

Health effects of phenoxy herbicides

A review

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STERLING TD, ARUNDEL AV. Health effects of phenoxy herbicides: A review. *Scand J Work Environ Health* 12 (1986) 161–173. A review of epidemiologic studies on the health effects of exposure to phenoxy herbicides suggests that exposure may be associated with an increased incidence of cancer and unfavorable outcomes of pregnancy. Studies on cancer have found increased risks of 5.3, 6.8 and 3.96 for soft-tissue sarcoma, 7.7 and 6.0 for stomach cancer, 2.05 for lung cancer, 4.8 for lymphoma, 2.3 for all cancers combined, and 5.2 for liver cancer after exposure to 2,4,5-T or dioxin contaminants. Several studies have suggested a possible increase in birth defects after paternal exposure. An increased risk of hydatidiform mole is suggested by Vietnamese studies on the effects of maternal exposure.

Key terms: birth defects, cancer, dioxins, hydatidiform mole, soft-tissue sarcoma, spontaneous abortion.

Chemical preparations derived from chlorophenols have been used for over 35 years as fungicides, pesticides, and wood preservatives and for a variety of other agricultural, industrial, and commercial uses. Sodium salts of penta- and tetrachlorophenolate have been used in antistain water-soluble formulations since the late 1930s. Perhaps the most commonly recognized preparations derived from a chlorophenol precursor are the herbicides 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2,4-dichlorophenoxyacetic acid (2,4-D). Both were widely used for the control of unwanted broad-leaved plant species in forestry and on rights-of-way and for a large number of applications in agriculture.

All commercial grades of chlorophenol preparations contain some amount of toxic dimer contaminants. The contaminants include dioxins such as 2,3,7,8-tetrachlorodibenzo-para-dioxin (commonly known as TCDD) and isomers of dibenzofurans, including tetra and penta dibenzofuran (49). The most toxic of the dioxin contaminants is 2,3,7,8-TCDD, and the most toxic furan contaminant is the chemically similar 2,3,7,8-tetrachlorodibenzofuran.

The specific dioxin and furan contaminants vary among the different chlorophenol-based compounds. For example, the herbicide 2,4-D does not appear to contain 2,3,7,8-TCDD, though it may contain other dioxin contaminants. The herbicide 2,4,5-T contains both furan and dioxin contaminants, including 2,3,7,8-TCDD, which are formed during the manufacture of the chlorophenol precursor. Dioxins may also be formed at a later date through the combustion

of products containing chlorophenols. Combustion of the herbicide 2,4,5-T in a laboratory experiment increased TCDD levels by approximately 1.5 ppm (55).

Experimental studies on several animal species have shown that only an extremely small amount of exposure to the herbicide contaminant TCDD is necessary to cause liver damage (24, 69) or cancer (33, 64). The carcinogenic effect of TCDD may be due to its strong promotor capacity (47, 48). Animal studies have also reported unfavorable pregnancy outcomes such as birth defects, fetal death, or spontaneous abortion after maternal exposure (22). Conversely, four animal studies on the effect of paternal exposure to TCDD on pregnancy failed to find any unfavorable effects (22), though unfavorable outcomes have been found after paternal exposure to seven other chemicals (32).

The results of animal studies strongly suggest that exposure to phenoxy herbicides constitutes a significant health hazard. However, the extent of a possible hazard to humans cannot be assessed conclusively without epidemiologic evidence from human populations. Ecological studies using aggregate data on herbicide use and the incidence of birth defects have been conducted in several countries. Case-referent or cohort studies on cancer and birth defects are available for occupationally exposed individuals and for American Vietnam veterans, Vietnamese war veterans, and Vietnamese civilians who were exposed to herbicides as a result of the United States (US) Air Force defoliation program known as "Operation Ranch Hand."

Over 1.7 million hectares of South Vietnam were sprayed between 1961 and 1971 during Operation Ranch Hand. Several formulations containing 2,4,5-T were used, as well as 2,4-D, Picloram (4-amine-3,5,6-trichloropicolinic acid), and Cacodylic acid (dimethyl arsenic acid). Test samples of Agent Orange, a mixture of 2,4-D and 2,4,5-T, showed peak concentrations

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of TCDD of up to 60 ppm with an average concentration of 2 ppm (57). Two other herbicide formulations used in the first four years of the spraying program, Agents Pink and Green, contained 99 ppm of TCDD (66). Agent Orange accounted for 61 % of the total volume of herbicides used in the war.

American Vietnam veterans who loaded or flew spray planes as part of Operation Ranch Hand or who passed through or stayed in sprayed areas were potentially exposed. Vietnamese combatants and civilians were exposed either by direct contact with herbicide sprays or by living in sprayed areas. In many cases entire villages were sprayed up to five times, the result being exposure of the majority of the inhabitants.

In the present report we review the available epidemiologic studies on phenoxy herbicides or TCDD and attempt to interpret the results with respect to cancer and pregnancy outcomes. The majority of Vietnamese studies on pregnancy outcomes have not been published by the original authors. Some of the studies have been reviewed by Westing (65) and by Sterling & Arundel (56). An extensive review has been recently published by Constable & Hatch (9).

Several studies have also noted chronic neurologic impairments, fatigue, abnormal liver function, and chloracne among chemical workers exposed to chlorinated phenols contaminated with dioxins. These studies have recently been reviewed elsewhere (39) and will not be discussed.

Cancer

Occupational exposure to phenoxy herbicides

In 1974 Axelson & Sundell (2) reported an increase in the incidence of cancer among Swedish railroad workers exposed to phenoxy herbicides. A follow-up study by Axelson et al (3) of the same cohort six years later found a statistically significant increase for all cancers combined and for stomach cancer among workers with a latency period of at least 10 years since first exposure.

These reports were followed by two Swedish case-referent studies by Hardell & Sandstrom (29) and Eriksson et al (19), both of which found a statistically significant association between exposure to phenoxy herbicides and soft-tissue sarcomas, and one study that found a significant association between lymphoma and phenoxy herbicide exposure (28). The histology for each case was reviewed by a pathologist in all of these case-referent studies. The two studies on soft-tissue sarcoma were not limited to soft-tissue sarcomas coded to the International Classification of Diseases (ICD) category 171; instead sarcomas of parenchymatous organs such as the stomach were also included. In the study on soft-tissue sarcoma by Eriksson et al (19), the histology was reviewed by two pathologists, who rejected 11 cases because of an incorrect or uncertain diagnosis.

The Swedish case-referent studies have been criticized, both in published articles (7) and in judicial proceedings, because of the possibility that past exposure was more likely to be recalled by the cases than the referents. However, the studies were carefully designed in order to avoid differential recall bias among either the cases or the referents. For example, reported exposures were verified against employment records, and exposure information obtained from the relatives of deceased cases was matched against exposure information obtained from the relatives of deceased referents. Hardell also tested for recall bias by using the same epidemiologic study design on colon cancer cases (26). The risk of colon cancer did not increase after exposure to phenoxy herbicides. An increase in colon cancer after exposure should have been found if cancer cases were more likely to recall past exposure than referents.

A further case-referent study by Hardell et al (27) investigated the effect of exposure to phenoxy acids, chlorophenols, or organic solvents on the odds of developing liver cancer. There was an elevated, though not statistically significant, odds ratio of 1.7 for liver cancer after phenoxy herbicide exposure.

A cohort study of a group of 74 chemical workers exposed to dioxins as a result of a 1953 industrial accident in Germany found results similar to those of Axelson et al. There was a statistically significant increase in stomach cancer after a 10-year latency period and a nonsignificant increase for all cancers combined (60). Conversely, an ongoing prospective cohort study of almost 2 000 Finnish herbicide applicators, exposed for a minimum of two weeks to phenoxy herbicides, found no increases for mortality from cancer or other causes after eight years of follow-up (50). However, the cohort was very young and showed a strong "healthy worker effect" for all causes of mortality, even after a 10- or 15-year latency period was allowed for (51). In addition, only 0.1 cases of soft-tissue sarcoma were expected for this cohort, so that the absence of any such sarcomas does not indicate that there was no effect of exposure, only that the risk of exposure was probably less than 10.0. The study was also unable to detect less than a fourfold increase in risk for lymphoma. Several more years of follow-up are required before the mortality experience of this cohort can be properly assessed.

A case-referent study from New Zealand did not find a statistically significant increase in soft-tissue sarcomas after more than 5 d of exposure to 2,4,5-T and after a 10-year latency period was allowed for (54).

Five cases of soft-tissue sarcoma were found among either trichlorophenol or dioxin-exposed production workers in two chemical plants in the United States, and two additional cases were later found in a third chemical plant (10, 44, 67, 68). The diagnosis and history of exposure for each of the seven cases was recently reviewed by Fingerhut et al (21). The review confirmed both a history of exposure and the diagnosis

of soft-tissue sarcoma for two of the seven cases. Both of the cases with confirmed exposure and soft-tissue sarcoma were from the original two chemical plants.

Honchar & Halperin (31) had previously made a crude estimate of 0.07 expected cases of soft-tissue sarcoma among the original two cohorts. Fingerhut et al did not estimate the expected number of cases in their review because they considered American death-certificate mortality rates for soft-tissue sarcoma to be inaccurate and therefore not comparable to their data, which were based on an expert pathological review. Death-certificate data include many misclassification errors which may result in an underestimate of the incidence of soft-tissue sarcoma (46). Death-certificate data may also exclude approximately 40 % of all soft-tissue sarcomas, as only those coded to the ICD category 171 are counted. However, even if the expected rate is quadrupled, to allow for the possibility that death-certificate data underestimate the true incidence, the number of observed cases of soft-tissue sarcoma in this cohort is still considerably more than expected.

A retrospective cohort study examined the cancer mortality experience of 3 390 male and 1 069 female employees of four Danish chemical companies that manufactured 2,4-D, MCPA (4-chloro-o-tolyl oxyacetic acid), and MCPP [2-(4-chloro-o-tolyoxy)propionic acid] (36, 37). The herbicide 2,4,5-T was manufactured from purchased 2,4,5-trichlorophenol, except for the years 1951 and 1952, when 2,4,5-trichlorophenol was made on site. A total of 690 men and 250 women was employed in the phenoxy herbicide manufacture and packaging department, and an additional 958 men and 238 women may have been exposed in other departments such as shipping or maintenance. It was not possible to differentiate between possible exposure to 2,4,5-T and other herbicides which were not known to be contaminated with TCDD.

The study found a significant increase in soft-tissue sarcoma among all of the male employees and a significant increase in lung cancer among the male herbicide manufacturing and packaging employees. The observed and expected rates of soft-tissue sarcoma were based on data which included both soft-tissue sarcoma of connective tissue (ICD category 171) and of internal organs. Eight of the eleven cases of lung cancer found among the male employees of the herbicide manufacturing and packaging department had latency periods in excess of 10 years, but the other three had latency periods of one, three, and one-half years. Unfortunately, an analysis of the observed versus expected incidence of lung cancer after allowance for 10 years of latency was not conducted.

One of the five cases of soft-tissue sarcoma was unlikely to have been exposed, as he was only employed for two weeks in the manufacture of pigments. All of the remaining four cases had latency periods in excess of 10 years and were probably exposed, as they were employed either in the herbicide manufacturing and

packaging department or in the shipping department. After allowance for 10 years of latency, there was a statistically significant increased risk of 3.96 for males. Though a link between soft-tissue sarcoma and exposure to phenoxy herbicides was suggested by this study, it is impossible to determine whether the increase was related to exposure to TCDD-contaminated 2,4,5-T or to exposure to other phenoxy herbicides.

In addition, four cases of rectal cancer occurred after 1964 among male herbicide manufacturing and packaging employees versus 0.98 expected, and five cases of cervical cancer were observed among female employees of this department versus 0.85 expected. Both of these increased risks were statistically significant, but were not based on an adjustment for latency.

In 1976 an industrial accident at the Industrie Chimiche-Meda-Società Arionaria (ICMESA) chemical plant near Seveso, Italy, potentially exposed local residents to trichlorophenols and dioxins. The accident occurred during the synthesis of 2,4,5-trichlorophenol. A preliminary report on cancer between 1977 to 1980 noted a higher than expected incidence of soft-tissue sarcoma (ICD 171) in the three zones of exposure near the plant. The expected incidence was based on the observed rate for the 11 municipalities surrounding the chemical factory. Eight cases were observed in exposure zones A, B, and R combined versus 3.79 expected. The increase in the occurrence of soft-tissue sarcoma in zone R was statistically significant (1).

It is unlikely that the increase in the incidence of soft-tissue sarcoma is related to dioxins released during the accident. The latency period of a minimum of six months to a maximum of 4.5 years is simply too short, particularly considering the long latency periods observed in the Swedish studies. A plausible alternative explanation is that the observed excess of soft-tissue sarcoma may be the result of occupational exposures received by employees of the ICMESA plant. This possibility should be tested through the determination of the occupational histories of all soft-tissue sarcoma cases in the Seveso region.

Exposure to phenoxy herbicides in Vietnam

Data on exposure to phenoxy herbicides in Vietnam are of special interest because of the large numbers of Vietnamese civilians and American and Vietnamese combatants with probable heavy exposure. Unfortunately, none of the studies on exposure to phenoxy herbicides in Vietnam were able to develop accurate and reliable exposure indices.

A study of 1 026 US Air Force veterans assigned to herbicide spraying operations in Vietnam found a statistically significant increase in skin cancer for the exposed applicators in a comparison with referents (35). The reference group consisted of veterans who were involved in the transport of air cargo in Southeast Asia during the same time period. The statistical analysis was based on Ranch Handlers and referents

who reported for a full physical examination. More Ranch Handers who reported having skin cancer on a preexamination questionnaire completed the physical examination than referents who had reported having skin cancer on the questionnaire. Consequently, the statistical significance of the increase in skin cancer may have been due to different rates of compliance.

A case-referent study in New York State examined the exposure history of 281 cases of soft-tissue sarcoma among men who were between the ages of 18 and 29 years during the time of the herbicide spraying program in Vietnam (23). Information on exposure was obtained from relatives for 130 of the 281 cases, whereas the same information was obtained directly from all of the referents. A second reference group, consisting of deceased referents, differed significantly from the cases in respect to several social class variables and was therefore unsuitable.

The study did not find an increased risk of soft-tissue sarcoma among Vietnam veterans or after reported exposure to Agent Orange in Vietnam or to dioxin or 2,4,5-T elsewhere. The lack of an association may be due to several factors: (i) better exposure recall among the reference group, (ii) the low statistical power of the study to detect an effect, and (iii) an inadequate latency period.

The fact that information on exposure was obtained from relatives for 46 % of the cases may have biased the determination of exposure to Agent Orange or to 2,4,5-T in favor of the reference group, as the relatives of deceased cases would be less likely than living cases or referents to know of possible exposure. The study by Erickson et al (17), for example, found that the wives of Vietnam veterans were poor predictors of whether or not their husbands had been exposed to Agent Orange.

The statistical power of the study to detect increased cancer risks after exposure was limited by the low incidence of exposure among the study population, as estimated by the proportion of referents that were exposed. Only two out of 281 referents or 0.7 % were exposed. A third referent was considered by the authors to have been exposed, as he reported "occasionally walking along the railway tracks," but this cannot be considered to represent actual or even probable exposure. In comparison, the Swedish study by Hardell & Sandstrom (29) confirmed exposure to phenoxy herbicides for more than one workday among 7.0 % of the referents.

In addition, an increase in soft-tissue sarcoma after possible exposure to Agent Orange in Vietnam may not have been detected in the New York study because

Table 1. Summary of cohort studies on cancer following exposure to 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) or phenoxy herbicides. (STS = soft-tissue sarcoma, 2,4,5-T = 2,4,5-trichlorophenoxyacetic acid)

Cohort ^a	Reference group	Type of exposure	Exposure data source	Type of cancer	Minimum exposure	Minimum latency	Exposed cases (N)	Relative risk ^b
3 390 male and 1 069 female Danish chemical plant workers (36)	National death rates	Phenoxy acids	Personnel records	STS	3 months	10 years	4	3.96
				Lung	2 weeks	None	11	2.06
				Rectum	Unknown	None	4	4.71
				Cervix	Unknown	None	4	4.08
Population of the three exposed zones near Seveso (1)	Population of the 11 municipalities near Seveso	Trichlorophenols, dioxins	Place of residence	STS	Unknown	6 months	8	2.11
1 031 male American Vietnam veterans assigned to herbicide spraying operations (35)	Matched referents	Phenoxy acids, Picloram, arsenicals	Military assignment records	Skin	Unknown	None	35	2.35
1 926 male Finnish herbicide applicators (50)	National death rates	Phenoxy acids	Personnel records	All	2 weeks	10 years	20	0.82
74 men exposed in a German industrial accident (60)	Local and national death rates	TCDD	Personnel records	Stomach	1 day	10 years	3	6.00
				Lung	1 day	10 years	3	2.80
Subgroup of 348 Swedish male railroad workers (3)	National death rates	Phenoxy acids	Personnel records	All	45 days	10 years	6	2.30
				Stomach	45 days	10 years	2	7.70
Review of two cohorts of chemical plant workers (21)	None	2,4,5-T or TCDD	Personnel records	STS	2,4,5-T: 1 year	12 years	2	>1.00
840 male Vietnam veteran deaths in Massachusetts (34)	Deaths among all white men in state	Vietnam service (1958—1973)	Vietnam veterans identified from state records	STS	Unknown	None	9	5.87
				Kidney	Unknown	None	9	4.04

^a The reference numbers are in parentheses.

^b Statistically significant ($p \leq 0.05$) relative risks are in italics.

^c The population size or incidence per 100 000 is not provided in the report.

of the short latency period between the first exposure and the diagnosis. The average latency period was 10.9 years with a range of 4.25 to 13.6 years, compared to an average of 16.2 years and a range of 9 to 27 years in the study by Hardell & Sandstrom (29).

A study on 840 deaths among Vietnam veterans living in Massachusetts found highly significant proportional mortality odds ratios (PMOR) for soft-tissue sarcoma and kidney cancer (34). The study results suggest a possible relationship between exposure to herbicides and soft-tissue sarcoma, but no definitive conclusions can be made, as no information was available on the exposure histories of the deceased veterans.

Two Vietnamese studies examined the relationship between exposure to herbicides and liver cancer. Ton That Tung examined the frequency of liver cancer in the Viet Duc Wu Hospital, which received about a thousand cancer patients a year. The frequency of liver cancer increased from 3 % of all patients before the onset of herbicide spraying in 1961 to 10 % in 1969 (62). No definitive conclusions can be drawn from this study of aggregate data as information on exposure for individual liver cancer cases was unavailable.

Do Duc Van (13) conducted a case-referent study in which 21 patients with liver cancer were compared to 42 age-matched patients with stomach cancers and intestinal ulcers. All the cases were admitted between January and September, 1982, and past herbicide exposure was determined by interview. There were the following three classes of exposure: none, light (less than six months in a sprayed region), and severe (more than six months in a sprayed region). The average length of exposure among the six exposed cases was 45 months, whereas only one of the three exposed referents was classified as severely exposed. The odds ratio for liver cancer after exposure to herbicides was 5.2.

The Swedish study by Hardell et al (27) did not find a statistically significant increase in the odds ratio for liver cancer after exposure to phenoxy herbicides, but the confidence limits of the two studies overlap. Therefore they may not contradict each other. On the other hand, there were many possible confounding variables in the exposures received by Vietnamese combatants that were not considered in the study by Do Duc Van. For example, combatants may also have

Table 2. Summary of case-referent studies on cancer following exposure to 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) or phenoxy herbicides. (95 % CI = 95 % confidence interval, STS = soft-tissue sarcoma, 2,4,5-T = 2,4,5-trichlorophenoxyacetic acid)

Number of cases and location ^a	Reference group	Type of exposure	Exposure data source	Type of cancer	Minimum exposure	Minimum latency	Exposed cases (N)	Odds ratio ^b	95 % CI
82 New Zealand (54)	Cancer patients	Phenoxy acids	Interview (relative if deceased)	STS	5 days	10 years	13	1.30	0.6—2.9
281 New York State (23)	Live referents from state records	2,4,5-T or Agent Orange	Interview (relative if deceased)	STS	Ever	None	7	0.70	0.17—2.9
52 Sweden (29)	National register (deceased cases matched to deceased referents)	Phenoxy acids	Postal questionnaire (relative if deceased)	STS	2 days	5 years	13	5.3	2.4—11.5
110 Sweden (19)	National register (deceased cases matched to deceased referents)	Phenoxy acids 2,4,5-T	Postal questionnaire (relative if deceased, exposure verified with employer)	STS	1 week (exposure to 2,4,5-T) 5 years (no exposure to 2,4,5-T)		14	6.80 17.00 4.20	2.6—17.3
102 Sweden (27)	National register (all cases and referents deceased)	Phenoxy acids	Interview (relatives only)	Liver	1 day	5 years	..	1.70	0.7—4.4
21 Vietnam (13)	Patients with stomach cancer or ulcers	Living in a sprayed area	Interview (subjects only)	Liver	several months	11 years	6	5.20	1.15—23.5
169 Sweden (28)	National register (deceased cases matched to deceased referents)	Phenoxy acids	Postal questionnaire (relative if deceased, exposure verified with employer)	Lymphoma	1 day 90 days (combined)	5 years 5 years	31 10	4.30 7.00 (4.80)	 (2.9—8.1)

^a The reference numbers are in parentheses.

^b Statistically significant ($p \leq 0.05$) odds ratios are in italics.

been exposed to arsenical herbicides, to explosives, and to other possibly toxic war materials.

The results of the epidemiologic studies on the relationship between exposure to phenoxy herbicides to TCDD and cancer are summarized in tables 1 and 2.

Unfavorable outcomes of pregnancy

The relationship between exposure to phenoxy acids or TCDD and unfavorable pregnancy outcomes has been examined by ecological studies in which either the mother or the father may have been exposed, by studies on paternal exposure in which the mother was either known or presumed not to have been exposed, and by a few studies on maternal exposure in which the father may also have been exposed.

Ecological studies

An epidemiologic study on the relationship between exposure to 2,4,5-T and pregnancy outcomes was conducted as early as 1970 by a US Army medical research team. Over half a million Vietnamese obstetrical records for the years 1960 to 1969 were examined. The study found no consistent increases in malformations or stillbirths after the start of the intense defoliation campaign known as Operation Ranch Hand (12).

A reanalysis of the army data found that 67 % of the data came from the capital district hospitals which did not serve the population from the sprayed regions (38). An analysis of the data from areas of heavy exposure only found an increase in the rate of stillbirths and malformations after the start of heavy spraying operations in 1965. The largest increases were from the Tay Ninh Hospital, which served a population living near the area of heaviest defoliation. The stillbirth rate in Tay Ninh was 68/1 000 births compared to an average of 31.2/1 000 births for all of the other districts used in the study. The analysis also found that the incidence of spina bifida, at the Tu Du Hospital in Saigon, increased from 0.7 % of all birth defects between 1959 to 1965 to 2.1 % between 1967 to 1968, and the incidence of cleft palate increased from 0.5 % of all birth defects to 2.6 % over the same time. Animal experiments with mice (11, 41) and hamsters (8) have linked cleft palate to 2,4,5-T exposure. An increase in the incidence of cleft palate has not been found for exposed rats (22).

The data from these two studies from Vietnam were generally discounted, partly because of the political climate of the time and partly because of doubts concerning the accuracy of hospital records from an undeveloped and war-torn country.

Several ecological studies on the relationship between birth defects and herbicides have been conducted outside of Vietnam (4, 16, 20, 25, 40, 61). With the exception of a study from Hungary (61), all of the published ecological investigations found a relationship between birth defects and herbicide use. However, the

increase in the incidence of cleft lip or palate over time in Arkansas was probably due to better case ascertainment, as there were similar increases in both high and low herbicide use areas (40).

The data from a New Zealand study, possibly the most thorough of the ecological studies, suggested a dose-response curve (25). The incidence of all birth defects combined increased consistently from areas of low to medium to high herbicide use for four of the five years examined. The relationship could not have been due to an increase in reporting over time as the comparisons were made for each year. The study also compared the frequency of birth defects averaged over the years during which spraying occurred with the frequency during years of no spraying. The ratio between the two frequencies was statistically significantly ($p < 0.05$) elevated for all birth defects combined, all heart malformations, hypo- and epispadias combined, and for talipes. A further analysis of the data using an exposure decay constant found these relationships to remain statistically significant when one of two decay constants was used. Only all birth defects combined was statistically significant when the second decay constant was used. No consistent increases were noted for cleft lip in any of the analyses.

A study (16) in Oregon by the Environmental Protection Agency has been the center of considerable controversy, even though it has never been published. The study examined the relationship between spontaneous abortion and environmental exposure among women living in an area sprayed by herbicides. The study compared the rate of spontaneous abortion in the exposed Alsea watershed area with those of one urban and one rural reference area. The spontaneous abortion rate in Alsea was significantly higher than in either of the two reference areas.

Some of the results of the Alsea study may be challenged, as the study relied primarily on hospital admissions for spontaneous abortion cases and a higher percentage of abortion cases were referred to hospitals by attending physicians in Alsea than by physicians in the urban reference area. However, the primary finding of the report was a consistent cyclic association between spraying and a subsequent sharp rise in spontaneous abortions in Alsea. This relationship was not dependent upon a comparison between the Alsea and reference areas and was therefore unaffected by differences in the method for determining the number of spontaneous abortions, though the statistical method used to test for the cyclic association has also been criticized (30).

Studies on paternal exposure

We are aware of only two studies, with adequate reference groups, on pregnancy outcomes after paternal exposure outside of Vietnam. A cohort analysis of male herbicide sprayers (using mostly 2,4,5-T) in New Zealand found only a nonsignificant increase in birth

defects among their children (53). The data were reanalyzed, with a case-referent format, after many of the referents were discovered to have been exposed to phenoxy herbicides. No increases in birth defects were found in the reanalysis (52). A study of Dow Chemical workers found no significant increases in birth defects or other unfavorable pregnancy outcomes among the wives of male workers who were exposed to trichlorophenol for at least one month. However, only 44 % of the originally identified cohort was followed up (63).

Suskind & Hertzberg (59) provided information on pregnancy outcomes for a cohort of 189 exposed and 155 unexposed fathers working in the Nitro, West Virginia plant. Exposure was defined as any employment in the 2,4,5-T production area. The unexposed group worked in the same plant but was never involved in any work in the 2,4,5-T production area. The spontaneous abortion rate was lower in the exposed group than in the unexposed one, but the stillbirth, neonatal death, and birth defect rates were higher in the exposed than in the unexposed group. None of the differences was statistically significant. The unexposed group was not, however, an adequate reference group. It differed considerably from the exposed group in respect to age, employment status, and education.

Paternal exposure to 2,4,5-T in Vietnam

The Ranch Hand study of American veterans involved in the aerial spraying of herbicides in Vietnam obtained data on pregnancy outcomes from an interview with the wives of the veterans (35). The outcomes were not medically verified. There was a statistically significant increase in all birth defects combined among the children of the Ranch Hand group after adjustment for the effect of the following five covariables: the mother's smoking, alcohol consumption and age, the father's age, and the incidence rate for pregnancy outcomes before the father's service in Southeast Asia. The increase in birth defects was not significant after skin defects were excluded from the analysis.

The Ranch Hand study also noted an increased risk, though not statistically significant, for stillbirth, neonatal death, learning disabilities, and physical handicaps among the children of the exposed group after adjustment for the difference in incidence rates before service in Southeast Asia. Infant death was the only type of unfavorable pregnancy outcome to have a lower incidence among the Ranch Handlers than among the referents.

The quality of exposure data for the Ranch Hand study is better than that of all other studies on Vietnam veterans, as at least some exposure to TCDD was almost certain, with the exception of a small group of administrative personnel. Nevertheless, there is still a strong possibility that many of the individuals in the exposed group received only minimal exposure and may therefore have diluted a possible

exposure effect. In addition, the reference group was not checked for possible exposure to phenoxy herbicides or chlorophenol-based preparations.

No increases in birth defects were found among Australian veterans who had served in Vietnam (14, 15). The study was unable to assess the effect of paternal exposure to herbicides on the incidence of birth defects as information on exposure was unavailable.

The study by Erickson et al (17, 18) for the Centers for Disease Control (CDC) examined the proportion of babies who had medically verified birth defects from the Atlanta region and who were fathered by Vietnam veterans. The analysis of exposure was based on the probability of exposure, as determined from military records on Agent Orange use and the fathers' assignments in Vietnam. The Exposure Opportunity Index was determined for 498 Vietnam veterans on the basis of military records, and for an additional 50 veterans, on the basis of assignments reported in the interview. Self-reported exposure was not used to compare the incidence of paternal exposure between Index babies with birth defects and the reference babies because of concern that the fathers of Index babies may have been more likely to recall exposure. Twenty-five percent of the Vietnam veterans reported exposure to herbicides.

Conclusions drawn from this study should be limited to white Vietnam veterans of an average to above-average socioeconomic status because of the low response rate among nonwhite and poor white fathers of identified case and reference babies. Only 31.7 % of all nonwhite fathers completed the interview, and only 22 % of the fathers of white babies born at a public hospital with a high proportion of welfare mothers were successfully interviewed (17).

There was no difference in the Exposure Opportunity Index among veterans who fathered children with birth defects compared to veterans who fathered children without birth defects. However, a series of analyses for individual birth defects found that veterans with higher scores on the Exposure Opportunity Index were more likely to father children with spina bifida, neoplasms, and cleft lip with or without cleft palate. The reference group consisted of all other Vietnam veterans who fathered children with birth defects.

Two studies conducted by Vietnamese investigators examined the incidence of unfavorable pregnancy outcomes among the unexposed wives of North Vietnamese veterans who had served in South Vietnam and were probably exposed to herbicides, though exposure was not directly verified. The reproductive experience of the unexposed wives of North Vietnamese veterans who had not served in South Vietnam were used as a reference group. The incidence of major externally detectable congenital defects and spontaneous abortion was significantly increased for the exposed group in a study by Nguyen Can (6). The incidence of hydatidiform mole was not statistically significantly

increased after paternal exposure, and the incidence of stillbirth was slightly lower than that of the reference group. In a second study by Ton Duc Lang, Ton That

Tung, and Do Duc Van, the incidence of major birth defects was significantly elevated after paternal exposure (9).

Table 3. Summary of studies on pregnancy outcomes after paternal exposure to 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) or phenoxy herbicides. (Exp = exposed, unexp = unexposed, 95 % CI = 95 % confidence interval, 2,4,5-T = 2,4,5-trichlorophenoxyacetic acid, 2,4-D = 2,4-dichlorophenoxyacetic acid)

Exposed group or cases ^a	Unexposed group or referents	Type of exposure	Exposure data source	Outcome data source	Pregnancy outcome	Exp cases (N)	Unexp cases (N)	Odds ratio ^b	96 % CI
737 conceptions caused by employees of a chemical company (63)	2 031 conceptions caused by unexposed employees	Minimum 1 month employment in a building where chlorophenols were made	Company records	Reported by mother	All congenital defects	30	87	0.96	0.62—1.50
					Spontaneous abortions	85	213	1.12	0.85—1.47
					All unfavorable outcomes	136	366	1.03	0.82—1.29
483 conceptions caused by herbicide applicators (52)	401 conceptions caused by unexposed applicators and agricultural workers	2,4,5-T exposure within the 2 years preceding conception outcome	Postal questionnaire	Reported by mother	All congenital defects	13	9	1.19	0.58—2.45
					Spontaneous abortions	43	40	0.89	0.61—1.30
32 069 conceptions caused by Vietnamese veterans (6,56)	121 993 conceptions caused by unexposed veterans	Service in South Vietnam	Military records	Reported by mother, outcomes medically verified	Stillbirth	576	2 512	0.87	0.78—0.94
					Hydatidiform mole	28	70	1.52	0.98—2.35
29 560 live births	114 025 live births	Service in South Vietnam	Military records	Reported by mother, outcomes medically verified	Major externally detectable congenital defects	189	521	1.38	1.18—1.65
					Cleft lip	65	39	2.31	1.55—3.14
					Cleft palate	119	48	1.55	1.09—2.14
3 147 live births caused by Vietnamese veterans (Lang, Tung & Van (9))	2 172 live births caused by unexposed veterans	Service in South Vietnam	Military records	Reported by mother, outcomes medically verified	Congenital defects	71	10	4.90	2.50—9.50
2 320 live births caused by American veterans of Operation Ranch Hand (35)	1 940 births caused by unexposed veterans	2,4-D, 2,4,5-T, Picloram, arsenicals	Military records	Reported by mother	All congenital defects combined	73	42	1.47 ^c	..
4 815 ^d babies with congenital defects (18)	2 967 ^d babies without congenital defects	Vietnam service	Interview, military records	Medical records	All congenital defects combined	428	268	0.97	0.83—1.14
3 924 ^e babies with congenital defects	2 379 ^e babies without congenital defects	Probability index for father's exposure to Agent Orange	Military records for location of service and spraying operations	Medical records	All congenital defects combined	(regression)	..	..	-0.04—0.1 ^f
	All babies with congenital defects	Probability index for father's exposure to Agent Orange	Military records for location of service and spraying operations	Medical records	Spina bifida	(regression)	..	1.2—2.7 ^g	..
					Cleft lip with or without cleft palate	(regression)	..	1.2—2.2 ^g	..

^a The reference numbers are in parentheses.

^b Statistically significant ($p \leq 0.05$) odds ratios are in italics.

^c Crude odds ratio reported here; statistical significance determined after adjustment for five covariables; confidence limits not reported by the authors.

^d Service in Vietnam determined from an interview with the mother.

^e Exposure data obtained from an interview with the father; fewer fathers than mothers were interviewed.

^f Regression coefficient 95 % confidence limits.

^g Odds ratios for exposure opportunity index scores between 1 (low probability) to 5 (high probability).

In both studies, maternally reported unfavorable pregnancy outcomes were checked against medical records, but it was not possible to check for unreported pregnancy outcomes. Consequently, it is possible that ascertainment bias may have affected the results. The same problem may also have occurred in the Ranch Hand study (35) and in the two studies on pregnancy outcomes after paternal exposure to chlorophenols outside of Vietnam (52, 63).

The studies on pregnancy outcomes after paternal exposure to phenoxy herbicides or TCDD are summarized in table 3.

Studies of exposed mothers

The effect of maternal exposure on pregnancy outcome, in addition to possible paternal exposure, has only been directly examined by a series of studies on the aftermath of the industrial accident in Seveso and by three studies from Vietnam. Consequently, any evaluation of the effect of maternal exposure must rely heavily on the ecological studies, particularly the Alsea study, and on the Vietnamese studies.

The industrial accident in Seveso potentially exposed a relatively large population to dioxins. There was a possible sharp increase in miscarriages in the first trimester of 1977 with a slow decrease afterwards to 1976 levels. The incidence of neural tube defects, hypospadias, and polydactyly were higher in the Seveso area than in the reference area of Lombardy. An excess of angioma was observed for the dioxin-exposed area in a comparison with the entire Seveso district (5).

The Seveso results have been difficult to interpret because of the small numbers involved and because of the absence of reliable incidence rates for birth defects in the Seveso area before the accident (5). In addition, analysis of the accident has been hampered by

difficulties in determining the amount of exposure received by individuals living in the Seveso area, the unknown effect on the data of the large number of therapeutic abortions that occurred among the exposed women after the accident, and the size (small) of the known heavily exposed group.

In a Vietnamese study by Nguyen Phuong and Le Thi Huong, the number of unfavorable pregnancy outcomes out of 7 327 pregnancies among exposed women was compared with the number and types of outcomes among a reference series of 6 690 pregnancies (9). The analysis did not adjust for the effect of the mother's age. The study found significantly elevated crude odds ratios of 2.5 for major externally detectable birth defects, 4.6 for hydatidiform moles, and 2.2 for spontaneous abortion.

Cung Binh Trung and Nguyen Chien examined the incidence of spontaneous abortion before and after spraying in three exposed villages and in one unexposed village (9, 65). The crude incidence rate for spontaneous abortion remained unchanged in the unexposed village but increased an average of 2.4 times in the three exposed villages. Nevertheless, it is difficult to evaluate the significance of the increase as the incidence rates were not standardized for maternal age. It is possible that the increase in spontaneous abortions in the sprayed villages is the result of unknown factors that increased the average maternal age at conception.

The third study, a case-referent study by Le Thi Huong and Nguyen Phuong, found an odds ratio of 12.0 for hydatidiform mole after exposure to herbicides (9).

The Vietnamese studies on reproductive outcomes after maternal exposure are summarized in table 4. Reproductive outcomes were determined by interview in each of the Vietnamese studies except for the case-

Table 4. Vietnamese studies on pregnancy outcomes after maternal exposure to herbicides. (95 % CI = 95 % confidence intervals)

Cases or exposed group ^a	Referents or unexposed group	Exposure data source	Pregnancy outcome	Exposed cases (N)	Unexposed cases (N)	Odds ratio ^b	95 % CI
7 327 conceptions from Thanh Phong Village (Phuong & Huong (9))	6 690 conceptions from the 10th district of Ho Chi Minh City	Interview, place of residence	Major externally detectable congenital abnormalities	81	29	2.5	1.6—3.8
			Hydatidiform mole	133	26	4.6	3.0—7.0
			Spontaneous abortion	587	243	2.2	1.9—2.5
2 292 conceptions from three villages before the onset of herbicide spraying (Trung & Chien (9))	1 562 conceptions after the onset of herbicide spraying	Interview, place of residence	Spontaneous abortion	129	217	2.4	1.9—3.0
85 cases of hydatidiform mole at Tu Duc Hospital (Huong & Phuong (9))	276 women hospitalized for minor birth complications	Interview	Hydatidiform mole	48	27	12.0	6.7—21.5

^a The reference numbers are in parentheses.

^b Statistically significant ($p \leq 0.05$) odds ratios are in italics.

referent study on hydatidiform moles. This procedure may have introduced recall biases, especially in respect to spontaneous abortion, which are difficult to assess accurately under the best of conditions. The low incidence rate for birth defects in the reference series in the Vietnamese studies on paternal and maternal exposure is largely attributable to the fact that only major, externally detectable defects were recorded (56).

Discussion and conclusions

The differences in the results of the epidemiologic studies on phenoxy herbicides have led some investigators to conclude that exposure does not cause long-term health problems other than chloracne or that the risk of exposure must be very low (58, 66). This conclusion is not justified. A review of the available studies indicates that there is an increased risk for cancer. An increase in the risk of soft-tissue sarcoma was found in two Swedish studies and in the study of Danish chemical plant workers, and such an increase is strongly suggested by the review of chemical plant workers in the United States. An increase in soft-tissue sarcoma was also found for Vietnam veterans living in Massachusetts, though the results of this study are not as reliable as those of the other studies. In the Massachusetts study exposure could not be verified, and only proportional mortality odds ratios could be determined.

The New Zealand study did not find an increase in soft-tissue sarcoma, even after a careful analysis of latency and exposure. This result introduces some doubt on the relationship between soft-tissue sarcoma and exposure to TCDD or phenoxy herbicides. However, the New Zealand study was less likely to detect an effect than the Swedish and Danish studies because only soft-tissue sarcoma cases that were coded to the ICD category 171 were included. Soft-tissue sarcoma of the stomach and other internal organs would not have been included, as they were in Sweden and Denmark, and may in fact have been included in the reference group, which consisted of cancer patients. Furthermore, the results of the studies from Germany, Denmark, and Sweden also suggest that exposure may be a factor in the development of other cancers. This result indicates that referents drawn from cancer patients may be particularly unsuitable for the assessment of exposure to phenoxy herbicides.

The relationship between exposure to phenoxy herbicides, 2,4,5-T, or dioxins and unfavorable pregnancy outcomes has not been adequately explored. The lack of adequate investigation in countries such as Canada and the United States, where heavy use has been made of these compounds, is difficult to understand.

The ecological studies point towards an increase in spontaneous abortion and birth defects after possible maternal exposure. An increase in both of these pregnancy outcomes has been found in the Seveso studies and in Vietnam. The Vietnamese studies also

suggest that maternal exposure is related to hydatidiform mole. The Seveso studies are inconclusive because of problems in determining exposure, background incidence rates, and the unknown effect of therapeutic abortions on the incidence rate for spontaneous abortion and birth defects. The Vietnamese findings should be interpreted cautiously because of several methodological problems such as poorly defined exposure levels, no adjustment for confounding variables, possible recall and ascertainment bias, and possible underreporting of unfavorable outcomes. Additional studies on the reproductive effects of maternal exposure should be conducted in Vietnam.

The results of Vietnamese and Western studies on pregnancy outcomes after paternal exposure to phenoxy herbicides or TCDD suggest that exposure may be associated with a small increased risk of birth defects. Both Vietnamese studies on paternal exposure found an increase in major externally detectable birth defects, while one study also reported an increase in spontaneous abortion. The study of US Air Force personnel who handled defoliants during Operation Ranch Hand found a higher than expected incidence of all types of birth defects combined in the exposed group, though the increase in major birth defects was not statistically significant. The results of the CDC study do not suggest an increase in risk for all birth defects combined after exposure, even though it is certainly the largest and most sophisticated study to date on American Vietnam veterans. However, there was an increase in the incidence of spina bifida and cleft lip with or without cleft palate for Vietnam veterans with a high probability of exposure. This may have been a chance finding. Conversely, an increased incidence of cleft lip and/or cleft palate was found in both Vietnamese studies on paternal exposure. The single Vietnamese study with data on spina bifida after paternal exposure did not find an increase in this type of birth defect.

The majority of studies on paternal exposure, including the CDC study, did not examine the effect of the time interval between conception and possible exposure to Agent Orange and the outcome of pregnancy. The exceptions are the study by Smith et al (52), which limited the analysis to outcomes which occurred within two years of exposure and did not find an increase in birth defects among the children of herbicide applicators, and the Vietnamese study by Ton Duc Lang et al, which found the incidence of unfavorable pregnancy outcomes to decrease with the ordinal number of pregnancy (table 9 in reference 9). A time-weighted analysis of paternal exposure and pregnancy outcome may be especially important because of the means by which paternal exposure may affect pregnancy outcomes. Male exposure to chemicals may cause point mutations or structural damage to chromosomes in the spermatogonia or developing sperm (45). Theoretically, chemicals may also be transmitted through the semen and result in maternal exposure, though this possibility

has not been investigated (43). These effects are more likely to occur if conception takes place soon after exposure, rather than several years or more later, because of the gradual excretion of toxic chemicals from the body or through the random loss of damaged daughter spermatogonia to spermatogenesis. Exposure to TCDD may lead to an increased risk of unfavorable pregnancy outcomes for several years, as TCDD stored in adipose tissue is released to the blood stream, but it is unlikely that permanent damage occurs. It would be of considerable interest to have the CDC data reanalyzed to take into account the time interval between exposure and conception.

Some of the inconsistencies in the results of the epidemiologic studies may be partially due to the fact that almost all of the studies depended upon incomplete or poorly defined exposure data. For example, the CDC study on birth defects among the children of American veterans (17) apparently did not consider exposure to Agents Purple, Green, or Pink; even though these formulations were more heavily contaminated with TCDD than Agent Orange. None of the Vietnamese studies differentiated between exposure to herbicide formulations containing 2,4,5-T versus formulations containing arsenic or Picloram. The study by Suskind (59) obtained a considerable amount of clinical data on pulmonary function, plasma lipids, neuropathy, and heart conditions among the exposed cohort, but dose-response analyses were not conducted, even though the cohort contained individuals who were exposed for as little as one month to as much as 20 years.

TCDD or other contaminant levels have also varied widely in time, and most likely by country or place of manufacture. Therefore, the absence or presence of a statistically significant health effect may have been due to differing levels of exposure to the dioxin or furan contaminants. Several of the studies were also unable to detect less than a three- or fourfold increase in the risk of cancer (23, 27, 51, 54) or unfavorable pregnancy outcomes (5, 52) after exposure.

It is possible that part of the suggested carcinogenic or teratogenic effect of the phenoxy herbicides is caused by uncontaminated phenoxy acids, furans, or by dioxins other than TCDD. For example, one study noted an odds ratio of 4.2 for soft-tissue sarcoma when exposure was limited to phenoxy acids other than 2,4,5-T (19), and animal studies have noted a carcinogenic effect after exposure to phenoxy acids other than 2,4,5-T (42) or a teratogenic effect that could not be attributed solely to TCDD (8).

Exposure to TCDD alone or as a contaminant of 2,4,5-T was confirmed in only three studies on cancer (19, 21, 60) and can be considered to be "highly probable" for an additional two studies (23, 35). In most of the remaining studies on cancer, exposure was only confirmed for "phenoxy acids," which may not have included exposure to 2,4,5-T, and in one study the respondent's service in Vietnam was used as the

indicator of exposure (34). Exposure to TCDD or to 2,4,5-T was probable in most of the studies on pregnancy outcomes, but exposure to other phenoxy acids was also probable for all of these studies except the one in Seveso. Consequently, it is unclear exactly which constituents of the phenoxy herbicides are possible carcinogens. Without better exposure data, it would be prudent to suspect not only TCDD but other dioxins, furans, and the phenoxy acids of carcinogenic effects and possibly unfavorable effects on pregnancy outcomes.

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