

Prevalence of adverse reproductive outcomes in a population occupationally exposed to pesticides in Colombia

by Mauricio Restrepo, MD,¹ Nubia Muñoz, MD,² Nicholas E Day, PhD,³ José E Parra, MS,¹ Laura de Romero, MS,¹ Xuan Nguyen-Dinh, MS²

RESTREPO M, MUÑOZ N, DAY NE, PARRA JE, DE ROMERO L, NGUYEN-DINH X. Prevalence of adverse reproductive outcomes in a population occupationally exposed to pesticides in Colombia. *Scand J Work Environ Health* 1990;16:232–8. A prevalence survey of adverse reproductive outcomes was carried out in a population of 8867 persons (2951 men and 5916 women) who had been working in the floriculture industry in the Bogotá area of Colombia for at least six months. These workers were exposed to 127 different types of pesticides. The prevalence rates for abortion, prematurity, stillbirths, and malformations were estimated for pregnancies occurring among the female workers and the wives of the male workers before and after they started working in floriculture, and these rates were related to various degrees of exposure. A moderate increase in the prevalence of abortion, prematurity, and congenital malformations was detected for pregnancies occurring after the start of work in floriculture.

Key terms: abortion, birth defects, floriculture, pesticides, prematurity, stillbirths.

Experimental and epidemiologic evidence indicates that certain industrial and environmental chemicals, and also some pharmaceutical products, can cause reproductive toxicity (1, 2). Among these chemicals, pesticides pose special concern due to their ever increasing use, their large number, their wide environmental distribution with vast potential for human exposure, and their toxicologic characteristics.

Many epidemiologic studies have already been devoted to the adverse reproductive effects of human exposure to chemicals (1, 2), but only a few deal with exposure to phenoxy herbicides and related dioxins (3–13).

The present study was undertaken in an attempt to ascertain the occurrence of certain reproductive events among a population occupationally exposed to a heterogeneous group of pesticides and to assess the possible association between adverse events and such exposure. The occurrence of fetal loss, prematurity, congenital malformations, and cancer was studied among the offspring of workers in the floriculture industry in Bogotá, Colombia, by means of a questionnaire administered by an interviewer.

Subjects and methods

The flower-growing industry is located on the Bogotá plateau at 2653 m above sea level. The mean temperature is 13°C without seasonal variations in the weather, and there are two periods of rain, one in May and the other in November. The flowers are grown within semiclosed polyethylene greenhouses and then exported. The importance of this relatively new enterprise is illustrated by the fact that 90 % of the 350 million cut flowers imported every year into the United States comes from Colombia (14).

All persons who had been working for a period of at least six months in 58 companies affiliated with the Colombian Association of Flower Growers (Asocol-flores) were defined as the study population. A list of 12 129 workers was obtained from the 58 companies, and 10 238 of the workers proved to be eligible for the study. After exclusions for various reasons (sickness, vacation, or retirement) 9328 were eligible for the interview, and 8867 (95 %) were actually interviewed.

A precoded questionnaire containing demographic information, detailed reproductive history of the female workers and all the partners of the male workers, and information about the length of time worked in floriculture and type of job was administered to each of the subjects by specially trained interviewers. The interview took place in 1981. It was usually conducted at the workplace and lasted approximately 10 min. It was supervised and assisted by the study statistician, who also checked each questionnaire for completeness and consistency before recording it onto a magnetic tape.

The reproductive history was oriented to establish the pregnancies of each woman and the outcome of each pregnancy. Such outcomes reported by each in-

¹ Instituto Nacional de Salud, Sanidad del Ambiente, Bogotá, Colombia.

² International Agency for Research on Cancer, Lyon, France.

³ MRC Biostatistics Unit, Cambridge, United Kingdom.

interviewee were recorded according to the following definitions: (i) pregnancy was defined as the subjective perception of this event by the study subject, (ii) abortion was fetal loss at less than 20 weeks of gestation, (iii) stillbirth was a fetus expelled after the 21st week of pregnancy, but without any evidence of life at birth, (iv) a premature baby was a baby born alive between the 21st and 36th week of gestation, (v) a full-term baby was a baby born alive after the 36th week of gestation, (vi) a malformed child was defined as one with some structural or functional defect as detected by the parents and/or the physician at birth or afterwards, (vii) a child with cancer was a child for whom this specific diagnosis was made by a physician.

The rates for the various outcomes were calculated as follows: (i) rate of abortion = number of abortions/number of pregnancies $\times 100$, (ii) rate of stillbirth = number of stillbirths/number of pregnancies $\times 100$, (iii) rate of prematurity = number of premature births/number of pregnancies $\times 100$, and (iv) the rate of congenital malformation = number of malformed children/number of births $\times 100$ — in these calculations “pregnancies” included abortions, stillbirths, premature births, and full-term births.

Assessment of exposure to pesticides

In a first stage, exposure or nonexposure was defined, with regard to the occurrence of each pregnancy, before or during the time the relevant parent worked in floriculture. Thus exposed pregnancies were those occurring during the time the relevant parent worked in floriculture, and unexposed pregnancies were those occurring before the parent worked in floriculture. The following two assumptions were made: (i) that, once the parent began to work in floriculture, he or she did not leave, and therefore all the pregnancies occurring after the date given by the parent as the starting date in floriculture were considered exposed and those occurring before that date were considered unexposed; (ii) that the parent did not change from one company to another or from one job to another during the time worked in floriculture, and therefore the company and the job given in the interview were taken into account to evaluate the exposure.

In a second stage, an assessment of different degrees of exposure was attempted with the use of the following variables: size of the company, amount of pesticides used, job category, and length of time worked in floriculture. Information on these variables was obtained during a survey on patterns of pesticide use conducted in each of the 58 floriculture companies. In addition, a pilot study was conducted in two floriculture companies by the University of Miami to assess specifically the exposure to Captan (1,2,3,6 tetrahydro-N-trichloro-methylthio-phthalimide), a fungicide, which is the most used pesticide in this industry. This pilot study was especially helpful in assessing the exposure associated with each job during the cultivation process. The main results of this pilot study are summarized in table 1.

Size of company. It was assumed that exposure to pesticides was lower in the large companies, which usually have industrial hygiene programs oriented to minimize exposure, and higher in small companies. The following three subgroups were considered according to size: small <100 workers, medium 100–400 workers, large >400 workers.

Amount of pesticides used. For an estimate of the amount of pesticides used a ratio was calculated, dividing the total amount used by the total cultivated area. Three subgroups were again considered, ie, low-use-of-pesticides ratio <120, medium-use ratio 120–400, high-use ratio >400.

Job type. Six main job types were considered during the cultivation process, and they were graded according to the degree of exposure, on the basis of the results of the pilot study that has already been mentioned, as follows: (i) administration: nonexposure, (ii) construction and maintenance of greenhouses: low exposure, (iii) soil preparation: low exposure, (iv) nursery of plants: low exposure, (v) cultivation: medium exposure, (vi) sorting and packing: high exposure.

Table 1. Air levels of Captan (1,2,3,6 tetrahydro-N-trichloro-methylthio-phthalimide) ($\mu\text{g}/\text{m}^3$) by type of job. (ND = not detectable)

Worker category	Company 1				Company 2			
	Mean	SD	Lowest value	Highest value	Mean	SD	Lowest value	Highest value
Cultivators & pruners	21.59	42.3	<0.01	106.3	135.5	85.1	38.9	243.5
Sorters	51.14	55.9	0.24	109.2	417.4	385.9	13.0	1201.4
Propagators	0.05	0.03	ND	0.1	69.2	67.5	0.58	180.0
Office workers	0.30	0.29	<0.1	0.5	1.59	2.5	0.21	6.1
Company overall	16.89	37.7	ND	109.2	175.9	257.0	0.21	1201.4

Length of exposure. According to the length of time worked in floriculture, the following three subgroups were considered: 6–11 months: low exposure, 12–36 months: medium exposure, >36 months: high exposure.

Statistical analysis

The statistical analysis used each pregnancy as a unit and was carried out in two stages. In the first stage, the prevalence rates for each adverse pregnancy outcome occurring before exposure to pesticides were compared with the corresponding rates observed after exposure to pesticides. The ratio of the two rates was interpreted as an odds ratio (OR). In the second stage, similar odds ratios were estimated for the variables used to estimate different degrees of exposure to pesticides (company size, amount used, job type, and length of exposure), and also for relevant covariables (age at interview, age at pregnancy, pregnancy order, year of pregnancy occurrence, and educational level).

The chi-square was used to estimate the statistical significance of the observed differences. These analyses were carried out separately for the female workers and for the wives of the male workers.

Results

The main characteristics of the study population are shown in table 2. Out of the 8867 workers, 33 % were men and 67 % women, and their mean ages were 29.2 years and 27.0, respectively. The majority of the workers had only primary education or no education. About 60 % of both the male and the female workers were or had been married (or lived maritally) and the average number of pregnancies among them was 2.9 for both the wives of the male workers and the female workers. The mean length of work in floriculture was about three years.

Fifty-nine percent of the 5916 female workers and 54 % of the 2951 wives of the male workers reported at least one pregnancy. Figure 1 shows the distribution of pregnancies which occurred among them before and after the start of work in floriculture. Out of the 10 680 pregnancies reported by the female workers, 199 were excluded because of missing or inadequate information, and, of the pregnancies of the wives of the male workers, 178 were excluded because of similar reasons and 961 because the wives themselves were also floriculture workers. The total number of pregnancies included in the analysis was then 13 984, and 10 481 of them had occurred among the female workers and 3 503 among the wives of the male workers.

The numbers and rates for the various pregnancy outcomes are shown in table 3. The lower rates reported by the male workers, especially for abortion and premature births, suggest that the fathers had little knowledge of their wives' pregnancies which terminated in abortion or a premature baby. As part of a separate study, the wives of the male workers were interviewed with the same questionnaire, and the degree of agreement between the responses given by the husband and wife was assessed; the results of this analysis, which will be reported elsewhere (Velema et al, "The Evaluation of Agreement by Means of Log-linear Models: Proxy Interviews on Reproductive History among Floriculture Workers in Colombia" submitted for publication), showed that the degree of agreement depended on the length of the reproductive history and on the age of both parents.

The rates and odds ratios for the various adverse outcomes of pregnancies occurring before and after exposure to pesticides in floriculture are summarized

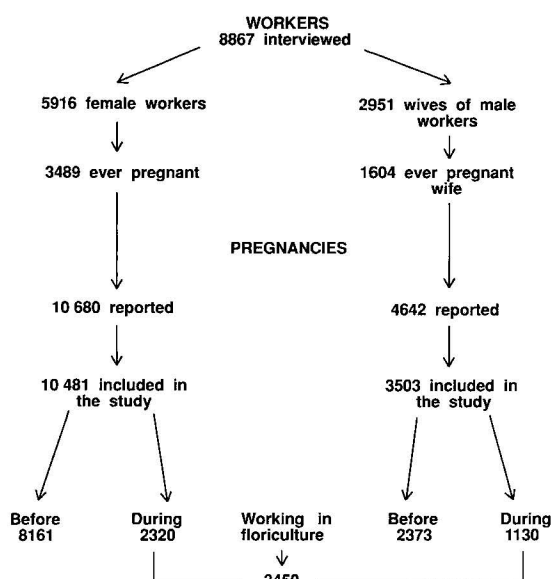


Figure 1. Schematic presentation of the study design.

Table 2. Characteristics of the study population.

	N	Mean age (years)	Education				Marital status			Mean number of pregnancies	Mean time in floriculture (months)
			None (%)	Primary (%)	Secondary (%)	Technical or university (%)	Single (%)	Married or living maritally (%)	Widowed or divorced (%)		
Men	2951	29.2	7.2	61.1	20.5	11.2	41.1	54.7	4.2	2.9 (wives)	36.7
Women	5916	27.0	4.3	68.3	23.1	4.3	37.8	42.0	20.2	2.9	35.0

Table 3. Frequency of different pregnancy outcomes among the floriculture workers.

Pregnancy outcome	Total population		Female workers		Wives of male workers	
	N	Rate (%)	N	Rate (%)	N	Rate (%)
Abortions						
Induced	204	1.46	185	1.77	19	0.54
Spontaneous	545	3.90	464	4.43	81	2.31
Births						
Stillbirths	175	1.25	141	1.35	34	0.97
Live births	13 060	.	9 691	.	3369	.
Premature	915	6.54	760	7.25	155	4.42
Full-term	12 320	.	9 072	.	3248	.
Total	13 235	.	9 832	.	3403	.
Total pregnancies	13 984	.	10 481	.	3503	.

Table 4. Rates and odds ratios (OR) for various adverse pregnancy outcomes before and after work in floriculture. (95 % CI = 95 % confidence interval)

Pregnancy outcome	Female workers				Wives of male workers			
	Prevalence rates (%)		OR	95 % CI	Prevalence rates (%)		OR	95 % CI
	Before exposure	After exposure			Before exposure	After exposure		
Induced abortion	1.46	2.84	1.98**	1.47—2.67	0.29	1.06	3.63**	1.51—8.70
Spontaneous abortion	3.55	7.50	2.20**	1.82—2.66	1.85	3.27	1.79**	1.16—2.77
Premature baby	6.20	10.95	1.86**	1.59—2.17	2.91	7.61	2.75**	2.01—3.76
Stillbirth	1.35	1.34	0.99	0.66—1.48	1.01	0.89	0.87	0.42—1.83
Malformed baby	3.78	5.00	1.34*	1.07—1.68	2.76	4.16	1.53*	1.04—2.25

* $P=0.05-0.01$; ** $P<0.01$.

in table 4. All the rates, except those for stillbirths, were higher for pregnancies occurring after exposure to pesticides among both the female workers and the wives of the male workers and thus gave significantly increased odds ratios for abortions, premature births, and malformed babies. The high odds ratios observed, even for induced abortion, are surprising and cast doubt on the reliability of the association between the observed increased risks and the exposure to pesticides.

Table 5 summarizes the odds ratios for spontaneous abortion for different degrees of exposure to pesticides. No dose-response relationship was observed with any of the variables used as indicators of degree of exposure; furthermore, an inverse relationship was observed with the two variables which could be regarded as more objective (type of job and length of time worked in floriculture). The highest odds ratios were observed for the unexposed jobs, eg, administration, and for workers with 6 to 11 months of work in floriculture. These results are not surprising if we consider that only exposure during a short critical period is relevant in the induction of embryotoxic effects.

Table 6 shows the odds ratios for spontaneous abortion according to some of the relevant covariables. The fact that the odds ratio increased with the age of the subject at interview and decreased for the most recent pregnancies suggests that the observed increased risk

Table 5. Risk of spontaneous abortion according to the variables used as indicators of various degrees of exposure to pesticides. (OR = odds ratio, 95 % CI = 95 % confidence interval)

Indicator variable ^a	Female workers		Wives of male workers	
	OR	95 % CI	OR	95 % CI
Company size				
Small (< 100 workers)	2.37**	1.27—4.43	1.75	0.53—5.74
Medium (100—400 workers)	2.26**	1.68—3.05	1.27	0.57—2.79
Large (> 400 workers)	2.14**	1.63—2.80	2.23**	1.23—4.03
Amount of pesticides ^a				
Low (ratio < 120)	2.01**	0.96—4.21	1.26	0.22—7.05
Medium (ratio 120—400)	2.31**	1.70—3.14	2.09*	1.03—4.27
High (ratio > 400)	2.21**	1.62—3.02	2.05*	1.03—4.08
Type of job				
Administration	3.17**	1.50—6.70	2.38*	1.13—5.02
Construction & maintenance			1.56	0.66—3.67
Plant nursery	0.94	0.41—2.14		
Cultivation	2.47**	2.01—3.04	1.96**	1.18—3.27
Sorting and packing	1.66*	1.12—2.46	0.73	0.10—5.29
Length of time working in floriculture (months)				
6—11	2.94**	2.12—4.09	2.22*	1.05—4.69
12—36	1.94**	1.48—2.54	1.18	0.55—2.53
> 36	2.16**	1.64—2.83	2.04	1.22—3.43

^a Ratio calculated by dividing the total amount used by the total cultivated area.

* $P<0.05$, ** $P<0.01$.

for abortion might be explained at least in part by recall bias.

Table 6. Risk of spontaneous abortion according to various covariables. (OR = odds ratio, 95 % CI = 95 % confidence interval)

Covariables	Female workers		Wives of male workers	
	OR	95 % CI	OR	95 % CI
Age at interview (years)				
≤25	1.61*	1.02–2.56	0.38	0.06–2.19
26–40	2.56**	2.03–3.24	1.43	0.79–2.59
>40	2.60*	1.19–5.68	2.16	0.93–4.98
Age at pregnancy (years)				
<19	2.36*	1.04–5.34	1.53	0.25–9.17
19–30	1.88**	1.49–2.38	1.61	0.95–2.75
>30	2.20**	1.50–3.22	2.53*	1.09–5.87
Pregnancy order				
1st to 3rd	2.43**	1.90–3.10	1.46	0.87–2.46
4th to 6th	2.27**	1.58–3.27	2.73	1.01–7.33
>6th	1.88*	1.08–3.26	3.68	0.98–13.90
Year of pregnancy				
1960–1969			3.25	0.46–23.09
1970–1973	1.25	0.50–3.16	0.57	0.07–4.46
1974–1977	2.01*	1.36–2.97	0.94	0.39–2.24
1978–1981	1.11	0.75–1.66	1.05	0.39–2.79
Level of education				
None	2.19	1.00–4.79	1.95	0.41–9.33
Primary	2.25**	1.81–2.79	1.73	0.94–3.16
Secondary	1.60	0.93–2.78	0.33	0.10–1.10
Superior	2.47	0.81–7.51	2.07	0.74–5.85

* $P < 0.05$, ** $P < 0.01$.

Table 7. The ten pesticides most commonly used in floriculture.

Generic name	Action	Chemical group	Use (%)	
			Solids	Liquids
Captan	Fungicide	Phthalimide	16.6	·
Propineb	Fungicide	Dithiocarbamate	7.0	·
Mancozeb	Fungicide	Dithiocarbamate	7.0	·
Chlorothalonil	Fungicide	Chlorinated	5.0	·
Benomyl	Fungicide	Carbamate	5.0	·
Zineb	Fungicide	Dithiocarbamate	4.5	·
Dienochlor	Insecticide	Chlorinated	4.0	·
Oxycarboxin	Fungicide	Carboxanilide	2.0	·
Tetradifon	Fungicide	Diphenyl sulfone	·	12.6
Dicofol	Insecticide	Chlorinated	2.0	·
Total			53.10	12.6

A similar analysis was done for prematurity, and no dose-response relationship was observed with various degrees of exposure to pesticides. The analysis by age of the subject at interview and by year of occurrence of the relevant pregnancies suggests that the increased risk observed for prematurity among the female workers was probably not due to recall bias.

In relation to congenital malformations, a moderately increased risk was observed for pregnancies which occurred after work in floriculture both among the female workers (OR 1.34, 95 % CI 1.07–1.68) and among the wives of the male workers (OR 1.53, 95 % CI 1.04–2.25). However, a subsequent study in which the reported presence or absence of malformation was validated by a physical examination of the children revealed that about half of the children reported as malformed by their parents were in fact normal, and about 10 % of those reported as normal were in fact

malformed. The results concerning confirmed malformations have been reported separately (15).

The parents reported 23 children as having had cancer; for 20 of them, additional information was obtained from the medical records. Only three of the 20 children were alive and none had cancer. Cancer was confirmed for only seven of the remaining 17 children (4 cases of leukaemia, 1 case of Wilm's tumor, 1 case of fibrosarcoma, and 1 case of brain tumor). However, all these cases occurred before their parents began to work in floriculture.

In relation to the pesticides to which the floriculture workers were exposed, 127 different products (chlorinates, organophosphorates, carbamates, dithiocarbamates, organotin, pyrethroids, and others) were used in the companies participating in the study. In 1981, the mean amount used per company was 2765 kg of solid and 1341 l of liquid pesticides per year. Table 7 shows the 10 most used pesticides, which accounted for 67 % of the total pesticides used in floriculture. Although fungicides were the most heavily used products and Captan the most used fungicide, it was obvious that the exposure to pesticides in this floriculture population was multiple.

Discussion

This study revealed a moderately increased risk for spontaneous abortion, prematurity, and congenital malformations among female workers and wives of male workers in floriculture after they began this work. The next question that needs to be answered is "Was this increased risk real or spurious?"

With regard to abortion, the risk was higher for the older women, and the increase in risk disappeared for pregnancies occurring in the most recent period. This finding suggests that the observed increased risk might not be related to exposure to pesticides in floriculture, but it might be due to recall bias, as women tend to have less recall of abortions which occurred in the distant past. Similar conclusions could be reached for prematurity among the wives of the male workers but not for prematurity among the female workers. No association at all was observed for stillbirth. It must be mentioned that, due to its low frequency, stillbirth has been considered a weak indicator of developmental toxicity in relation to environmental chemicals (16).

The results concerning spontaneous abortion deserve further comment. Besides chemical exposures, spontaneous abortion can be caused by several other factors that can act as confounders within a study (17–19). Spontaneous abortion, especially if it occurs early in pregnancy, is an excellent indicator of embryotoxicity (17, 20, 21). Unfortunately, it has been widely recognized that recording the event appropriately is a very difficult task (19, 22). There is a high probability for women not to recognize the event as such but to perceive it as a delayed menstrual period if it occurs very early in pregnancy (19, 23). On the other hand,

there is a tendency to forget the event with time even when it has been adequately perceived (21).

When the overall rates obtained in this study are examined, it is obvious that there was a severe underreporting of spontaneous abortion, and the underreporting is more important when the information on the reproductive history of the woman is given by her husband. It has been reported that spontaneous abortion rates vary from 5 to 49 % (22–27), depending upon the way in which the event is detected. When the event is ascertained retrospectively by means of a questionnaire, the rates are between 5 and 10 % (27), and those found in this study ranged from 1.8 to 7.5 %.

The observed underreporting can be explained by a lack of perception, which is a good explanation in the case of the wives of the male workers. In the case of the female workers, it can be considered possible that the majority of the spontaneous abortions were very early and therefore were not recognized by the women. Such an occurrence would indicate the possible action of an environmental embryotoxic agent. The data in this study cannot support this explanation given that the problem of perception was the same for the pregnancies occurring before and after work in floriculture. A more plausible explanation is a problem with recalling the event (21). In fact, when the rates are considered according to the year of occurrence, it appears that, for the more recent period (1978–1981), the rates for spontaneous abortion before and after work in floriculture were 6.9 and 7.6 %, respectively, ie, rates very similar to the ones reported by other populations (27).

Another potential problem which must be considered in the interpretation of our results is random misclassification of exposure. The accurate identification of a critical exposure period and of a specific agent is necessary for random misclassification not to occur and for a dampening of the relative risk to be avoided (28, 29). Using the total duration of exposure might mask effects that might otherwise have been apparent if only the exposure during the critical time had been considered (29). Multiple exposures not only pose the problem of identifying the toxic chemical responsible, but also the problem of interaction between chemicals in the expression of toxic effects (30). Given the assumptions made to estimate exposure within this study and the multiple exposure that has been considered, it seems clear that a random misclassification of exposure can play a role biasing the risk estimators towards the null. Unfortunately, it was not possible with the available information, or by means of external sources, to assess the degree of such a bias and, most important, to correct it.

For congenital malformations, we should also consider the possibility of misclassification, not only of the exposure, but also of the outcome. To validate the diagnosis of congenital malformation as reported by the parents, a case-referent study was nested in our prevalence survey, and the presence or absence of mal-

formation was ascertained by a physical examination of the children. The results of this study, which is being reported separately (15) revealed that 53 % of the children reported as malformed by their parents were in fact normal, and 8 % of those reported as normal were in fact malformed. This finding suggests that no conclusions can be drawn in the present study concerning congenital malformations.

The overall results of no association or a moderate increase in risk for some adverse pregnancy outcomes which might be due to recall bias and/or to misclassification of exposure are in agreement with the results reported previously for other populations (3–9, 11–13). Although some ecological studies in Seveso, Italy, and in Vietnam suggested an increase in spontaneous abortions after possible maternal exposure to phenoxy herbicides and dioxins, the various methodological problems related to the difficulties in assessing exposure and in eliminating possible confounding and bias prevent definitive conclusions from being drawn from these studies. Similar limitations apply to ecological studies on paternal exposure to these substances (31). This and previous studies on the subject should then be considered as preliminary approaches to a very complex problem that must be a matter of further research.

Acknowledgments

We would like to thank Dr E Guerrero, National Health Institute, Bogotá, Colombia, for his assistance during the initial phases of this investigation; Drs J Davies and R Pfaffenberger, University of Miami, Miami, Florida, for conducting the pilot study to assess the different degrees of exposure to Captan in the various floriculture jobs; Dr B Miller, National Cancer Institute, Bethesda, Maryland, for his valuable advice; Drs H Vainio and R Cabral, International Agency for Research on Cancer, Lyon, France, for their helpful discussions and encouragement; and the 58 floriculture companies and the Colombian Association of flower growers (Asocolflores) for their cooperation.

This study was supported by the United States Environmental Protection Agency under contract 68-01-6251 between the Agency and the Pan-American Health Organization.

References

1. Hemminki K, Axelson O, Niemi ML, Ahlborg G. Assessment of methods and results of reproductive occupational epidemiology: spontaneous abortions and malformations in the offspring of working women. *Am J Ind Med* 1983;4:293–307.
2. Hemminki K, Vainio H. Occupational epidemiology and reproduction. In: Harrington JM, ed. *Recent advances in occupational health*. Edinburgh: Churchill Livingstone, 1984:117–28.
3. Nelson CJ, Holson JF, Green HG, Gaylor DW. Retrospective study of the relationship between agricultural

- use of 2,4,5T and cleft palate occurrence in Arkansas. *Teratology* 1979;19:377—84.
4. Field E, Kew C. Herbicide use and incidence of neural tube defects. *Lancet* 1979;1:1341—2.
5. Thomas HF. 2,4,5T use and congenital malformation rates in Hungary. *Lancet* 1980;2:214—5.
6. Brogan WF, Brogan CE, Dadd JT. Herbicides and cleft lip and palate. *Lancet* 1980;2:597.
7. Gordon JE, Shy CM. Agricultural chemical use and congenital cleft lip and/or palate. *Arch Environ Health* 1981;36:213—21.
8. Hanify JA, Metcalf P, Nobbs CL, Worsley KJ. Aerial spraying of 2,4,5T and human birth malformations: An epidemiological investigation. *Science* 1981;212:349—51.
9. Smith AH, Fisher BS, Pearce N, Chapman CJ. Congenital defects and miscarriages among New Zealand 2,4,5T sprayers. *Arch Environ Health* 1982;37:197—200.
10. La Vecchio FA, Pashayan HM, Singer W. Agent orange and birth defects. *N Engl J Med* 1983;308:719—20.
11. Erikson JD, Mulinare J, McClain PN, et al. Vietnam veterans' risks for fathering babies with birth defects. *JAMA* 1984;252:903—12.
12. Roan CC, Matanoski GE, McIlroy CQ, et al. Spontaneous abortions, stillbirths, and birth defects in families of agricultural pilots. *Arch Environ Health* 1984;39:56—60.
13. Goldsmith JR, Potashnik G, Israeli R. Reproductive outcomes in families of DBCP-exposed men. *Arch Environ Health* 1984;39:85—9.
14. Morse DL, Baker EL, Landrigan PJ. Cut flowers: a potential pesticide hazard. *Am J Public Health* 1979;69:53—6.
15. R  strepo M, Mu  oz N, Day NE, et al. Birth defects among children born to a population occupationally exposed to pesticides in Colombia. *Scand J Work Environ Health* 1990;16:239—46.
16. World Health Organization. Principles for evaluating health risks to progeny associated with exposure to chemicals during pregnancy. Geneva: World Health Organization, 1984. (WHO environmental health criteria; 30.)
17. Stein Z, Susser M, Warburton D, Wittes J, Kline J. Spontaneous abortion as a screening device: the effect of fetal survival on the incidence of birth defects. *Am J Epidemiol* 1975;102:275—90.
18. Lauritsen JG. Aetiology of spontaneous abortion: a cytogenetic and epidemiological study of 288 abortuses and their parents. *Acta Obstet Gynecol Scand Suppl* 1976;52:1—29.
19. Potts M, Diggory P, Peel J. Abortion. Cambridge, MA: Cambridge University Press, 1977.
20. Kline J, Stein Z, Strobino B, Susser M, Warburton D. Surveillance of spontaneous abortions: power in environmental monitoring. *Am J Epidemiol* 1977;106:345—50.
21. Wilcox AJ, Horney LF. Accuracy of spontaneous abortion recall. *Am J Epidemiol* 1984;120:727—33.
22. James WH. The incidence of spontaneous abortion. *Popul Stud (London)* 1970;25:241—5.
23. Anonymous. Spontaneous abortion. *Lancet* 1975;2:591—2.
24. Miller JF, Williamson E, Glue J, Gordon YB, Grudzinskas JG, Sykes A. Fetal loss after implantation: a prospective study. *Lancet* 1980;2:554—6.
25. Golden WL. Reproductive histories in a Norwegian twin population: evaluation of the maternal effect in early spontaneous abortion. *Acta Genet Med Gemellol (Roma)* 1981;30:91—169.
26. Czeizel A, Bognar Z, Rockenbauer M. Some epidemiological data on spontaneous abortion in Hungary, 1971—80. *J Epidemiol Community Health* 1984;38:143—8.
27. Hemminki K, Niemi ML, Saloniemi I, Vainio H, Hemminki E. Spontaneous abortions by occupation and social class in Finland. *Int J Epidemiol* 1980;9:149—53.
28. Hogue CJR. Reducing misclassification errors through questionnaire design. In: Lockey JE, et al, ed. *Reproduction: the new frontier in occupational and environmental health research*. New York, NY: Alan R Liss Inc, 1984:81—97.
29. Lemasters GK, Selevan SG. Use of exposure data in occupational reproductive studies. *Scand J Work Environ Health* 1984;10:1—6.
30. Barlow SM, Sullivan FM. Reproductive hazards of industrial chemicals. London: Academic Press, 1982.
31. Sterling TD, Arundel AV. Health effects of phenoxy herbicides: a review. *Scand J Work Environ Health* 1986;12:161—73.

Received for publication: 14 August 1989