12-15-86
CASWELL FILE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY 005638

DEC 15 1986

MEMORANDUM

SUBJECT: TILT®; Study of Congenital Malformations in New South Wales; Caswell #323EE; EPA ID#4E3026; Action Code 350; Accession #263065; Record #174759; Tox Project #2075.

TO: Lois Rossi
Product Manager (21)
Registration Division (TS-767C)

FROM: Alan C. Katz Alan C Katz 12/12/86
Reviewer, Toxicology Branch
HED (TS-769C)

THROUGH: Marcia van Gemert, Ph.D. M. van Gemert 12/12/86
Head, Section 3
Toxicology Branch/HED (TS-769C)
and
Theodore M. Farber, Ph.D. Theodore M. Farber 12/15/86
Chief, Toxicology Branch

Action Requested

Review Australian epidemiologic data on Tilt®.

Review/Recommendations

Study Title: "Report on the Incidence of Major Congenital Malformations in the Coffs Harbour Region of New South Wales."

Authors: Drs. P. Lancaster and J. Baker
(National Perinatal Statistics Unit, School of Public Health and Tropical Medicine, University of Sydney)

Date: December 1985

This report (attached) describes the methods and results of an epidemiological study of congenital malformations in the Coffs Harbour, Bellingen, and Nambucca areas of New South Wales during the period 1981-1984. The study was initiated following recognition of a cluster of infants born with cleft lip and palate at Coffs Harbour Hospital in October and November, 1984. Results of the study indicate that there was a temporal association between reported widespread aerial spraying of bananas in Coffs Harbour and the critical period of organogenesis (7-8 weeks after fertilization) of five infants with cleft lip and palate in 1984.

In addition to the deficiencies in data collection noted in the report, this reviewer also finds that some of the results may be biased due to differences in methods of obtaining data from cases vs. controls. On page 6, the report states that the parents of malformed infants born in hospitals in the Coffs Harbour region in 1984 "were either interviewed or completed a questionnaire that was sent to them." On page 7, it is reported that "Parents of non-malformed infants were also requested to complete the same questionnaire"; i.e., there is no indication that any of the parents of the control group were interviewed. Therefore, comparisons of answers to questions such as those relating to exposures to chemical agents are considered generally unreliable.

Overall, the study results provided no basis for concluding that the malformations cited were caused by exposure to pesticides in general, or Tilt® in particular. However, the Agency should request follow-up data in order to conduct a more comprehensive evaluation. For example, studies of chemicals in the Coffs Harbour water supply and of viral antibody titres in Coffs Harbour residents were reportedly performed; data should also be available on the incidence of congenital malformations in New South Wales (and specifically in the Coffs Harbour area) during 1985, while use of Tilt® was continued. Results of any other follow-up studies which may have been conducted, such as those recommended on page 3 of the study report, should be made available to the Agency for its consideration.

Background/Correlation with Animal Data

Technical propiconazole (CGA 64 250, 88% a.i.) was not considered teratogenic in the rat at doses up to and including 300 mg/kg. Maternal toxicity (decreased body weight gain and food consumption) was found at 300 mg/kg, while fetotoxicity (ossification retardation) occurred at 100 and 300 mg/kg. The NOEL's for maternal and developmental toxicity were 100 and 30 mg/kg, respectively.

The technical compound was not found to be teratogenic, fetotoxic or maternally toxic in the chinchilla rabbit at doses up to and including 180 mg/kg. A cleft palate was found in 1 of 123 fetuses in the high dose group. According to the study report submitted by the registrant, "this malformation is considered of a spontaneous origin. Missing palatal closure was recorded to occur spontaneously in rabbits of control populations at a rather high incidence." A contradiction to this rationale is noted in the EPA Toxicology Branch review (Tox Document #000789; W. Dykstra, 4/30/81, p.12), which stated: "although this malformation may not be considered compound-related; the historical control data has no fetuses with cleft palate of 928 examined." Due to this and other concerns which were noted by the Toxicology Branch (Tox Document #004316; A. Katz, 2/28/85), the rabbit study was considered "only marginally acceptable as CORE-Minimum data."

In order to increase confidence in the animal data, the registrant should be advised to consider repeating the rabbit study; pertinent historical control data should also be submitted to the Agency. At the same time, the Toxicology Branch may reconsider its CORE-classification of the original rabbit study. These issues will be brought before the Toxicology Branch Peer Review Committee in the near future.

005638

REPORT ON THE INCIDENCE OF MAJOR CONGENITAL MALFORMATIONS IN THE COFFS HARBOUR REGION OF NEW SOUTH WALES

The report was prepared for the NSW Department of Health by Dr. Paul Lancaster and Dr. Jennifer Baker of the National Perinatal Statistics Unit, School of Public Health and Tropical Medicine, University of Sydney.

December, 1985.

SUMMARY OF MAIN FINDINGS

- In the period 1981-1984, the reported incidence of major congenital malformations in the combined local government areas of Bellingen, Coffs Harbour and Nambucca was similar to that in New South Wales.

- A significant cluster of infants with cleft lip and palate occurred in the combined areas of Bellingen, Coffs Harbour and Nambucca in October and November 1984.

- In 1984, the reported incidence of major congenital malformations in Coffs Harbour was higher than the statewide figure. This higher overall incidence was due to the additional infants with cleft lip and palate. When these infants were excluded from the analysis, the incidence of major malformations in Coffs Harbour in 1984 was similar to that for New South Wales.

- No common causal factors were identified in the answers to questions about possible causes given by the parents whose infants had cleft lip and palate.

- Although there was a temporal association between the widespread use of a new fungicide in Coffs Harbour and the period of organogenesis of the cluster of infants with cleft lip and palate, there was no direct evidence to implicate this, or any other, chemical pesticide as the cause of these congenital malformations.

- The mothers of malformed infants born in the Coffs Harbour region in 1984 were significantly more likely than mothers of non-malformed infants to give a history of exposure before pregnancy to occupational outdoor pesticides and to indoor pesticides (excluding fly-sprays).

- There was no significant difference between mothers of malformed and non-malformed infants in reported exposures to the following chemicals and other substances in the first three months of pregnancy: household cleaning agents, paints and paint solvents, outdoor and indoor pesticides, chemical cleaning agents, town water supply, tea, coffee, vitamins, cigarettes and alcohol; or to outdoor pesticides before pregnancy.

- The fathers of malformed infants were significantly more likely to give a history of occupational exposure to pesticides after conception than the fathers of non-malformed infants, but there was no significant difference in their exposures before conception.

- The association of more maternal or paternal exposures to various chemicals and other agents and the occurrence of congenital malformations in their infants does not prove that the two are causally related.

RECOMMENDATIONS

1. The data on the reported incidence of congenital malformations in the Coffs Harbour, Bellingen and Nambucca areas in 1985 should be analysed by the National Perinatal Statistics Unit when the final figures are available in 1986.

2. Follow-up studies of chemicals in the Coffs Harbour water supply and of viral antibody titres in residents of Coffs Harbour are in progress. Where possible, the results of these studies should be correlated with the results of the current study of congenital malformations.

3. A follow-up study should be conducted to determine whether there is any clustering of the residential areas of families with malformed infants and whether the occupations of the parents of malformed infants differ from those of non-malformed infants.

4. Other areas in New South Wales that use chemicals similar to those used in the Coffs Harbour area should be identified by the NSW Department of Agriculture so that the pattern of congenital malformations in these areas can be studied. Similar areas in other States and other countries should also be identified to enable more widespread comparisons.

5. The NSW Department of Health should provide regular printouts and summary reports of data to hospitals and health regions in the State to enhance the quality and local use of the data.

6. The NSW Department of Health should collect data on congenital malformations diagnosed after the first week of life and up to at least one year of age so that better ascertainment of major congenital malformations is achieved. Similar data are now being collected in most other States.

INTRODUCTION

In October and November 1984, staff at Coffs Harbour Hospital noted an unusual number of births of infants with cleft lip and palate. In January 1985, the National Perinatal Statistics Unit (NPSU) was informed by the Regional Council for Social Development that six babies with this birth defect had been born in the Coffs Harbour region in the period from May to November. The NPSU notified the NSW Department of Health and prepared a brief report confirming the occurrence of a cluster of infants with cleft lip and palate and recommending further investigation of possible causes.

The Department subsequently used questionnaires to obtain information from the parents of malformed and non-malformed infants about the characteristics of their families and about possible exposures during pregnancy to various agents.

This report provides data on the incidence of major congenital malformations in the Coffs Harbour region and in New South Wales and summarises the results of the study of possible causes of these malformations.

Congenital malformations and their causes

Congenital malformations are structural defects that are present at birth. They include those conditions listed in the chapter of congehital anomalies in the International Classification of Diseases. An arbitrary distinction can be made between major and minor congenital malformations. Major malformations are either lethal or have an adverse effect on function. In this report, we have used the same criteria for excluding minor malformations as for the national monitoring system.

Cleft lip with or without cleft palate (CL +/- CP) and isolated cleft palate (CP) differ embryologically and are usually regarded as two distinct types of congenital malformations. The so-called critical period of development of the lip and palate, when these structures in the embryo are most susceptible to teratogenic influences, is in the 7th and 8th week after fertilization or the 9th and 10th week after the first day of the last menstrual period in 28-day cycles.

As with many other types of congenital malformations, the causes of cleft lip and palate are usually not known, but familial, genetic and teratogenic causes are sometimes identified. Several Australian studies

have shown an increased incidence of CL +/- CP in rural areas and one study showed seasonal variations in conception, with a higher occurrence of conceptions in August and October. Any seasonal variations in incidence have not been linked to maternal viral or other infections.

It has been suggested that environmental chemical exposures, particularly to aerial spraying of banana plantations, may be the cause of some malformations in the Coffs Harbour region. This type of hypothesis is extremely difficult to prove or disprove because of the lack of data on actual exposures and the problems in establishing a dose-response gradient.

Data collection on congenital malformations in New South Wales

The NSW Department of Health introduced a reporting system for all births in the State, including infants with congenital malformations, in 1981. These perinatal notifications provide the main source of data to the NPSU for monitoring malformations in New South Wales. At this stage, the perinatal collection has still not achieved coverage of all births in the State, but reporting from hospitals outside Sydney has generally been better than that from some metropolitan hospitals. Data collection in 1984 was adversely affected by industrial disputes in hospitals.

Because of deficiences in reporting from hospitals in New South Wales since the perinatal collection began in 1981 and the need to obtain better data, staff of the NPSU have regularly visited the two children's hospitals in Sydney to obtain information about malformed infants transferred soon after birth for treatment in these hospitals.

Other sources of data on congenital malformations include perinatal death certificates, reports from cytogenetics laboratories (since 1982), and autopsy reports from some hospitals. With the exception of chromosomal abnormalities which are reported up to one year of age, only congenital malformations detected at, or soon after, birth are presently reported in New South Wales. In most other States, malformations are notified up to at least one year of age.

Computer printouts of notified cases of major congenital malformations are sent each quarter to the NSW Department of Health and quarterly monitoring reports are sent by the NPSU to the Department for distribution to the regions and to all hospitals where births occur.

In the national monitoring system for congenital malformations, data

on malformed infants born in October-December would usually reach the NPSU in the following February after data processing of forms from hospitals by the Health Statistics Unit of the NSW Department of Health. The cluster of infants with cleft lip and palate was therefore recognised before the data had been obtained by the NPSU.

METHODS

In analysing the data for the Coffs Harbour region, the years 1981-1984 were chosen because 1984 was the year in which the cluster of cases of cleft lip and palate occurred and, as previously described, data had been collected since 1981. To some extent, Coffs Harbour Hospital acts as a referral centre for the surrounding region, so the data on malformed infants and total births are given for the mothers' local government areas of residence.

In our initial report on the cluster to the Department, we suggested that further information should be obtained by interviewing the parents of affected infants and also the parents of other infants without major congenital malformations. A questionnaire that had been field-tested previously by Dr. Susan Quine of the NPSU and used in other case-control studies was made available to the Department. The questionnaire aims to obtain information about the demographic characteristics of the family; family history and the outcomes of previous pregnancies; maternal diseases and illnesses during pregnancy; personal habits and exposures to drugs and chemicals before and during pregnancy; and any occupational exposures of both parents to chemicals. The questionnaire was designed to include a fairly broad range of information about pregnancies and can be modified as necessary for hypothesis-testing studies. Since exposures to chemical substances were of particular interest in Coffs Harbour, it was suggested that additional questions about the sources of water supply should be added to the questionnaire.

Twenty-one malformed infants born in Coffs Harbour Hospital and other hospitals in the region in 1984 were identified from hospital records. Three families could not be traced. The parents of the other 18 infants were either interviewed or completed a questionnaire that was sent to them. These 18 families included 14 of the 19 infants that had been notified to the NPSU, 3 of 5 infants identified from other sources in Coffs Harbour, and 1 infant initially regarded as having a congenital malformation but subsequently recognised to have a condition

acquired postnatally.

Parents of non-malformed infants were also requested to complete the same questionnaire. Fifty infants were identified from hospital records. An attempt was made to obtain three control infants for each case. These controls were born in the same hospital as the cases and had dates of birth as close as possible to those of the cases.

Initial analysis of the completed questionnaires was undertaken in Coffs Harbour. Subsequently the data were coded and computerised by the NSW Department of Health and tabulated figures were made available to the NPSU. Crude odds ratios for exposure to various substances were calculated. Small numbers in the malformed group precluded further stratification of the data.

RESULTS

1. Reported incidence of major congenital malformations

Table 1 shows the numbers of reported infants with major congenital malformations, the total numbers of liveborn and stillborn infants, and the reported incidence rates per 10,000 births for infants born in various areas in the years 1981-1984.

The annual number of births to mothers resident in the Bellingen, Coffs Harbour and Nambucca local government areas is relatively small. This factor must be considered in interpreting the annual rates in these areas. In the four-year period, the reported incidence of infants with major congenital malformations in these combined local government areas (154.4 per 10,000 births) was similar to that in New South Wales (148.0 per 10,000 births). The rate for Coffs Harbour was similar to that for the combined areas while, with much smaller numbers of births, the rates for the Bellingen and Nambucca areas were slightly lower and higher respectively.

In 1984, the reported incidence rates in Coffs Harbour and in the combined areas were higher than the statewide rate. The higher rate in Coffs Harbour and the combined areas was due to the 5 reported infants with cleft lip and palate. If these 5 infants were excluded from the totals of malformed infants, there were 10 malformed infants reported in Coffs Harbour and 14 in the combined areas compared with expected numbers of 8.4 and 14.2 respectively. In the earlier years, the rate in Coffs

Harbour was similar to, or less than, that in New South Wales.

Table 2 compares the reported incidence rates of cleft palate and cleft lip +/- cleft palate in the combined local government areas of Bellingen, Coffs Harbour and Nambucca with the rest of the Clarence subdivision and with New South Wales. The incidence of isolated cleft palate was similar in all areas, but the incidence of cleft lip +/- cleft palate in the combined areas (which included Coffs Harbour) was more than double the rate in New South Wales (19.9/10,000 births compared with 9.0/10,000 births).

2. Investigation of apparent clustering of infants with cleft lip and cleft palate

Using the scan statistic of Wallenstein, the 10 cases of cleft lip with or without cleft palate occurring in the Clarence subdivision in the period 1981-1984 were tested for clustering in time, based on a window of 60 days. The four reported infants with cleft lip and palate born between 3.10.84 and 18.11.84 constitute a cluster. A fifth infant who was not reported was born on 20.11.84. The probability of these five malformed infants being born in a two-month period is 3 in 1,000, confirming the statistical significance of this cluster.

In 1981, five infants with either cleft lip or cleft palate were born in Coffs Harbour Hospital. There was no temporal clustering of these births. The main diagnoses, month of birth and local government area of residence of the mothers of these infants were: cleft palate and encephalocele, February, Bellingen; cleft lip, March, Coffs Harbour; cleft lip, July, Coffs Harbour; cleft lip, October, Bellingen; and cleft palate (Pierre Robin syndrome), November, Coffs Harbour. No infants with either cleft lip or cleft palate were born in these areas in 1982 and 1983.

3. Infants with major congenital malformations born in the Bellingen, Coffs Harbour and Nambucca areas in 1984

These infants who were identified from various sources are listed in Table 3. As well as the five infants with cleft lip and cleft palate born in October and November, there was another infant with the same malformation born in May. One infant with cleft lip and palate had an inherited syndrome while another also had congenital heart defects. Otherwise, no specific pattern of congenital malformations was evident.

Most infants who were not reported to the NPSU through the usual sources but who were identified by a local survey in Coffs Harbour had malformations that are frequently not recognised at birth (e.g. congenital heart defects, eye malformation). Nevertheless, these infants would usually be reported if notification extended beyond the early neonatal period.

4. Data from questionnaires for infants with cleft lip and cleft palate

The questionnaires completed by the parents of the infants with cleft lip and cleft palate were included in the comparison with the control group of all malformed infants born in 1984, but the questionnaires were also examined for common factors that might indicate possible causes (Table 4). In particular, the details of possible exposures to environmental and household chemicals in the first three months of pregnancy were scrutinised. Only two mothers gave a history of exposure to aerial spraying of bananas. One lived about one kilometre from the areas that were sprayed while the other had a genetic cause for the infant's cleft lip and palate. Lack of a history of exposure to aerial spraying does not necessarily exclude the possibility of such exposure in an area where spraying is quite widespread.

All six mothers reported exposure to household insect sprays. Such exposure is, of course, very common in any pregnancy. A much larger study would be required to determine whether there were any risks associated with such exposure.

Five of the six mothers used the town water supply and two of these also used either water from a local stream or from a dam. One family used water from a home tank.

Apart from nausea and vomiting in four pregnancies and the use of antiemetics by two of these women, no other common factors were identified in the families of the infants with cleft lip and palate.

5. Comparison of reported exposures to various substances of the parents of malformed and non-malformed infants

Data from questionnaires, completed at interviews or by the parents themselves, were analysed to compare the reported exposures of the parents to various substances before pregnancy or during the first three

months of pregnancy. Table 5 gives the numbers of parents of malformed (cases) and non-malformed (controls) infants with a history of exposure to pesticides and other chemical agents and substances.

The data are presented in columns to show the numbers exposed (exp.) and not exposed (not exp.) to particular agents and also the crude odds ratios and their 95% confidence limits. An odds ratio of greater than 1.0 indicates that the risk of exposure to that agent was greater for cases than controls, while a ratio of 1.0 or less indicates that the exposure was more common in controls than cases. The 95% confidence limits for an odds ratio indicate the range of values that might occur due to random variability. If the 95% confidence limits do not include 1.0, the odds ratio is regarded as significantly high or low (at the 5% level), indicating greater or lesser exposure to an agent among cases than controls.

Using these criteria, the risk was significantly greater for cases than controls for maternal exposure before pregnancy to occupational outdoor pesticides (odds ratio of 4.5) and to indoor pesticides (excluding fly-sprays) (odds ratio of 6.9) and for paternal occupational exposure after conception to pesticides (odds ratio of 6.9). Maternal exposure to other outdoor pesticides before pregnancy (odds ratio of 3.1) and to occupational outdoor pesticides in the first three months of pregnancy (odds ratio of 3.7) and paternal occupational exposure to pesticides before conception (odds ratio of 4.5) were of borderline significance. Women whose work was home duties accounted for most of those with a history of occupational exposure to pesticides.

Other maternal and paternal exposures to various substances were not significantly higher in cases than controls, but it should be noted that the numbers were quite small.

EXPOSURE TO CHEMICAL PESTICIDES

Local concerns in Coffs Harbour about the possible adverse effects of agricultural chemicals on the health of the community have focussed mainly on chemical pesticides used for aerial and ground spraying of banana plantations. Banana-growing is a major industry in the town and figures from the NSW Department of Agriculture show that there are 780 banana growers in the district with a total of 2,619 hectares of banana plantations.

Various chemicals have been used in the banana plantations to reduce infestations by fungi, mites, worms and banana weevil borers. These chemicals include aerial and ground applications of mineral oil; fungicides - Tilt (a triazole compound) and Mancozeb; miticides - Tedion (a chlorinated hydrocarbon), Plictran (a trialkyltin compound), and Kelthane (an organochlorine); nematicides - Nemacur and Mocap (organophosphates); and agents for banana weevil borers - dieldrin and Tokuthion (an organophosphate). Other chemicals may also be used by individual banana growers from time to time.

A relatively new fungicide (Tilt) was first used in several small areas in 1982 and 1983 and on a more widespread basis in February to April/May 1984 and again in the same months of 1985. This fungicide must be sprayed quite close to the ground when there is no wind to avoid dissemination onto adjoining plantations.

The reservoir for the town water supply is in an area called Red Hill. The reservoir was covered in 1982. The Division of Analytical Laboratories of the NSW Department of Health is conducting a survey of chemicals in the water supply and in breast milk.

DISCUSSION

The findings in this type of study must be interpreted cautiously because of the methods of data collection, the relatively small number of malformed infants, and the number of statistical comparisons that were made. Also, with the intense publicity given to the topic in the media shortly after the cluster was recognised, the answers to questions about possible exposures before and during pregnancy to chemicals and other substances may have been influenced by this publicity. Because environmental exposure to chemicals usually cannot be measured directly, it is difficult to assess any dose-response relationship between exposure levels and the outcomes that are studied. Such a relationship is important in trying to establish causation. Finally, many different chemicals are frequently used in areas where crops and fruit are grown.

When the questionnaires containing information about possible chemical exposures among the parents of infants with cleft lip and palate were reviewed, no common exposures to environmental chemicals were identified. Nevertheless, the period in February to May 1984 of widespread spraying of banana plantations with the relatively new

fungicide (Tilt) did coincide with the period of organogenesis and susceptibility to teratogens (the 7th and 8th weeks after fertilization) of this cluster of infants. It should also be noted that similar chemicals were again used in 1985 and anecdotal information does not indicate another cluster of malformed infants. Data held by the Commonwealth Department of Health on embryotoxicity and teratogenicity studies of Tilt in rats and rabbits do not show any evidence of teratogenicity. The concurrence of the widespread use of Tilt in Coffs Harbour and the cluster of infants with cleft lip and palate indicate that further studies are needed of the incidence of cleft lip and palate in other areas where this fungicide is used.

There is scanty information about human studies of exposures to agricultural chemicals and major congenital malformations. One case-control study of the association between agricultural chemical use and cleft lip and/or cleft palate suggested an effect when a multiple exposure index of agricultural chemicals was made. Several studies in Western Australia have shown a higher incidence of oro-facial clefts in conceptions in rural areas, but no data on chemical exposures were given.

The high odds ratios for exposures to some chemicals should be interpreted cautiously for the reasons already given. Nevertheless, further studies of these associations are necessary. Maternal exposures to chemicals before pregnancy and paternal exposures to chemicals after conception are not consistent with a teratogenic effect of chemicals on the embryo during the first trimester of pregnancy. It should be noted, however, that maternal occupational exposure in the first three months of pregnancy to outdoor pesticides and paternal occupational exposure to pesticides before conception were of borderline significance.

Further studies are required to identify other regions in Australia and in other countries where these chemicals are used so that the pattern of congenital malformations can be examined. In our view, the findings in this study of the Coffs Harbour region do not warrant any specific restrictions - other than those imposed for any other reasons - of the use on banana plantations of Tilt or other chemicals.

Because of the temporal clustering of the births of infants with cleft lip and cleft palate, the possibility of congenital infections should be considered. A study of viral antibody titres of families will be undertaken in Coffs Harbour.

Residents of Coffs Harbour have suggested that the families of infants with major congenital malformations are more likely to live in particular areas of Coffs Harbour near banana plantations. Also, the fathers of infants with one type of congenital malformation were noted to have similar occupations. Follow-up studies of spatial and temporal clustering of malformed infants and all births in the region are required. Additional information about the occupations of parents of malformed and non-malformed infants born in the period 1981-1985 should also be obtained.

ACKNOWLEDGEMENTS

We gratefully acknowledge the assistance given in preparing this report by the staff of the National Perinatal Statistics Unit and by other people:

Jennifer Burn, Jocelyn Mann, Fiona Tulip (National Perinatal Statistics Unit)

Dr. Peter Christopher, Gary Eckstein, Jannifer Armstrong (NSW Department of Health)

Leanne Wallace (Division of Analytical Laboratories, NSW Department of Health)

Dr. Derek Harris, Dr. Owen Spencer (North Coast Health Region)

Dr. Robin Jelliffe, Dr. Gary Dissevelt and other doctors and staff in Coffs Harbour Hospital

Lorraine Wright (Women for Health, Coffs Harbour)

Harvey Baker (Registrar of Pesticides, NSW Department of Agriculture)

Peter Davey (Acting Regional Director of Agriculture), Greg Ireland - North Coast Region, NSW Department of Agriculture

Dr. Alan Black, Dr. A. Browning, Airdrie Mann (Commonwealth Department of Health)

Dr. Neill Stacey (National Occupational Health and Safety Commission)

REFERENCES

Burman NT. Epidemiological aspects of oro-facial clefts in Western Australia. Aust Dent J 1983;28:227-232.

Wallenstein S. A test for detection of clustering over time. Am J Epidemiol 1980;111:367-372.

Leck I. Correlations of malformation frequency with environmental and genetic attributes in man. In: Wilson JG, Fraser FC, eds. Handbook of teratology. Vol.3. Comparative, maternal, and epidemiologic aspects. New York: Plenum Press, 1977:243-324.

Moore KL. The developing human: clinically oriented embryology. 3rd ed. Philadelphia: WB Saunders, 1982.

Quine S. 'Does the mode matter?' - a comparison of three modes of questionnaire completion. Community Health Stud 1985;9:151-156.

Gordon JE, Shy CM. Agricultural chemical use and congenital cleft lip and/or palate. Arch Environ Health 1981;36:213-221.

Table 1

Reported incidence of major congenital malformations in Coffs Harbour area and New South Wales, 1981-1984

1981*

Local Government Area	Number of infants	Total births	Rate/ 10,000
Bellingen	6	181	331.5
Coffs Harbour	9	568	158.5
Nambucca	3	203	147.8
Combined LGA	18	952	189.1
Clarence subdivision	21	1,481	141.8
New South Wales	755	47,715	158.2

* Reporting from many hospitals was incomplete

1982

Local Government Area	Number of infants	Total births	Rate/ 10,000
Bellingen	1	159	62.9
Coffs Harbour	8	640	125.0
Nambucca	8	203	394.1
Combined LGA	17	1,002	169.7
Clarence subdivision	23	1,568	146.7
New South Wales	1,309	84,593	154.7

1983

Local Government Area	Number of infants	Total births	Rate/ 10,000
Bellingen	1	153	65.4
Coffs Harbour	6	659	91.0
Nambucca	1	232	43.1
Combined LGA	8	1,044	76.6
Clarence subdivision	14	1,602	87.4
New South Wales	1,256	83,893	149.7

Table 1 (cont.)

1984

Local Government Area	Number of infants	Total births	Rate/ 10,000
Bellingen	1	166	60.2
Coffs Harbour	15	605	247.9
Nambucca	3	247	121.5
Combined LGA	19	1,018	186.6
Clarence subdivision	26	1,579	164.7
New South Wales	1,044	78,636	132.8

1981-84

Local Government Area	Number of infants	Total births	Rate/ 10,000
Bellingen	9	659	136.6
Coffs Harbour	38	2,472	153.7
Nambucca	15	885	169.5
Combined LGA	62	4,016	154.4
Clarence subdivision	84	6,230	134.8
New South Wales	4,364	294,837	148.0

Table 2

Incidence of cleft lip and/or cleft palate
Coffs Harbour region and New South Wales, 1981-1984

Local government area	Cleft palate	Cleft lip +/- cleft palate	Total cleft lip and/or cleft palate
Bellingen, Coffs Harbour Nambucca			
- number of infants	2	8	10
- total births	4,016	4,016	4,016
- rate /10,000 births	5.0	19.9	24.9
Rest of Clarence subdivision			
- number of infants	1	2	3
- total births	2,214	2,214	2,214
- rate /10,000 births	4.5	9.0	13.6
Clarence subdivision			
- number of infants	3	10	13
- total births	6,230	6,230	6,230
- rate /10,000 births	4.8	16.1	20.9
New South Wales			
- number of infants	165	264	429
- total births	294,837	294,837	294,837
- rate /10,000 births	5.6	9.0	14.6

Table 3

INFANTS WITH MAJOR CONGENITAL MALFORMATIONS
COFFS HARBOUR REGION, 1984

Date of birth	LGA of residence	Hospital of birth	Infant's sex	Congenital malformations	Source			Quest.
					NPSU	CHD	Other	
24.2.84	CH	CH	F	Coarctation of aorta, atrial septal defect, patent ductus arteriosus			•	Y
25.2.84	CH	CH	M	Down syndrome (translocation)	•		•	Y
6.4.84	CH	CH	M	Down syndrome (T21)	•		•	Y
17.4.84	CH	CH	F	Pulmonary artery stenosis			•	N
26.4.84	CH	Dorrigo	M	Hypospadias/absent left kidney			•	N
10.5.84	CH	CH	F	Bilateral cleft lip and palate	•		•	Y
15.5.84	CH	CH	M	Upper limb reduction defect (three metacarpals, shortened humerus and radius)	•		•	N
27.5.84	Nam.	Macksville	M	Spina bifida, talipes, undescended testis	•			N
17.6.84	CH	CH	F	Pulmonary stenosis	•	•		N
21.6.84	Nam.	CH	M	Tetralogy of Fallot	•	•	•	N
23.6.84	CH	Bellingen	M	Diastematomyelia, horseshoe kidney	•			Y
13.7.84	CH	CH	F	Cataract of left eye			•	Y
31.7.84	CH	CH	M	Hypospadias	•		•	N
21.8.84	Bell.	CH	F	Spina bifida, talipes	•		•	Y
22.9.84	CH	CH	F	Hypoplastic left heart syndrome	•	•	•	Y
25.9.84	CH	CH	F	Iniencephaly	•			Y
3.10.84	CH	CH	M	Bilateral cleft lip and palate, Aarskog syndrome	•		•	Y

Table 3 (cont.)

Date of birth	LGA of residence	Hospital of birth	Infant's sex	Congenital malformations	Source			Que:
					NPSU	CHD	Other	
8.10.84	CH	CH	M	Unilateral cleft lip and palate	•		•	Y
3.11.84	CH	CH	M	Pulmonary atresia, ventricular septal defect, patent ductus arteriosus	•	•	•	Y
12.11.84	CH	CH	F	Bilateral cleft lip and palate	•		•	Y
16.11.84	Nam.	CH	M	Upper limb reduction defect (unilateral, transverse)	•			Y
18.11.84	CH	CH	F	Cri du chat syndrome (chromosome five p-)	•		•	Y
18.11.84	CH	CH	F	Unilateral cleft lip and palate, coarctation of aorta, patent ductus arteriosus	•		•	Y
20.11.84	Nam.	CH	F	Cleft lip and palate			•	Y
Doubtful or excluded cases								
16.7.84				Talipes			•	
22.11.84	CH	CH	F	Unusual appearance			•	

Sources: NPSU - National Perinatal Statistics Unit
CHD - study of congenital heart defects in New South Wales by NPSU
Other - data from Women for Health survey in Coffs Harbour and local doctors

Abbreviations: CH - Coffs Harbour
Nam. - Nambucca
Bell.- Bellingen

Table 4

Data from questionnaires completed by parents of infants with cleft lip and cleft palate

Area of residence	Maternal age	Previous pregnancies	FH of CL/CP	Maternal illnesses[a]	Maternal drugs[a]	Exposure to chemicals[a]		Water supply	Cigarette smoking[a]	Alcohol[a]
						Environmental	Household			
1.CH	24	2+0	-	Vomiting, hay fever, cold	Ancolan	Spraying of bananas - 1km. away; paint spray	Fly spray insect repellant	Town	-	-
2.Bonville (CH)	36	0+2	-	Nausea, headache	Panadeine, aspirin, marihuana	Aerial spraying of bananas	Fly spray, aerogard, oven cleaner	Town and local stream	-	+
3.Mullaway (CH)	25	1+0	-	-	-	-	Fly spray	Home tank	-	+
4.CH	21	2+0	-	Nausea, vomiting, urinary tract infection	-	-	Baygon, Fabulon, fibreglass	Town	++	-
5.Dorrigo	30	1+2	-	Nausea, vomiting, cold	Ancolan	-	Johnson Bolt, fertiliser, fly spray	Town, dam	-	-
6.Macksville	29	2+1	-	-	-	-	Fly spray, cockroach spray	Town	-	-

[a] in first 3 months of pregnancy

Table 5

Summary of odds ratios (and their 95% confidence limits) of exposures either before or during the first 3 months of pregnancy among cases and controls

Exposures	Number of cases (18)		Number of controls (50)		Odds ratio	95% confidence limits
	Exp.	Not exp.	Exp.	Not exp.		
Maternal exposures before pregnancy						
. outdoor pesticides	11	7	17	33	3.1	0.98 - 9.5
. outdoor pesticides (occupational)	6	12	5	45	4.5	1.2 - 17.3
. indoor pesticides (excl. fly-sprays)	4	14	2	48	6.9	1.1 - 41.4
. indoor pesticides (incl. fly-sprays)	14	4	35	15	1.5	0.4 - 5.3
. water supply (town/other)	13	5	40	10	0.7	0.2 - 2.3
Maternal exposures in first three months of pregnancy						
. chemical cleaning agents	7	11	24	26	0.7	0.2 - 2.1
. paints	2	16	16	34	0.3	0.1 - 1.3
. oil-based or varnish paints	1	17	8	42	0.3	0.04 - 2.7
. paint remover, thinner or solvent	2	16	6	44	0.9	0.2 - 5.0
. glues and adhesives	0	18	7	43	-	-
. outdoor pesticides	6	12	7	43	3.1	0.8 - 11.2
. outdoor pesticides (occupational)	6	12	6	44	3.7	1.0 - 13.4