		X
Oesophageal atresia with/ without tracheo-oesophagal fistula	X	X	X
Duodenal atresia or stenosis	X	X	X
Atresia or stenosis of other parts of small intestine	X	X	X
Ano-rectal atresia and stenosis	X	X	X
Hirschsprung's disease	X	X	X
Atresia of bile ducts	X	X	X
Annular pancreas	X	X	X
Diaphragmatic hernia	X	X	X
Abdominal wall defects	X		X
Gastroschisis	X	X	X
Omphalocele	X	X	X
Urinary	X		X
Bilateral renal agenesis including Potter syndrome	X	X	X
Cystic kidney disease	X	X	X
Congenital hydronephrosis	X	X	X
Bladder extrophy and/or epispadia	X	X	X
Posterior urethral valve and/or prune belly	X	X	X
Genital	X		X
Hypospadias	X	X	X
Indeterminate sex	X	X	X
Limb	X		X
Limb reduction	X	X	X
Upper limb reduction	X	X	X
Lower limb reduction	X	X	X
Complete absence of a limb	X	X	X
Club foot - talipes equinovarus	X	X	X
Hip dislocation and/or dysplasia	X	X	X
Polydactyly	X	X	X
Syndactyly	X	X	X
Arthrogryposis multiplex congenita	X	X	X
Musculo-skeletal	X		X
Thanatophoric dwarfism	X		X
Jeunes syndrome	X		X
Achondroplasia	X		X
Craniosynostosis	X	X	X
Congenital constriction bands/amniotic band	X	X	X
Other malformations	X		X
Asplenia	X	X	X
Situs inversus	X	X	X
Conjoined twins	X	X	X
Disorders of skin	X	X	X
Teratogenic syndromes with malformations	X		X
Fetal alcohol syndrome	X	X	X
Valproate syndrome	X	X	X
Warfarin syndrome	X	X	X
Maternal infections resulting in malformations	X	X	X
Genetic syndromes & microdeletions	X		X

Chromosomal	X		X
Down's syndrome	X	X	X
Patau syndrome/ trisomy 13	X	X	X
Edward syndrome/ trisomy 18	X	X	X
Turner's syndrome	X	X	X
Klinefelter's syndrome	X	X	X
Cri-du-chat syndrome	X	X	X
Wolff-Hirschorn syndrome	X	X	X

APPENDIX 3

Investigating a cluster of birth defects
Elisabeth Robert-Gnansia, Lyon FRANCE

Investigations vary according to the anomaly of interest and local conditions. Elisabeth Robert has prepared notes to guide investigations of clusters arising from statistical monitoring, based on long experience in the Central East France register and elsewhere.

A cluster can be defined as a space-time aggregation of occurrences, in this context of birth defects. An example of such a cluster is the occurrence of 5 infants with a given malformation born in a geographic area during 4 months and with 3,000 annual births. If the overall rate for this malformation in the region is 1/6,000, it means that the expected number of cases during the 4 months is 0.17, and 5 were found. Such aggregations can have many causes. The reason for being interested in them is that the cases may have been caused by some local source of exposure. One often thinks of industrial pollution as a cause, but other factors may explain the cluster, including many artefactual events.

Clusters may be identified as a local observation by people living in a specific area, by health care workers, or by the routine surveillance of congenital malformations or other pregnancy outcomes. In rare cases, the detection of a cluster is forwarded from the news media, or a pressure group who may perceive that a specific source of pollution may cause birth defects and therefore a cluster must have occurred around that source. It then becomes our responsibility to investigate the identified cluster. Some review articles and papers on statistical methodology have questioned the usefulness of investigating clusters, and of monitoring programs in general for the detection of a newly introduced teratogen.

There are many arguments against cluster investigations. First, there is a great statistical probability that many clusters occur by chance alone, because there are many serious congenital malformations monitored routinely and repeated evaluations. Second, in evaluating situations in which an environmental agent has been evidenced as harmful, it appears that most clusters have occurred in areas where no registry was operative or where the hypothesis came from observations made by astute clinicians. Third, clusters are often alleged in relationship to a perceived environmental hazard, such as a toxic waste site, and the investigating team often must extend the investigation far beyond what is indicated scientifically in order to respond to community concerns.

Among the possible explanations for a cluster, one thinks first of a local harmful factor, but the actual cause may be different: local temporal variations in diagnosis, in ascertainment, local aggregation of genes, e.g. due to population migrations, demographic or socioeconomic variations, and finally a random phenomenon. Clusters are different to long time trends: a steep increase of urinary flow anomalies has occurred from the early 1980s, obviously due to better and earlier diagnosis through fetal ultrasonography. After having excluded all artefactual explanations, sometimes one nevertheless may be unable to answer the question "Is there a cluster?"

Examples can be given of surveillance events that may or may not be clusters: a marked increase in the prevalence at birth of hypospadias was observed in several registries in the world from the end of the 1980s, but no clear cut explanation can be given: improved ascertainment of minor forms or real increase? An sharp increase of the incidence of gastroschisis has been observed as well in many western registries since the beginning of the 90s, the reality of which is much less questionable than the one of hypospadias, but no explanation has been found so far.

When a cluster is considered as likely, other questions are to be answered:

1. To follow up or not to follow up? The decision to follow-up means spending time and money, and run the risk of spreading rumours.

2. How to follow up?

This should be performed in 4 stages, which might be called (a) nosodetermination, (b) chronodetermination, (c) geodetermination, (d) etiodetermination.

The first stage (*nosodetermination*) consists in confirming the case status, with exact diagnoses, and definition of inclusion and exclusion criteria: it should be checked that the cluster is not due to inclusion of minor forms of the studied malformations, which were not included in the baseline data. This is especially true for limb reduction defects (inclusions of missing phalanges?) or hypospadias (distal forms). Also diagnostic methods or medial personnel might have changed (e.g. more trained ultrasonographist or neonatologist), and explain an increased number of cases.

The second stage (*chronodetermination*) consists in checking the clustering in time: dates of birth or of termination of pregnancy are to be clearly assessed. Gestational ages are to be taken into consideration, especially when dealing with a cluster arising over a short period of time.

The third stage (*geodetermination*) should check the clustering in space. Some malformed babies might be transferred in utero for a better management of a surgical malformation at birth. One should then eliminate the possibility of a concentration of cases in university hospitals that attract patients with rare malformations, by assessing correctly the place where the child's family actually lived during pregnancy.

The fourth stage (*etiodetermination*) is the most difficult one, and consists in collecting detailed exposure information on cluster cases. A more detailed form than the routine one is to be used in order to collect all this information. If an environmental exposure is suspected, one should try to study similarly exposed areas, and to set up a case-control study within the area (3). In any case, it is essential to continue the surveillance.

The experience of registries that have investigated numerous clusters of congenital malformations shows that:

- Clusters will occur and will be found if looked for
- Most clusters have technical explanations or are artefacts
- Most clusters will go away when you look them “in the eyes”
- Nevertheless, clusters may be important for the identification of hazards in the environment and we have to investigate them

To decide whether one should follow up a cluster or not is difficult and depends mainly on available resources. If one investigates a cluster, most likely no explanation will be found. A unique example of a routine cluster investigation that led to an environmental factor as a possible explanation is given by a study led in the county of Östergötland, in Sweden. A higher prevalence at birth of congenital malformations was noticed (1), and looking at data revealed that cardiovascular malformations (CVM) explained the differences in rates. A case-referent study was performed (2), which retrieved several known risk factors for CVM (maternal diabetes, body mass index over 29, involuntary childlessness, previous spontaneous abortion, first trimester exposure to thyroid drugs and NSAIDs). All the significantly high ORs were higher in the studied county than in the rest of Sweden. Geographic comparisons of CVM were made within the county (3), and the hypothesis arose that the clustering in time and space showed that drinking water chlorination might be a mild risk factor for CVM (4).

Acknowledgement
This summary was adapted from a lecture by Pr Bengt Källén (Lund), with permission.

References
1. Blomberg M, Selbing A, Kallen B.Congenital malformations in the southeast of Sweden--a registry study with validation. Acta Paediatr. 2000 Oct;89(10):1238-43 2. Cedergren MI, Selbing AJ, Kallen BA. Risk factors for cardiovascular malformation--a study based on prospectively collected data. Scand J Work Environ Health. 2002;28:12-7.
3. Cedergren M, Selbing A, Kallen B. Geographic variations in possible risk factors for severe cardiac malformations. Acta Paediatr. 2002;91:222-8.
4. Cedergren MI, Selbing AJ, Lofman O, Kallen BA. Chlorination byproducts and nitrate in drinking water and risk for congenital cardiac defects. Environ Res. 2002;89:124-30.

APPENDIX 4.

EUROCAT Data Management Program (EDMP) output – an explanation

For each registry, the results are output in:

I. An EXCEL file containing 4 worksheets (Read me, Trend, Trend2, Clusters). This must be examined first. See Figure 1a.
II. An Adobe file ("Registry name_tr graphs") containing graphs of anomaly subgroups with significant trends. See Figure 2
III. An Adobe file ("Registry name_cluster cases") containing a full case list of cases within the subgroup where a cluster was identified. See Figure 3.

I. EXCEL file:

It is important to read the EXCEL "Read me" instructions (first Sheet, see Figure 1a), as this explains some of the key elements of the Statistical Monitoring exercise.

The second sheet "Trend" shows the five year trend results. Output is in the same format as explained below for "Trend2".

Ten year trend analysis results are in the third sheet "Trend2" (see Figure 1b) – output shows:

i. the number of cases per subgroup per 2 year period, and the total number of cases over the time period.
ii. A Chi square test for trend and direction of significant trend (increasing linear / decreasing linear or non-linear heterogeneous) is presented.
iii. If trend is significant, the statistical significance level (probability) is reported.
iv. The last column shows the change in rate over the period.

Cluster analysis results are in the fourth sheet "Clusters" (Figure 1c).

i. Type of cluster analysis run (date of conception or date of birth), the number of cases in the most significant cluster, the start and end date of most significant cluster, the number of expected cases in the time period of the most significant cluster, and the level of statistical significance (p-value and lamda)
ii. The total number of valid cases within the subgroup (i.e. must have valid date of birth) and the proportion of cases with missing gestational age is presented.
iii. The next column explains if an excess of cases was reported (cluster) or if less cases than expected were reported (deficit)
iv. The last column shows the trend test result run on the same five years of the cluster monitoring, to establish if the cluster may be part of an overall trend.

II. Adobe file " Registry name_tr graphs" shows graphical displays of significant trends. See Figure 2 below.

III. Adobe file "Registry name_cluster cases" gives more detail on all significant clusters. See Figure 3.

i. ALL cases in the anomaly subgroup both within and outside cluster are listed with local ID, date of conception, date of birth, gestational age (GA), estimated GA, and day case occurred.

ii. Lambda values for the most significant cluster are listed, along with the lambda values for all possible overlapping clusters. The highest lambda value indicates the most unusual cluster.

iii. Many clusters may overlap in time, with the inclusion or exclusion of individual cases changing their significance. The "most" significant cluster (highest "lambda" value) is listed first, followed by all significant clusters, with "cluster group" showing groups of highly overlapping clusters.

iv. A timeline shows the occurrence of all cases within the anomaly subgroup over the time period. A solid line displays the most significant cluster within the time period with a dotted line on either side showing the longest extent of the cluster group.

v. It is important to remember that if a cluster is detected using DATE OF CONCEPTION, the timeline represents the date of conception of those cases.

Figure 1a: EXCEL file showing output of Statistical Monitoring.

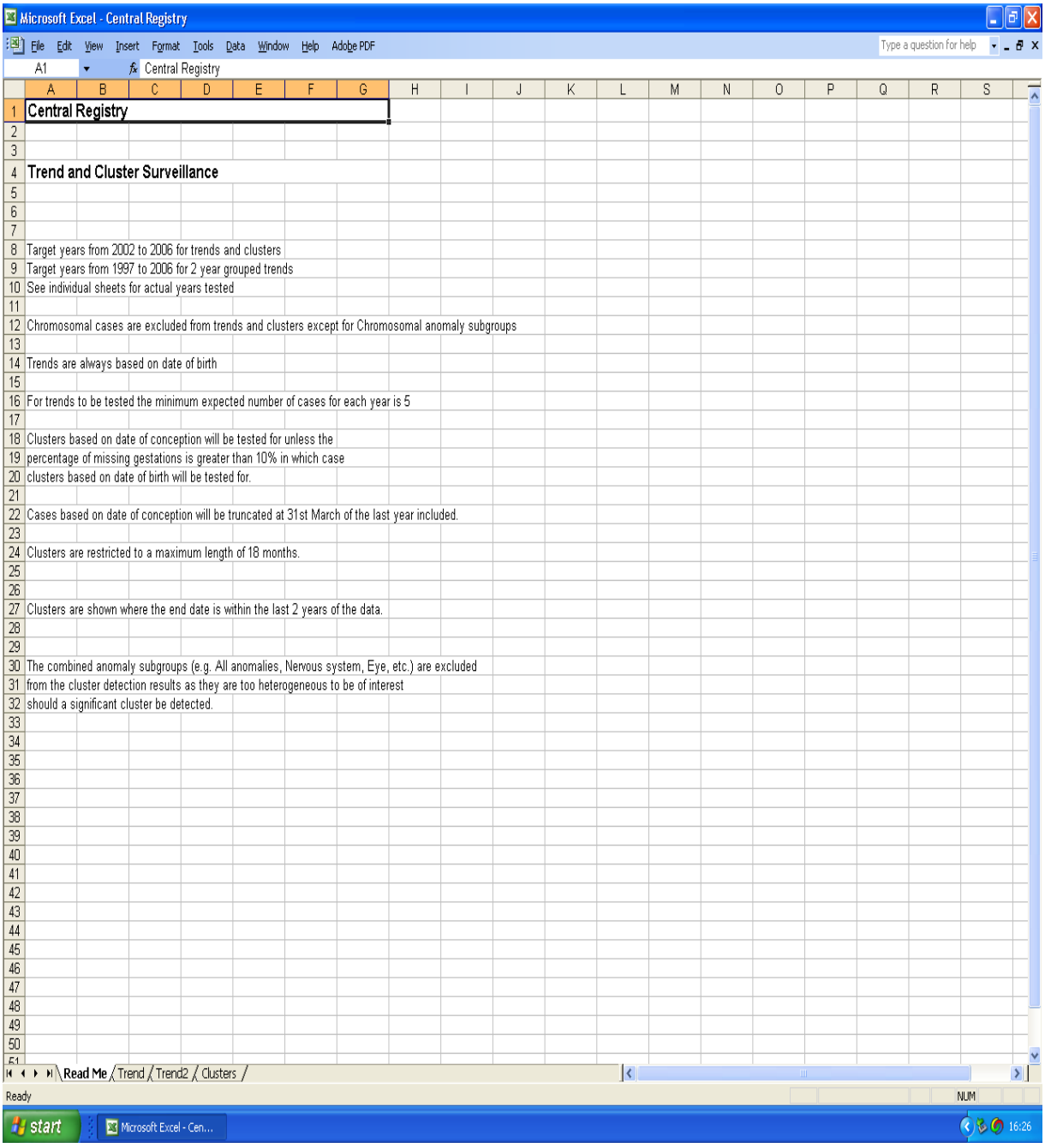
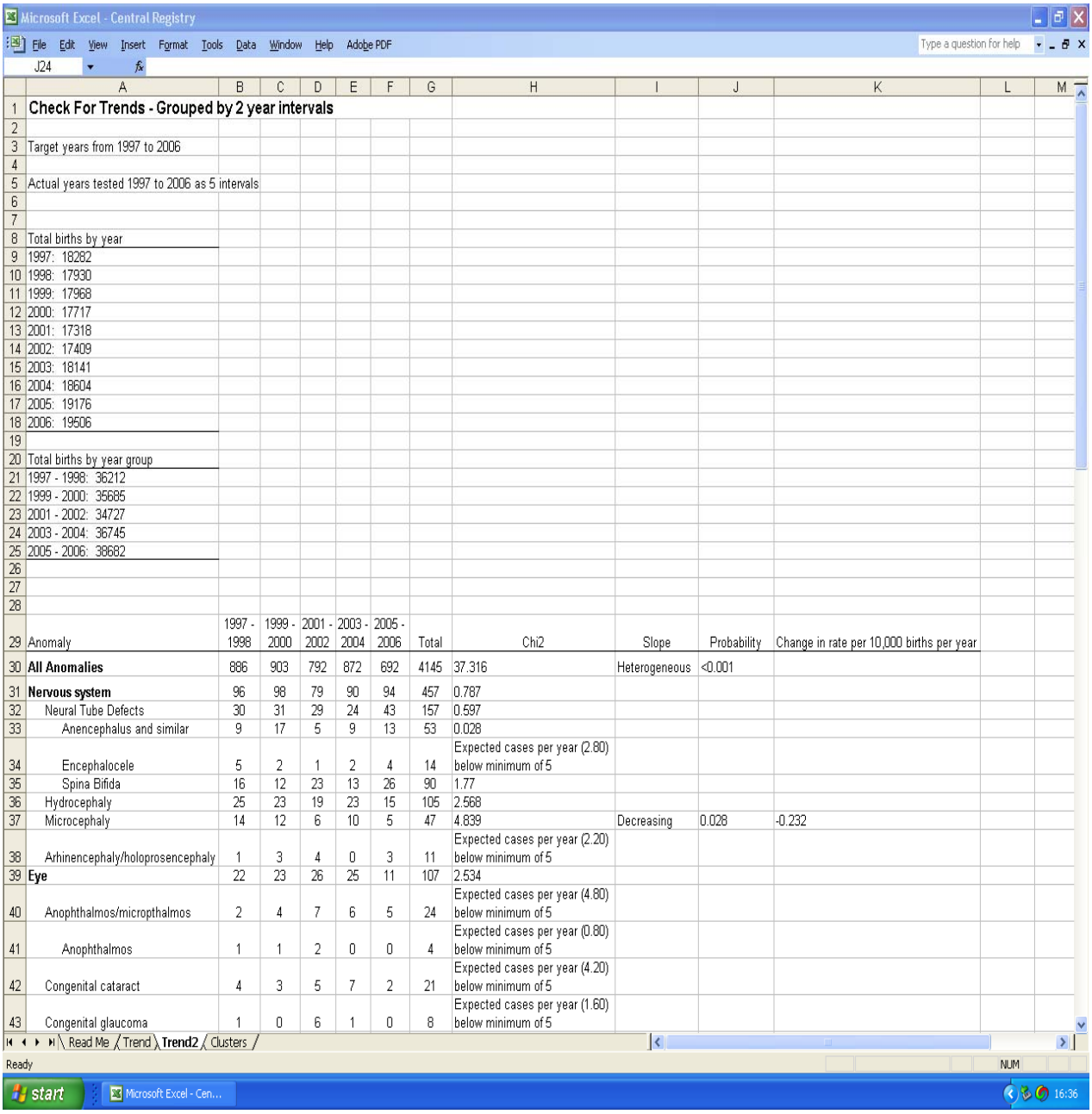


Figure 1b: EXCEL output showing the results of the trend test analyses.



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	A	B	C	D	E	F	G	H	I	J	K	L	M
1	**Check For Trends - Grouped by 2 year intervals**												
2													
3	Target years from 1997 to 2006												
4													
5	Actual years tested 1997 to 2006 as 5 intervals												
6													
7													
8	Total births by year												
9	1997: 18282												
10	1998: 17930												
11	1999: 17968												
12	2000: 17717												
13	2001: 17318												
14	2002: 17409												
15	2003: 18141												
16	2004: 18604												
17	2005: 19176												
18	2006: 19506												
19													
20	Total births by year group												
21	1997 - 1998: 36212												
22	1999 - 2000: 35685												
23	2001 - 2002: 34727												
24	2003 - 2004: 36745												
25	2005 - 2006: 38682												
26													
27													
28													
29	Anomaly	1997 - 1998	1999 - 2000	2001 - 2002	2003 - 2004	2005 - 2006	Total	Chi2	Slope	Probability	Change in rate per 10,000 births per year		
30	**All Anomalies**	886	903	792	872	692	4145	37.316	Heterogeneous	<0.001			
31	**Nervous system**	96	98	79	90	94	457	0.787					
32	Neural Tube Defects	30	31	29	24	43	157	0.597					
33	Anencephalus and similar	9	17	5	9	13	53	0.028					
34	Encephalocele	5	2	1	2	4	14	Expected cases per year (2.80) below minimum of 5					
35	Spina Bifida	16	12	23	13	26	90	1.77					
36	Hydrocephaly	25	23	19	23	15	105	2.568					
37	Microcephaly	14	12	6	10	5	47	4.839	Decreasing	0.028	-0.232		
38	Arhinencephaly/holoprosencephaly	1	3	4	0	3	11	Expected cases per year (2.20) below minimum of 5					
39	**Eye**	22	23	26	25	11	107	2.534					
40	Anophthalmos/micropthalmos	2	4	7	6	5	24	Expected cases per year (4.80) below minimum of 5					
41	Anophthalmos	1	1	2	0	0	4	Expected cases per year (0.80) below minimum of 5					
42	Congenital cataract	4	3	5	7	2	21	Expected cases per year (4.20) below minimum of 5					
43	Congenital glaucoma	1	0	6	1	0	8	Expected cases per year (1.60) below minimum of 5					

Read Me | Trend | Trend2 | Clusters

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Figure 2: Graphical representation of trend surveillance

Trend Surveillance

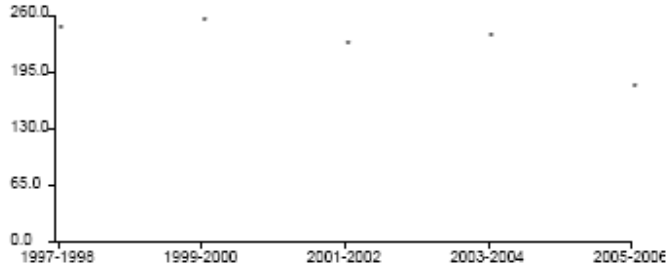
Significant trends found between 1997 and 2006

Anomaly Subgroup: **All Anomalies**

Chi2	37.316
p value	<0.001
Slope	Heterogeneous

Year groups:	Cases:	Total births:
1997 - 1998	886	36212
1999 - 2000	903	35685
2001 - 2002	792	34727
2003 - 2004	872	36745
2005 - 2006	692	38682

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



Anomaly Subgroup: **Microcephaly**

Chi2	4.839
p value	0.028
Slope	Decreasing
Rate of change	-0.232 (Cases per 10,000 births per year)

Year groups:	Cases:	Total births:
1997 - 1998	14	36212
1999 - 2000	12	35685
2001 - 2002	6	34727
2003 - 2004	10	36745
2005 - 2006	5	38682

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth

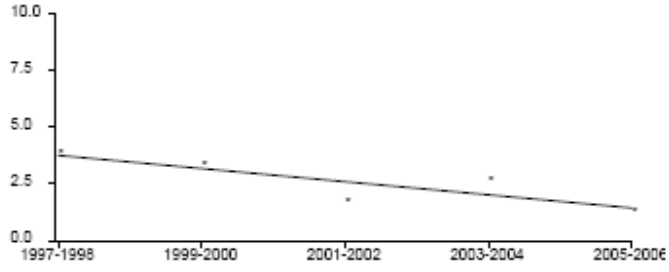
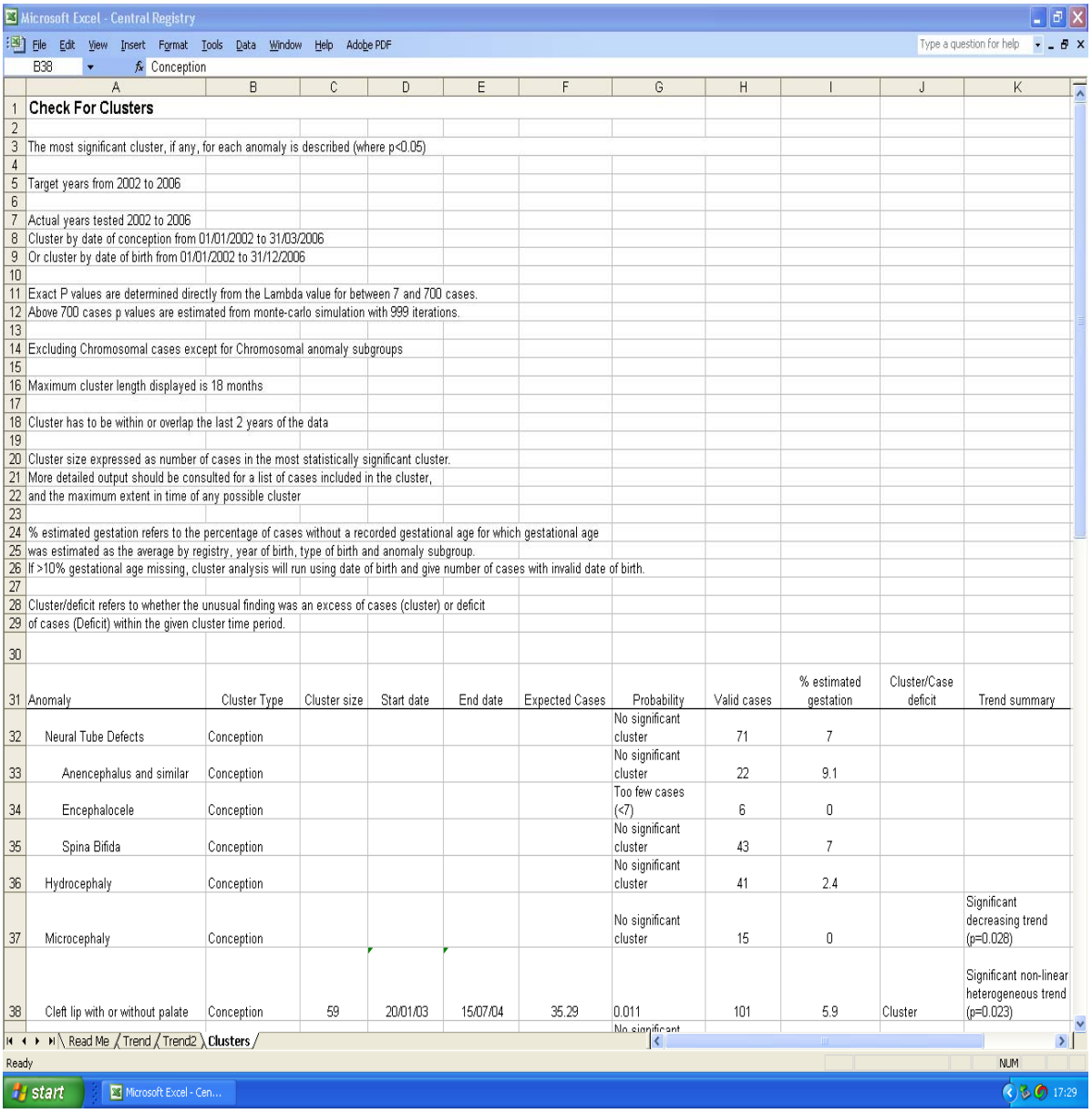


Figure 1c: EXCEL output showing the results of the cluster monitoring



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B38 Conception

Check For Clusters

The most significant cluster, if any, for each anomaly is described (where p<0.05)

Target years from 2002 to 2006

Actual years tested 2002 to 2006
Cluster by date of conception from 01/01/2002 to 31/03/2006
Or cluster by date of birth from 01/01/2002 to 31/12/2006

Exact P values are determined directly from the Lambda value for between 7 and 700 cases.
Above 700 cases p values are estimated from monte-carlo simulation with 999 iterations.

Excluding Chromosomal cases except for Chromosomal anomaly subgroups

Maximum cluster length displayed is 18 months

Cluster has to be within or overlap the last 2 years of the data

Cluster size expressed as number of cases in the most statistically significant cluster.
More detailed output should be consulted for a list of cases included in the cluster,
and the maximum extent in time of any possible cluster

% estimated gestation refers to the percentage of cases without a recorded gestational age for which gestational age
was estimated as the average by registry, year of birth, type of birth and anomaly subgroup.
If >10% gestational age missing, cluster analysis will run using date of birth and give number of cases with invalid date of birth.

Cluster/deficit refers to whether the unusual finding was an excess of cases (cluster) or deficit
of cases (Deficit) within the given cluster time period.

Anomaly	Cluster Type	Cluster size	Start date	End date	Expected Cases	Probability	Valid cases	% estimated gestation	Cluster/Case deficit	Trend summary
Neural Tube Defects	Conception					No significant cluster	71	7		
Anencephalus and similar	Conception					No significant cluster	22	9.1		
Encephalocele	Conception					Too few cases (<7)	6	0		
Spina Bifida	Conception					No significant cluster	43	7		
Hydrocephaly	Conception					No significant cluster	41	2.4		
Microcephaly	Conception					No significant cluster	15	0		Significant decreasing trend (p=0.028)
Cleft lip with or without palate	Conception	59	20/01/03	15/07/04	35.29	0.011	101	5.9	Cluster	Significant non-linear heterogeneous trend (p=0.023)

Read Me | Trend | Trend2 | Clusters

Ready NUM

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Figure 3: Adobe File "Registry name_cluster cases". Graphical representation of detected clusters.

Anomaly Subgroup: **Asplenia**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2002 and 31/03/2006
Most significant cluster
Number of cases: 7 Expected number of cases: 1.603 p value: 0.037
Start date: 05/06/2005
End date: 17/01/2006

Record	Date of conception	Days	Date of birth	Gestation	GA estimated	Local ID
1	16/08/2002	227	24/01/2003	23	☐	200329036
2	12/11/2003	680	04/08/2004	38	☐	200430056
3	27/01/2004	756	03/08/2004	27	☐	200437120
4	25/05/2004	875	22/02/2005	39	☐	200536302
5	05/06/2005	1251	19/02/2006	37	☐	200626028
6	26/06/2005	1272	25/12/2005	26	☐	200526113
7	18/07/2005	1294	09/01/2006	25	☐	200537004
8	23/07/2005	1299	28/01/2006	27	☐	200629003
9	12/09/2005	1350	09/01/2006	17	☐	200629001
10	30/12/2005	1459	02/06/2006	22	☐	200538077
11	17/01/2006	1477	16/05/2006	17	☐	200538070

Lambda:	No cases:	expected:	Start case:	Start date:	End date:	p value:	cluster group:	Type
990.71	7	1.6	5	05/06/2005	17/01/2006	0.037	1	Cluster
714.34	5	0.7	5	05/06/2005	12/09/2005	0.042	2	Cluster

Distribution of cases

* = cases with gestation entered, ? = cases with estimated gestation

Tick marks for the 1st of each month.
Solid line represents span of most significant cluster, dotted lines indicate span of cases in clusters of the same group.