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REPORT OF A JOINT WHO/ICBDMS/ICBD MEETING  
ON METHODOLOGY FOR BIRTH DEFECTS MONITORING:

2. STATISTICS

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## 1. INTRODUCTION

Previously in the Clearinghouse, statistics had been a mainly theoretical art discussed by only a few, and rarely with results which could be implemented in a way which was acceptable to all. The present Statistics Committee of the ICBDMS therefore wanted to show practical interpretations and uses for the routinely collected data. These are presented here in Section 2 'Baselines' and Section 4 'Attributable proportions of Down Syndrome due to high maternal age'.

Most programmes collect far more data than that reported centrally to the Clearinghouse. The Clearinghouse has long had a reputation for collaborative ventures examining more detailed information (eg drug exposure) at individual case level, yet little exploratory work had been done using summary statistical information. The first step in this direction has been made with the presentation in Section 5 on congenital malformations by birthweight and proportion of stillbirth which uses data collected specifically for this analysis.

Finally, but most importantly, statistics is not an art to be used and enjoyed by a privileged few. It has its application in all the various monitoring exercises we all undertake. Therefore, we felt that it was important to also consider an application in specific areas of the Clearinghouse's work - detecting new teratogens and monitoring multiple malformations. A summary is presented in Section 3 on can birth defects monitoring detect new teratogens?.

## 2. BASELINES: 'Cry Wolf' - Principles and purposes of baselines in the monitoring of congenital malformations

### 2.1 Introduction

The routine monitoring practice, quarterly and annually, of the International Clearinghouse for Birth Defects Monitoring Systems relies fundamentally on the use of baselines - the expected rates of specific congenital malformations. Most - if not all - of the comments from the programme directors concerning 'special events' in the quarterly communications deal with statistical significant deviations between baseline values and observed values of the different reported malformations.

Also, most of the statistical monitoring methods such as Cusum, Set and Cuscore techniques all take for granted the existence of a baseline for each of the considered malformations (Lie et al, 91).

The baseline principle has been addressed several times in the Annual Report of the Clearinghouse. For instance in the 1986 report we can read 'Definition of baseline: A baseline is defined as a good estimate of the incidence of the malformation expected for the next monitoring period (eg month, quarter or year), based on prior knowledge of the incidence of that malformation in the area in question. For statistical purposes, the baseline is usually assumed to be a constant, ie, with a negligible standard error.'

Although we are interested in the evaluation and explanation of differences in baseline values between different programmes, the prime

focus of monitoring is the detection of sudden changes in malformation rates within a programme. A key assumption for the monitoring process is constant ascertainment within a programme for the actual period as well as for the period on which the baseline is based. In this context the current data are alarming, and indicate that this basic assumption of constant ascertainment may be violated in several of the programmes for many of the malformation categories monitored. The data for the 22 malformations given in the most recent annual reports (1988 and 1989) have more than 25% significant deviations between observed and expected values (using a 5% significance level) (Bailar and Ederer, 64). This number is obviously far more than expected using a Poisson distribution.

There seems to be a need to reconsider the current use of baselines in routine monitoring. Here we will focus on some simple factors that influence these basis estimates and some mechanisms that might reduce bias in these.

## 2.2 Estimation principles

From the Annual Reports, evaluating the baseline estimates used by the different programmes, we find three main principles for baseline estimation:

- (a) Accumulated data for all previous (available) years (used by, for instance, Czechoslovakia and the USA - Atlanta).
- (b) Fixed number of years, early period (used by, for instance, Sweden, Norway and the USA - 1200 hospitals).
- (c) Moving 'window', using a fixed number of years (for instance 3 years) for the most current period (used by, for instance, Canada and Italy - IPIMC).

We can also add, even though not shown by the practice of the programmes so far:

- (d) Each malformation uses a separate period, estimated with principles that rely on analytical results.

All of these strategies for baseline estimation have their advantages. However, only the last method can take sufficient care of the divergent evolution of the different malformation categories.

## 2.3 Precision

According to the statutes of the Clearinghouse, the baseline must be an estimate based on at least 100,000 births (for full members). This sample size is sufficient for common malformations. With a low prevalence, however, the baseline will be uncertain. For instance, for a malformation with an estimated rate of 10 malformations in 100,000, the baseline estimate has a large standard error - too large to be the baseline reference value (the 95% confidence interval being 7-21 per 10,000). We do not feel comfortable with this kind of uncertainty in a baseline estimation since a baseline is thought of as a constant reference value - thus with no uncertainty attached. At present, there are several

malformations within programmes in the Clearinghouse which use baselines below this level of precision.

Again, reading from the 1986 annual report of the ICBDMS: 'Ideally a baseline should be a known, constant value with no statistical variation. In practice, baselines are obtained from observations made over a fixed period of time. Therefore, there is always uncertainty about the validity of any given baseline. Furthermore, for baselines obtained from observations of populations, the uncertainty will be greater for rates for rarer defects than for commoner defects. This fact suggests that it may be wise for programmes (that accrue data on a relatively fixed number of births per year) to use longer periods for rare defects than for the more frequent defects.'

#### 2.4 Sources of variation

Some basis sources of variation in baseline rates are:

- changing ascertainment (better diagnostic techniques, or better record review)
- secular changes in defect prevalence
- seasonal variations
- demographic changes: parity, maternal age, marital status.
- lower level of gestational age for stillbirth reporting
- use of (selective) prenatal screening and eventually inclusion (or not) of data for aborted fetuses

From the 1986 report: 'These factors, and others that might affect the validity of a baseline as a predictor of the expected value for the next monitoring period, need to be considered when choosing a baseline.'

##### 2.4.1 Distribution - discard the Poisson assumption?

The Poisson distribution is usually used for significance evaluations for observed/expected ratios. One reason for the high number of significant deviations observed in the quarterly and annual reports may be that this assumption of a Poisson distribution is false. An alternative strategy is, given the large number of data gathered over the many years, to use the empirical distribution extracted from these data (Yashchin, 92). This type of non-parametric approach may give more credit to natural variation in birth defect data, and will thus improve the alertness of the monitoring strategy.

##### 2.4.2 Trends

What if trends are observed? When trends are obvious in the annual or quarterly data for a malformation, the implication is to use regression methods for estimating expected numbers. The use of a constant baseline on data with a gradual reduction in prevalence will quickly lead to systematic O/E ratios below unity.

An easy example here is the Spina Bifida data for England and Wales: For instance, using baseline data from 1981-83 1986 data indicate an O/E ratio of 0.49. For 1987 the baseline was based upon

data for the period 1984-86, but still the O/E ratio was 0.6 and clearly significant. In 1988, using the same baseline, the O/E ratio was 0.44. This reduced incidence could be predicted exactly using a simple linear trend based on, for instance, 1980-85 data. An alarm should be sounded when this trend ceased or slowed down. Also, this baseline would be a better tool for an 'alerted' monitoring process when a sudden and unexpected increase occurs.

#### 2.4.3 Follow-up period

In many Clearinghouse programmes births are followed up for diagnosis until 1 year - to achieve more complete ascertainment of malformations. The baseline estimates will reflect this accumulated case-load. However, routine monitoring is based on data with a one week or one month follow-up. This practice will lead to an obvious biased O/E ratio towards values less than unity. Again, a sudden increase in prevalence may be missed or detected later than with a baseline more comparable to the data. The importance of striving for complete ascertainment of malformation occurrences need not ruin the precision in monitoring - the baseline and routine data must be comparable under a null-hypothesis of a stable prevalence.

#### 2.4.4 Population changes

During the last decades most populations of births have had a change in maternal age and parity distribution. Also, stillbirth reporting and the presence of prenatal screening, possibly followed by selected abortion, all differ between programmes and change by period. Aspects of these factors are dealt with in other presentations.

#### 2.5 Beauty of diversity?

In the start of the Clearinghouse (1972) it was normal to have divergent practices with regard to baseline estimation, to have divergent practice for follow-up, for inclusion of stillbirths as well as for period for baseline estimation. This will also be the case for a new programme starting up a monitoring activity. However, the established programmes with long experience and large amount of data could benefit by using more homogeneous principles in their monitoring practice.

The assumption or principle of constant ascertainment based upon an average of 20 years' data, starting from the 1960s, may be questioned. This holds especially for the malformation categories that are influenced by programmes for fetal screening. On the other hand, given data that cover a long period of time, analysing each malformation for trends soon disclose departures from a constant level. Although it is cumbersome, this analytical approach in the presentation of the baseline period/number of births will give different baseline periods for different malformations. Also, when rare and more common malformations are monitored in the same time period, ie a quarter, this leads to a need for such a practice due to the sample size requirements.

## 2.6 To whom do the baselines apply?

It is well documented that selective fertility influence perinatal data: Women will most often want to replace a perinatal death (Skjærven et al, 88). Also, women with repeated losses are more prone to have several pregnancies, their risk for adverse outcome is high and they seriously influence the cross-sectional data in high parity births. On the other hand, reduced fertility may be the result following a surviving malformed child - due to, among other things, the stress imposed on the family situation due to extra need of care. For instance: Only 4 women had two consecutive single Down Syndrome births in first and second births in Norway during 24 years (Medical Birth Registry of Norway, 1967-1990).

Thus, questions we will impose on you are: Do the average baseline apply to all births? Do the average baseline apply to all women?

### 2.6.1 Recurrent events

What is the chance of a malformed child in the next pregnancy given a healthy firstborn? What is the chance of a malformed child in the next pregnancy given a malformed firstborn - of the same kind and of any kind.

Cleft lip and/or cleft palate have high recurrences. Using data from Norway for 1967-1989, the risk for a cleft lip/palate in second birth given cleft lip/palate in the first is 0.040, ie 4 per cent while the baseline for all second births is 18.74 per 10,000 (total baseline 1967-71: 18.30), giving a Relative Risk (RR) of 21.3. For Club foot, comparable Norwegian data are 100/2878 = 0.035 compared with a baseline based on all second births of 54.17 per 10,000, giving a RR of 6.5.

These Norwegian data also show that following a cleft in the first birth, 5.9% have a registered malformation in the next birth. Following any malformed firstborn, the chance of a malformed birth in the next pregnancy is estimated at 5.4%, compared to 2.3% for those with no malformation in the first birth. This gives a RR of 2.33. Similarly, following a perinatal loss in the first pregnancy, there is a more than two-fold increased risk of a malformed birth in the next pregnancy. These calculations are all based on singleton births.

The conclusion is that the baseline we use do not apply to births in general; do not apply to any particular woman. However, with the available data we can give better estimates than those we use today.

## 2.7 Conclusions

It is claimed that there exists two approaches to malformation monitoring; the statistical and the teratological (ICBDMS, 91). It is, however, difficult to see that detailed examination by an experienced teratologist and 'careful scrutiny of the population of newborn infants in the search for unusual events' (pg 166) stand in contrast to improved principles for baseline estimation and other ways of improving the

analyses of data. These improvements may bring the monitoring process towards alertness for sudden and unexpected changes in malformation rates. However, instead of focusing on baselines, maybe it is time to approach the monitoring problem with more informative epidemiological (descriptive analytical) methods.

We cannot let sleeping dogs lie in the monitoring of congenital malformations - let us simply assume that there are no baselines!

### 3. CAN BIRTH DEFECTS MONITORING DETECT NEW TERATOGENS?

#### 3.1 On the ability of birth defects monitoring to detect new teratogens

Recent concerns have been raised about the ability of birth defects monitoring to detect increases in the incidence of birth defects following the introduction of new teratogens. The authors illustrate how most monitoring programs in the United States and Europe are limited in their ability to detect new teratogens because of a combination of parameters: the small population size, the low population frequency of exposure to the new teratogen, the weakness of many suspected teratogens (measured in terms of relative risk R), the low background rate, and the etiologic heterogeneity in the measured defects. In a system that monitors 25,000 births per year, it can be shown that although a new teratogen such as thalidomide (R = 175) can lead to a significant increase in the number of observed cases in 1-2 weeks of monitoring, even strong teratogens such as valproic acid and isotretinoin (R = 20-25) require more than 20 years of monitoring to show a significant increase in the number of cases because of low exposure frequency. Also, most mild to moderate teratogens (R = 2-5) can be totally missed. To improve the ability of birth defects monitoring programs to detect new teratogens, it is suggested that surveillance systems ought to examine subsegments of the population with maximal exposure potential, classify birth defects into more etiologically homogeneous groups, and expand the sample size of the monitored population.

#### 3.2 Monitoring for multiple malformations in the detection of epidemics of birth defects

Although most known human teratogens often produce a combination of birth defects in an affected infant, surveillance programmes aimed at detecting epidemics of birth defects usually only monitor rates of individual defects. A drawback to this approach is that an increase in the rate of infants affected with a specific combination of defects may lead to little or no increase in the rates of component defects. Using the Poisson distribution, we show that, compared with monitoring for individual defects, monitoring for combinations of two and three defects may require fewer numbers of births to detect an epidemic. In general, an increase can be detected more rapidly by monitoring the rates of defect combinations than by monitoring the rates of individual defects if most affected infants have combinations of defects rather than isolated defects. For example, in the case of Congenital Rubella Syndrome (CRS), monitoring for the combination of cataracts with deafness and/or patent ductus arteriosus could have led to earlier detection of an epidemic than could monitoring for cataracts alone. In contrast, in the case of

thalidomide embryopathy, monitoring for reduction defects of upper limbs in combination with reduction defects of lower limbs and/or microtia/anotia would not have led to earlier detection of an epidemic than would monitoring for reduction defects of upper limbs alone. This is due mainly to the low frequency of defect combinations among affected cases. When used with regular monitoring for individual defects, surveillance of defect combinations can enhance the ability of monitoring programmes to detect epidemics of birth defects.

#### 4. ATTRIBUTABLE PROPORTIONS OF DOWN SYNDROME DUE TO HIGH MATERNAL AGE

##### 4.1 Background

It is well known that the incidence rates of Down Syndrome increase with increasing maternal age. The magnitude of these rates will also depend on antenatal screening programmes in different countries and the availability of and the attitude towards induced termination. The impact on a population of the higher rates at older ages will, however, depend very much on the number of births at older maternal ages. Therefore, attributable proportions of Down Syndrome due to high maternal age are presented here. This single measure describes the percentage of cases of Down Syndrome which can be attributed to high maternal age, in this case women of age 35 or more.

##### 4.2 Data used

Each year the number of Down Syndrome cases and birth denominators by maternal age are reported to the Clearinghouse. These data for 1980-88, grouped into three 3-year periods, were used in this analysis, separated into two groups, women aged under 35 and those aged 35 and over. Data were available for nineteen programmes, but only nine of these covered data for all nine years.

##### 4.3 Results

###### 4.3.1 Age distribution

The percentage of all births which were to women aged 35 and over varied between programmes from 3-4% in Czechoslovakia to 11-15% in France (Paris). Despite these differences, nearly all the programmes showed an increase over time in the percentage of births to older women. The major exception was Spain whose percentage of births to older women fell from 11 per cent in 1980-82 to 8% in 1986-88.

###### 4.3.2 Age specific rates

Down Syndrome rates for women aged under 35 did not vary considerably between programmes. The lowest rates (5-6 per 10,000 births) were seen in England and Wales, and the highest rates (10-11 per 10,000 births) in Sweden. There was much more variation in the Down Syndrome rates for women aged 35 and over. Again there were low rates in England and Wales (22-30 per 10,000), but the lowest rates (9-10 per 10,000) were in Denmark. The highest rates were

reported from Mexico (61-77 per 10,000), South America (ECLAMC) (65-77) and Spain (70-93).

#### 4.3.3 Relative risk

Rates for the two age groups may be affected by differences in the age distribution within the age groups. Therefore differences in the relative risks between the two age groups may be real or due to the maternal age distribution itself. With such different rates for women aged 35 and over between countries, but generally similar rates for women aged under 35, it is not surprising that the highest relative risks were for countries such as Mexico (ranging from 7.7 to 9.5) and Spain (8.7-11.0), which had the highest rates for older women. Sweden, which had relatively high rates for younger women and low rates for older women, had amongst the lowest relative risks (2.9-4.1). Relative risks for Denmark were close to unity (1.0-1.4).

#### 4.3.4 Attributable proportion

These different patterns of maternal age distribution of births and relative risks are brought together in the 'attributable proportion'. This measure uses the excess incidence at older ages to calculate the number of cases in the population of births to older women which can be attributed to the excess risk at these ages. This number is then expressed as a proportion of the total notified cases. This proportion varied considerably between programmes, from close to zero in Denmark, 9-17% in USA (Atlanta) and 14-17% in Czechoslovakia, to 43-46% in South America and 40-51% in Spain. The high proportions in these latter programmes are not surprising given their high relative risks and high percentages of births to older women.

#### 4.4 Discussion

The low Down Syndrome rates for England and Wales are due, at least in part, as a result of under-notification. Differences between programmes in rates for older women are affected by their different antenatal screening and induced termination practices. The very low rates for women aged 35 and over in Denmark is likely to be due to a highly effective antenatal screening practice followed by induced termination of affected fetuses. It is not surprising, therefore, that the programmes where induced abortion is illegal (Mexico, South America, and Spain until July 1985) have the highest rates in this age group.

### 5. CONGENITAL MALFORMATIONS BY BIRTHWEIGHT AND PROPORTION OF STILLBIRTH

#### 5.1 Background

This paper assesses differences in reporting congenital malformations by studying variation due to the contribution of stillbirths and the influence of birthweight. The variation between programmes in rates for specific malformations reported to the Clearinghouse is partly due to different criteria for reporting of stillbirths, varying between 16

and 28 weeks of gestation (or 500 to 1000 grams birthweight). Also during the 1980s there has been increasing attention paid to low birthweight fetuses and births. This can be assumed to have changed both the diagnostic ascertainment and reporting to the Clearinghouse. Differences in prenatal screening and abortion practices will also influence the rates.

## 5.2 Data used

Twelve Clearinghouse programmes provided data for this analysis. Gestational age is either not collected or is missing for a large proportion of cases reported routinely from many of the programmes. Therefore, birthweight has been used here in place of gestational age. Results are given for anencephaly, spina bifida and Down Syndrome. These conditions were chosen because they are clearly defined and generally well ascertained. They are largely influenced by prenatal screening techniques, so time trends were examined. Data for 1980-88 were analyzed combined and also divided into three 3-year periods.

## 5.3 Results

### 5.3.1 Anencephaly

Between 1980 and 1988, rates for anencephaly fell considerably in many countries. For instance in England and Wales the rate for all births fell from 3.9 per 10,000 in 1980-82 to 0.6 per 10,000 in 1986-88. Simultaneously there was a decrease over time in the proportion of these births which were anencephalic stillborn (from 78.8% in 1980-82 to 59.3% in 1986-88). This pattern differs from other programmes such as Japan, Norway, France:RAA and France:Paris. In these latter programmes the proportion of stillbirths increased over time. In Japan and Norway the proportion of stillbirths was slightly above 90% in the period 1986-88. However, in USA:Atlanta the proportion was lower and reduced during the period from 54.5% in 1980-82 to 43.7% in 1986-88. The USA:1200 programme also had a low proportion of stillbirths, 29.5%.

For the anencephalic cases the peaks (modes) of the birthweight distributions were between 1000 and 1500 grams for many of the programmes with a right tail stretching towards higher weights (4000 grams or more), giving highly skewed distributions.

The very high proportion of fetuses weighing less than 1000 grams in Norway is due in part to induced abortions being included in the reported data. Other mechanisms, however, may affect secular trends. This is seen in the data from Norway, due to the low gestational age limit (16 weeks) for reporting stillbirths.

### 5.3.2 Spina bifida

Fewer spina bifida births are stillborn, and there are few trends in the proportion of these births which are stillborn. However, large variations between programmes can be seen. For instance, in the last period 1986-88, the proportion of reported stillbirths was low in both USA programmes and in France:RAA and the

Atlanta data (from 4-8%), compared with other programmes such as France:Paris (58% in 1986-88), Norway and Israel (both 27% in the same period). For France:Strasbourg, abortions can be reported as either live and still born, and these fetuses contribute 40 and 30% of the live and still born cases, respectively.

In England and Wales there was a consistent reduction in the proportion of stillborn spina bifida cases, from 19.1-8.6%, and a similar reduction in rates from 9.9-3.0 per 10,000 births over the nine year period.

For the two programmes in the USA and in South America (ECLAMC), stillbirths are few and only visible in the curves below 1500 grams. This is clearly different from the pattern observed for the European programmes and for Japan. As for anencephaly, the induced abortions reported in some of the programmes contribute to large residuals in the weight distributions.

The weight distributions of spina bifida live births are reasonably similar between programmes. The mean birthweight of the liveborn cases ranged between 2660 grams in Israel and 3220 grams in Norway.

#### 5.3.3 Down Syndrome

Throughout the period a constant proportion of Down Syndrome cases were reported as stillbirths for England and Wales (2.0%). Similar low values were found for USA:1200 (2.1%), Japan (from 3.2 to 2.3), South America (ECLAMC) (from 0.1 to 2.4) and France:RAA (0.7 to 1.3).

A clear increase in the proportion of stillbirths was observed over time in France:Paris (from 7.8-15.8%). In Norway and USA:Atlanta there were similar increases and the proportion of stillbirths in the last period was 8%, ie four times higher than in England and Wales.

The weight distribution for total Down Syndrome cases show only small differences between programmes. The only difference is in the residual part of the distribution, presumably due to differences in stillbirth criteria and registration of abortions following prenatal screening. Stillbirths, however, contribute very little to the birthweight distribution. The mean of the liveborn cases varied between 2820 grams in Japan and 3400 grams in Czechoslovakia.

#### 5.4 Discussion

This study demonstrates over the chosen time periods systematic differences between programmes, as well as within programmes, in the contribution of stillbirths to the total anencephaly, spina bifida and Down Syndrome cases. This variability would be expected due to differences in the gestational age and/or birthweight limits for reporting of stillbirths and thus for congenital malformation reporting. Other differences between programmes as to whether prenatally diagnosis and

termination is available and whether such fetuses are reported to the Clearinghouse along with stillbirths and live births also highly influence the results. Some programmes, for instance England and Wales, have a systematic registration of prenatally diagnosed and terminated pregnancies in separate systems but these are not routinely reported to the Clearinghouse.

The increase in birthweight seen for instance in the England and Wales data for both anencephaly and spina bifida may imply that terminations are performed on fetuses which would be relatively smaller at birth had the pregnancies continued, since pregnancy terminations represent the main mechanism for the reduction of cases. The decrease in birthweight is seen in the programmes where abortions are included, for instance Norway, France:Paris, USA:Atlanta and France:Strasbourg. Japan does not include abortions in their reporting, still, there is a similar reduction in birthweight as seen in the latter programmes. Some details on the availability of prenatal diagnosis and selective abortion for Clearinghouse programmes were presented in a previous annual report, exemplified by data on neural tube defects and Down Syndrome.

The total number of cases of a given malformation reported by a programme is a complicated web of stillbirth criteria, frequency of abortions (terminations) and the reporting practice of these abortions. To be optimally alerted to a real change in occurrence through studies of secular trends in malformations, these factors should be considered. Distribution of cases by birthweight, as well as stillbirth/livebirth indicator, might be helpful here.

#### 6. LIST OF PARTICIPANTS

Professor M. Ashizawa, The Japanese Red Cross College of Nursing, 4-1-3 Hirowo, Shibuya-Ku, 150 TOKYO, Japan

Dr L. Botto, Clinica Pediatrica, Università Cattolica, Largo Gemelli 8, 00168 ROME, Italy

Dr A. Chan, Pregnancy Outcome Unit, South Australian Health Commission, P.O. Box 6, RUNDLE MALL, SA 5000, Australia

Miss K. Clark, South Australia Birth Defects Register, AMCWC, 72 King William Road, NORTH ADELAIDE, SA 5006, Australia

Dr A. Daltveit, Institute for Hygiene and Social Medicine, 5016 HAUKELAND SYKEHUS, Bergen, Norway

Dr C. Elek, Department of Human Genetics and Teratology, National Institute of Hygiene, Gyali ut 2-6, 1966 BUDAPEST, Hungary

Mr A. Ericson, National Board of Health FAP 3, 106 30 STOCKHOLM, Sweden

Dr D.J. Erickson, Birth Defects and Developmental Disabilities Division, Center for Environmental Health, Centers for Disease Control, ATLANTA, GA 30333, USA

Dr C. Francannet, Institut Européen des Génomutations, B.P. 31, 63401  
CHAMALIERES CEDEX, FRANCE

Dr M. Frommer, Reproductive Health, Epidemiology and Health Services Evaluation  
Branch, Department of Health NSW, Locked Bag No. 961 P.O., NORTH SYDNEY, NSW  
2059, Australia

Dr J. Goujard, INSERM, 123 blvd de Port-Royal, 75014 PARIS, France

Ms S. Hardeng, Senior Engineer, State Pollution Control Authority, P.O Box 8100  
Dep, 0032 OSLO 1, Norway

Dr B. Hareide, Director-General, National Institute of Public Health,  
Geitmyrsveien 75, 0462 OSLO 4, Norway

Dr L. Irgens, Institute for Hygiene and Social Medicine, 5016 HAUKELAND SYKEHUS,  
Bergen, Norway

Ms S. Kidd, Research Assistant, National Perinatal Statistics Unit, Building  
A27, University of Sydney, SYDNEY, NSW 2006, Australia

Ms Y. Kirwan, Reproductive Health, Epidemiology and Health Services Evaluation  
Branch, Department of Health NSW, Locked Bag No. 961 P.O., NORTH SYDNEY, NSW  
2059, Australia

Dr M. Khoury, Birth Defects Branch, Centres for Disease Control, ATLANTA, GA  
30333, USA

Dr J. Kucera, Department of Population Teratology and Epidemiology, nabr.  
Podolské 157, 147 10 PRAGUE 4 - PODOLI, Czech Republic

Dr J. Lumley, Victorian Perinatal Data Collection Unit, Health Department  
Victoria, GPO Box 4003, MELBOURNE, VIC 3001, Australia

Professor P. Merlob, Head, Neonatal Department, Beilinson Medical Centre, 49100  
PETAH TIKVA, Israel

Dr O. Mutchinick, Departamento de Genetica, Inst. Nac. Nutricion S. Zubiran,  
Vasco de Quiroga 15, Delegacion Tlalpan, 14000 MEXICO D.F.

Professor I.M. Orioli, Department of Genetics, Federal University of Rio de  
Janeiro, RIO DE JANEIRO, Brazil

Mr E. Pedisich, Research Assistant, National Perinatal Statistics Unit, Building  
A27, University of Sydney, SYDNEY, NSW 2006, Australia

Professor P.W.J. Peters, Director, International Centre for Birth Defects,  
Armauer Hansen Building, 5021 BERGEN, Norway

Dr E. Robert, Institut Européen des Génomutations, 86 rue Edmond Locard, 69005  
LYON, France

Mrs A. Ruusinen, The National Agency for Welfare and Health, Siltasaarekatu  
18a, P.B. 223, 00531 HELSINKI 53, Finland

Dr A. Seida, Japan Association for Maternal Welfare, Hokken Kaikan 1-2,  
Sadohara-cho, Ichigaya Shinjuku-ku, 162 TOKYO, Japan

Dr E. Shafir, Research Assistant, National Perinatal Statistics Unit, Building  
A27, University of Sydney, SYDNEY, NSW 2006, Australia

Professor R. Skjaerven, International Centre for Birth Defects, University of  
Bergen, 5021 BERGEN, Norway (Co-Chairman)

Dr Y. Sumiyoshi, Director, Yokohama Maternity Hospital, 4-270 Minami-ku,  
YOKOHAMA 232, Japan

Mr G. Tun, Research Assistant, National Perinatal Statistics Unit, Building A27,  
University of Sydney, SYDNEY NSW 2006, Australia

Dr Kunze Xiao, Director, National Centre for Birth Defects Monitoring, West  
China University of Medical Sciences, Renminnanlu Section 3, No. 17, CHENGDU  
61004, People's Republic of China

#### ICBDMS SECRETARIAT

Professor E. Castilla, Chairperson, Eclamc/Genetica/Fiocruz, CP 926, 21040 RIO  
DE JANEIRO, Brazil

Dr P. Lancaster, Vice-Chairperson, National Perinatal Statistics Unit,  
University of Sydney, SYDNEY, NSW 2006, Australia

Ms B. Botting, Secretary/Treasurer, O.P.C.S., St. Catherine's House, 10  
Kingsway, LONDON WC2B 6JP, UK (Co-Chairwoman and Rapporteur)

#### WHO SECRETARIAT

Dr V. Boulyjenkov, Responsible Officer, Hereditary Diseases Programme, Division  
of Noncommunicable Diseases and Health Technology, 1211 GENEVA 27, Switzerland

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Beverley J. Botting  
Muin J. Khoury  
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