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ORIGINAL REPORT

The potential of the European network of congenital anomaly registers (EUROCAT) for drug safety surveillance: a descriptive study[†]

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SUMMARY

Background European Surveillance of Congenital Anomalies (EUROCAT) is a network of population-based congenital anomaly registries in Europe surveying more than 1 million births per year, or 25% of the births in the European Union. This paper describes the potential of the EUROCAT collaboration for pharmacoepidemiology and drug safety surveillance.

Methods The 34 full members and 6 associate members of the EUROCAT network were sent a questionnaire about their data sources on drug exposure and on drug coding. Available data on drug exposure during the first trimester available in the central EUROCAT database for the years 1996–2000 was summarised for 15 out of 25 responding full members.

Results Of the 40 registries, 29 returned questionnaires (25 full and 4 associate members). Four of these registries do not collect data on maternal drug use. Of the full members, 15 registries use the EUROCAT drug code, 4 use the international ATC drug code, 3 registries use another coding system and 7 use a combination of these coding systems. Obstetric records are the most frequently used sources of drug information for the registries, followed by interviews with the mother. Only one registry

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uses pharmacy data. Percentages of cases with drug exposure (excluding vitamins/minerals) varied from 4.4% to 26.0% among different registries. The categories of drugs recorded varied widely between registries.

Conclusions Practices vary widely between registries regarding recording drug exposure information. EUROCAT has the potential to be an effective collaborative framework to contribute to post-marketing drug surveillance in relation to teratogenic effects, but work is needed to implement ATC drug coding more widely, and to diversify the sources of information used to determine drug exposure in each registry. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS — pregnancy; congenital anomalies; drug exposure; post-marketing surveillance

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INTRODUCTION

Population-based registries of congenital anomalies in the European Union collaborate in European Surveillance of Congenital Anomalies (EUROCAT)^{1,2} which collects data on more than 1 million births per year, over 25% of all births in Europe. A sister organisation operating worldwide is the International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS).³ Many of the congenital anomaly registries were initiated following the thalidomide disaster in the 1960s, resulting in more than 5000 infants with severe birth defects worldwide.⁴ In order to detect new teratogens as early as possible, registries could on the one hand detect trends or clusters in the frequency of congenital anomalies and on the other hand look directly at drug exposure by recording the drugs used during pregnancy.^{5–7} One would intuitively expect that collaborative networks such as EUROCAT and ICBDMS to increase the statistical power of any analyses.

While some of the registries participating in ICBDMS (including some EUROCAT registries) collaborate to monitor associations between drugs and malformations,⁷ the EUROCAT central database has been less systematically used,^{8,9} and awaits full exploitation. Individual EUROCAT registries have investigated drug exposures in relation to birth outcomes.^{10–13} The aim of this study was to assess the EUROCAT database as a resource for pharmacovigilance studies, and to assess what changes are required to provide EUROCAT with a stronger role in drug safety surveillance in the future.

MATERIALS AND METHODS

In November 2003, the EUROCAT central database consisted of data from 40 registers, 34 full members

contributing individual data to the central database, and 6 associate members contributing only to the aggregate number of cases. All registries are population based with geographically defined populations. The registries are based on multiple sources of information and include information about livebirths, stillbirths and terminations of pregnancy. All structural malformations, syndromes and chromosomal anomalies are included in the database. Minor malformations are excluded according to a specified list of exclusions.¹⁴ The methods for case ascertainment of EUROCAT are described elsewhere.¹⁵

A questionnaire was sent to the registries requesting information on their source of data for drug exposure (mother, medical or pharmacy data), on prospective and/or retrospective collected data, the kind of data available (name of the drug, dose, frequency, etc.), and if there is the possibility to go back to records or parents in case additional information is needed. If information on drug exposure was collected, we asked which system was used for coding the data. The options were (i) the EUROCAT coding system with 23 codes dividing all drugs into groups (Table 1), (ii) the ATC coding system (Anatomical Therapeutic Chemical) which is the WHO hierarchical system allowing any level of drug specificity to be coded and/or analysed, or (iii) a unique coding system of the registry itself. We also asked whether data on drug exposure of non-malformed births was also recorded.

The first trimester drug exposure data obtained from the responders, which was available in the central EUROCAT database was summarised for the years 1996–2000. Drug exposure in the first trimester can be completed on a per case basis with space for a maximum of three different EUROCAT drug groups to be recorded (Table 1).¹⁴ If all three fields were empty, data was considered to be missing. A case was considered exposed during the first trimester if at least

Table 1. EUROCAT codes for drug groups (EUROCAT Guide 1.2¹⁴)

00	No drugs
01	Atropinics and antispasmodics
02	Anaesthetics, local and general
03	Hypnotics, sedatives and psychotropics
04	Antiepileptics
05	Analgesics, antipyretics and antiinflammatory agents
06	Histamine antagonists
07	Antiasthmatic agents incl. methylxanthines
08	Antiarrhythmic and antihypertensive agents
09	Diuretics
10	Tocolytics
11	Antiseptics, antibiotics, viral, parasitic, fungal agents
12	Antiproliferative and immunosuppressive agents
13	Anticoagulant, antithrombotic and thrombolytic drugs
14	Thyroid and antithyroid drugs
15	Oestrogens, progestagens, androgens, inclusive contraceptives
16	Adrenocortical steroids
17	Insulin and oral hypoglycemic agents
18	Vaccins
19	Vitamins and minerals
88	Other
98	Drug(s) taken but no information available
99	Not known

one drug group was reported, including vitamins and minerals or otherwise mentioned. In addition, there were also three associated text fields that could be used to provide more detailed information, if available. If registries did not work with the EUROCAT drug codes they could use these text fields, but only the 15 registries providing EUROCAT drug codes were analysed.

RESULTS

Of the 40 registries that were invited to participate in this study, 29 (25 full members and 4 associate members) replied to our questionnaire (response 73%). Four of these responders (Styria, Trent, Wessex and Oxford) do not collect data on maternal drugs at all and were therefore excluded from further analysis. Of the remaining 25 useable responses from registries, data sources of drug information and the used coding systems are shown in Table 2 and 3. We also examined the EUROCAT central database for the non-respond-

Table 2. Sources for drug exposure information as stated in the questionnaires (25 registries)

Registry	Recorded before birth (prospectively)				Recorded after birth (retrospectively)	
	Obstetric record	Midwife record	GP record	Pharmaceutical record	Questionnaire mother	Interview mother
Full members						
Antwerp (Belgium)	X	—	X	—	—	—
Zagreb (Croatia)	X	—	X	—	—	—
Odense (Denmark)	X	X	X	—	—	—
Strasbourg (France)	X	X	—	—	—	X
Paris (France)	X	X	—	—	—	—
Mainz (Germany)	X	X	—	—	—	—
Cork & Kerry (Ireland)	X	—	X	—	—	—
Dublin (Ireland)	X	—	—	—	—	—
Emilia Romagna (Italy)	—	—	—	—	X	—
North East Italy	—	—	—	—	—	X
South-East Sicily (Italy)	—	—	—	—	—	X
Tuscany (Italy)	—	—	—	—	—	X
Malta	X	—	—	—	—	Sometimes
Northern Netherlands	—	—	—	X	X	X
Southern Portugal	X	—	—	—	—	X
Asturias (Spain)	X	X	—	—	—	X
Basque Country (Spain)	X	X	—	—	—	—
El Valles (Spain)	X	—	—	—	X	X
Vaud (Switzerland)	X	—	X	—	—	—
Glasgow (UK:Scotland)	X	—	—	—	—	—
North Thames (UK:England)	X	X	—	—	—	—
Associate members						
Finland	X	—	X	—	—	—
Central-East France	—	—	—	—	X	X
Norway	—	X	—	—	—	X
ECEMC (Spain)	—	—	—	—	—	X

Table 3. Coding systems used by EUROCAT registries participating in this study, as reported in the questionnaires (25 registries)

Registry	Coding system used since 1990			
	EUROCAT		ATC Own coding	
	Numeric	Text		
Full members				
Antwerp (Belgium)	X	X		
Zagreb (Croatia)	X	X		
Odense (Denmark)	X	X		
Strasbourg (France)	X			
Paris (France)			X*	X*
Mainz (Germany)	X	X		X**
Cork & Kerry (Ireland)	X			X***
Dublin (Ireland)			X	
Emilia Romagna (Italy)	X			X
North East Italy			X	
South-East Sicily (Italy)				X†
Tuscany (Italy)	X			
Malta	X			
Northern Netherlands		X	X	
Southern Portugal	X			
Asturias (Spain)	X	X		
Basque Country (Spain)	X‡	X‡	X‡	
El Valles (Spain)	X	X		
Vaud (Switzerland)	X	X		
Glasgow (UK, Scotland))	X			
North Thames (UK, England)				X
Associate members				
Finland	X	X	X	X
Central East France			X	
Norway			X	
ECEMC (Spain)				X

*Own coding until 2000, based on DCI which can be easily translated into ATC-codes; ATC since 2001.

**Own Coding of 36 groups and specific drugs.

***Actual drug is noted.

†Drug description, no code.

‡90–98 ATC codes used; 99-present EUROCAT numeric and text codes.

ing registries and found 6 out of 11 non-responders had coded drug data.

Seventeen registries (68%) use obstetric or midwife records as source of information on drug exposure. Interview or questionnaire with the mother is the second most used source of information (13, 52%). Northern Netherlands is the only registry that uses pharmacy data. The majority of registries (18, 72%) use more than one source to obtain information about drug use during pregnancy.

Most registries use the EUROCAT drug codes (Table 3). ATC-codes are used by Paris, Dublin, North East Italy, Northern Netherlands, Basque Country (until 1998) Finland, Central East France and Norway.

Sicily, ECEMC, and North Thames use their own coding system. Emilia Romagna (Italy) and Mainz (Germany) use their own codes in addition to the EUROCAT codes. Drug information on non-malformed births is collected in four registries, Strasbourg, Mainz, ECEMC and Asturias.

Since the central EUROCAT database only contains information on drugs of full members using the EUROCAT coding, 15 responding registries fulfil both criteria and their information about the drugs registered are presented in Table 4 and 5. From 1996 to 2000 a total of 2771 out of 18 576 cases (12.2%) were recorded with at least one drug group exposure, excluding vitamins and minerals (Table 4). The percentages of cases with reported drug group exposure during first trimester varied from 4.4% in El Valles to 36.1% in Mainz. The use of vitamins and minerals were highest for the Basque Country and the Asturias registries. Excluding vitamins and minerals, up to 26% (Mainz) of women were reportedly exposed to any medication during the 1st trimester. Most cases were reported to be exposed to only one drug group. The percentages coded as missing or unknown varied from 0% for Emilia Romagna to over 40% in Antwerp, Odense, Strasbourg, Tuscany, and Basque Country.

Table 5 displays women's exposure to the different EUROCAT drug groups during the first trimester (as a proportion of all exposed cases) for each registry. Large differences existed between the registries, for example, the proportion of cases exposed to any drug where the mother had been exposed to antibiotics varied from 2.8% in Glasgow to approximately 43% in Asturias.

DISCUSSION

Twenty-five of the 29 responding registries participating in EUROCAT collect data on first trimester drug exposure. Of these full members, 15 use the present numeric EUROCAT coding system and 6 use another coding system, primarily the classification ATC. Three of the four associate members use the ATC system. Among the full members who use the EUROCAT code there was a wide variation in drug exposure during the first trimester, ranging from 4.4 to 26%, excluding vitamins and minerals.

It is well known that the ascertainment of drug exposure during pregnancy can be difficult, particularly for over-the-counter preparations. In an earlier study, De Vries *et al.*¹⁶ compared data on maternal drug use obtained from physicians and midwives from

Table 4. Number and proportion of cases exposed to drugs in first trimester (with and without vitamins/minerals), 15 full member EUROCAT registers 1996–2000

	Total cases	Missing/not known <i>N</i> (%)	Not exposed to drugs <i>N</i> (%)	Exposed to drugs <i>N</i> (%)	Exposed to drugs excl. vitamins/min <i>N</i> (%)
Antwerp (Belgium)	1909	1322 (69.3)	447 (23.4)	140 (7.3)	139 (7.3)
Zagreb (Croatia)	483	40 (8.3)	371 (76.8)	72 (14.9)	70 (14.5)
Odense (Denmark)	652	279 (42.8)	318 (48.8)	55 (8.4)	54 (8.3)
Strasbourg (France)	2003	982 (49.0)	767 (38.3)	254 (12.7)	247 (12.3)
Mainz (Germany)	751	90 (12.0)	390 (51.9)	271 (36.1)	195 (26.0)
Cork & Kerry (Ireland)	807	275 (34.1)	426 (52.8)	106 (13.1)	99 (12.3)
Emilia Romagna (Italy)	2219	0	1894 (85.4)	325 (14.6)	325 (14.6)
Tuscany (Italy)	2632	1134 (43.1)	1058 (40.2)	440 (16.7)	397 (15.1)
Malta	798	59 (7.4)	649 (81.3)	90 (11.3)	90 (11.3)
Southern Portugal	1082	109 (10.1)	871 (80.5)	102 (9.4)	100 (9.2)
Asturias (Spain)	850	183 (21.5)	367 (43.2)	300 (35.3)	150 (17.6)
Basque Country (Spain)*	1506	890 (59.1)	182 (12.1)	434 (28.8)	85 (5.6)
El Valles (Spain)	298	75 (25.2)	210 (70.5)	13 (4.4)	13 (4.4)
Vaud (Switzerland)	1380	314 (22.7)	971 (70.4)	95 (6.9)	93 (6.7)
Glasgow (UK, Scotland)	1206	133 (11.0)	859 (71.2)	214 (17.7)	214 (17.7)
Total	18 576	5885 (31.7)	9780 (52.6)	2911 (15.7)	2271 (12.2)

*Only data of 1999–2000 since ATC-codes were used before 1999.

the EUROCAT-registry in the Northern Netherlands (NNL) to prescription data obtained from community pharmacies. The cases were not linked and comparisons were made at population level. Compared to pharmacy data, the estimate of completeness of physician/midwife data varied between 0% for sympathomimetics, dermatological preparations, expectorants and products containing local anaesthetic to 59% for iron preparations. This study has led to changes in the ascertainment of data on maternal drug exposure in EUROCAT-NNL, including pharmacy data and a questionnaire for the mother as sources of information.^{17,18}

Our questionnaire showed that the obstetric records are the main sources used for data on drug exposure although other sources, such as an interview with the mother are additionally used. Northern Netherlands was the only registry to directly access pharmaceutical records from community pharmacies.

Compared to the literature, the percentage of cases who were exposed to drugs in the first trimester was low in registry data, probably reflecting the limited sources of information used.^{8,19–22} Nevertheless, in the period 1996–2000, 2271 out of 18 576 cases (12.2%), originating from 15 registries, were recorded in the central database as having been exposed to medication (excluding vitamins and minerals). Although there is no systematic reference information on drug exposure in most registries, the existing data

can be used for both hypothesis generation and hypothesis testing. Hypothesis generating analyses look for statistical associations between specific drugs and specific malformations, the method used by the Netherlands register and the international MADRE project.^{5–7} For hypothesis testing, the central database can be used to examine whether among the cases exposed to a drug of concern, a specific malformation is in excess relative to other malformations or whether the drug of concern is more frequent among cases of a specific anomaly.^{8,9} Where the EUROCAT codes have been used, it will usually be necessary to use more specific text information on the type of drug, dosage and timing, or re-examine the original records for further information.

The 23 category EUROCAT coding system was specially developed to monitor for any possible drug-related foetal malformation. In order to improve the data coding on drug exposure from 2005, EUROCAT will recommend that registries instead record drug exposure data using the ATC classification²³ to ensure that maximum detail on drug type is coded. With respect to missing data on drug exposure, or cases misclassified as unexposed, individual registries can only solve this problem by using more data sources for drug exposure, for example, utilising pharmacy data. Each type of data source, whether pharmacy data, maternal interview, or obstetric record, can be expected to have its own advantages and disadvantages

Table 5. Proportion (%) of the 2271 drug exposed cases reportedly exposed to any one of the 20 drug groups (excluding vitamins and minerals) in the first trimester per registry

Eurocat code groups (code)	Antwerp (Belgium)	Zagreb (Croatia)	Odense (Denmark)	Strasbourg (France)	Mainz (Germany)	Cork & Kerry (Ireland)	Emilia Romagna (Italy)	Tuscany (Italy)	Malta	Southern Portugal	Asturias (Spain)	Basque Country (Spain)	El Valles (Spain)	Vaud (Swit zerland)	Glasgow (UK)	Total
N	139	70	54	247	195	99	325	397	90	100	150	85	13	93	214	2271
Atropinics and antispasmodics (01)	1.4	0.0	3.7	23.9	0.5	1.0	0.0	3.5	0.0	1.0	5.3	0.0	0.0	1.1	2.8	
Anaesthetics (02)	0.0	0.0	0.0	1.6	0.0	0.0	1.5	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
Hypnotics, sedatives and psychotropics (03)	6.5	7.1	14.8	4.0	0.5	7.1	1.2	6.3	12.2	9.0	6.7	7.1	23.1	6.5	19.6	
Antiepileptics (04)	7.9	1.4	7.4	4.9	0.0	4.0	0.0	2.0	4.4	0.0	1.3	12.9	0.0	6.5	4.2	
Analgesics, antipyretics and antiinflammatory (05)	12.9	5.7	14.8	11.7	1.0	14.1	8.3	20.7	22.2	13.0	22.0	5.9	0.0	26.9	15.0	
Histamine antagonists (06)	1.4	0.0	5.6	0.8	0.0	1.0	0.0	0.8	1.1	3.0	7.3	25.9	0.0	1.1	2.3	
Antisthmatics (07)	4.3	0.0	24.1	1.2	1.0	18.2	0.0	0.8	23.3	0.0	7.3	2.4	0.0	4.3	37.4	
Antiarrhythmics and antihypertensives (08)	6.5	8.6	1.9	7.7	4.1	2.0	1.2	1.0	2.2	10.0	0.7	9.4	7.7	2.2	4.2	
Diuretics (09)	1.4	1.4	5.6	0.4	0.0	2.0	0.0	0.0	0.0	0.0	0.0	1.2	0.0	0.0	0.5	
Tocolytics (10)	1.4	37.1	7.4	0.0	0.5	0.0	28.0	24.4	0.0	0.0	2.7	0.0	0.0	0.0	0.0	
Antibiotics <i>et al</i> (11)	22.3	25.7	9.3	30.4	16.9	15.2	13.2	14.9	5.6	29.0	43.3	7.1	0.0	25.8	2.8	
Immunosuppressives (12)	0.7	0.0	0.0	0.0	0.0	0.0	0.0	0.8	1.1	1.0	0.0	1.2	0.0	0.0	0.5	
Anticoagulants <i>et al</i> (13)	0.7	0.0	0.0	1.6	1.0	0.0	1.2	2.3	1.1	0.0	2.0	1.2	0.0	1.1	0.9	
Thyroid and antithyroids (14)	7.9	2.9	9.3	8.5	8.2	7.1	0.0	10.8	4.4	6.0	2.0	9.4	23.1	6.5	4.7	
Hormones (15)	15.1	17.1	1.9	14.2	1.0	29.3	18.2	12.1	33.3	6.0	2.7	4.7	0.0	2.2	7.5	
Adrenocortical steroids (16)	4.3	1.4	5.6	1.6	3.1	1.0	0.0	1.8	3.3	3.0	2.0	1.2	0.0	1.1	0.0	
Antidiabetics (17)	2.9	1.4	9.3	4.5	4.6	6.1	0.0	1.8	6.7	4.0	2.7	7.1	23.1	11.8	5.6	
Vaccines (18)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.7	0.0	0.0	0.0	0.9	
Other (88)	28.8	11.4	11.1	10.9	71.8	2.0	5.5	8.6	3.3	10.0	14.7	16.5	23.1	22.6	8.9	
Drugs taken but no information (98)	0.0	0.0	0.0	0.0	0.0	2.0	44.3	22.7	0.0	12.0	0.0	0.0	0.0	0.0	1.9	

Because a case can be exposed to more than one drug the row percentages can total over 100.

with respect to knowing which drugs were prescribed, which were actually taken and when, and which over the counter preparations were taken. Linkage with other electronic databases can be particularly powerful, whether pharmacy databases or clinical databases referring to women with a chronic illness such as epilepsy or diabetes or asthma.

A further type of study for which the database can be used is to assess how many cases in the population have been exposed to known teratogens with characteristic malformation patterns, and thus how successful prevention of early pregnancy exposure to known teratogens has been. For example, an assessment of the number of isotretinoin and related drug exposed cases was made in the past by EUROCAT⁸ and other registries. The remarketing of thalidomide will require this type of surveillance. For this type of investigation, an additional retrospective drug exposure enquiry should be made for all cases with the characteristic malformation pattern.

Case-control surveillance, where the same exposure information is collected for malformed cases and non-malformed controls would strengthen post-marketing drug surveillance. However, for registries with limited budgets, it is often not possible to allocate resources to collecting information on controls. Moreover, it can be difficult to ensure that the data sources are identical for cases and controls.

The variation between the registries in the proportion of exposure to the different drug groups may be due to variation in drug prescription policies among the European countries⁸ as well as to variation in data sources used, variation in coding, differences in populations and population sizes, and the level of interest and resources of the registry for pharmacovigilance. Since the prevalence of anomalies can also vary between registries, careful control for registry is needed when pooling data and looking for drug-malformation associations. Conversely, diversity in drug prescription policy can be an advantage when aiming to dissociate the effects of the drug for use in pharmacovigilance studies.²⁴

Congenital anomaly register-based studies are only one of a variety of approaches needed for effective post-marketing drug surveillance, each with its own strengths and limitations. Other approaches include the yellow card system of cases reports of adverse exposure despite its problem of incomplete and biased reporting and lack of control information, and databases such as the General Practice Research Database (UK) where certain drug data may be well and prospectively recorded²⁵ but congenital anomaly data would be less well recorded and restricted mainly to surviving livebirths. In the

future, especially with improvements in coding and sources of information used for drug exposure, EUROCAT can be an effective collaborative framework to contribute to the post-marketing drug surveillance to monitor and identify teratogens.

KEY POINTS

- To assess safety of drugs used before and during pregnancy, data from a large population is required;
- The EUROCAT network consists of 40 registries in the European Union and surveys over a million births per year; over a quarter of all births in Europe;
- At least half of the registries within the EUROCAT network collect information on drug use in the first trimester for which obstetric records and interviews with the mother are the most used sources;
- The EUROCAT database is a resource for post-marketing drug surveillance, which will be improved with the introduction of ATC coding, and the diversification of sources of information on drug exposure.

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