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Pesticide Exposure and Women's Health

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Background *Research on pesticide-related health effects has been mostly focused in industrialized countries and in men. This paper discusses critical issues related to women's pesticide exposure and its effects on women's health.*
Methods *The literature on pesticides was reviewed with emphasis on data related to women. Attention was focused on research suggesting different conditions of exposure or different response to pesticides by sex. Studies on cancer and reproductive effects were used as illustrative examples.*
Results *Women are increasingly exposed to pesticides in developing countries, where women's poisoning and other pesticide-related injuries seem to be greatly underestimated. Many of the effects of pesticides in human health will be the same for men and women, but not always. Some organochlorine pesticides have been related to breast cancer in post-menopausal women. However, knowledge about other pesticides is much more limited. Epidemiological studies assessing maternal exposure to individual pesticides and abortion, fetal death, or congenital defects are not conclusive, although some suggestive associations have been observed.*
Conclusions *Gender-sensitive research is needed to properly address the study of women's pesticide exposures and related adverse outcomes. A better understanding of potential gender–environment and sex–environment interactions related to pesticide exposure and health effects in women is needed.* Am. J. Ind. Med. 44:584–594, 2003.

KEY WORDS: pesticides; exposure; women's health; cancer; reproduction

INTRODUCTION

When reviewing the evidence on pesticide exposure and women's health, it becomes apparent that epidemiological studies have been mostly focused on the conditions of exposure and the health problems more prevalent in industrialized countries and in males. Information from developing countries is more scarce and frequently is not published in the international, mainly English-language, scientific literature compiled in biomedical databases such as Medline [London et al., 2002]. Occupational groups such as farmers are frequently considered in epidemiological research. However, other exposed occupational groups, such as pesticide production workers [García, 1998], or exposure conditions and potential effects in the general population through, for example, contaminated water or food [Porta et al., 2002], are lacking.

The production and use of synthetic pesticides was mostly developed after World War II and it has exponentially increased until now. The use of pesticides in developing countries at the end of the 20th century showed a markedly increasing trend, while total world use was stable [World Health Organization (WHO), 1990]. It is not easy to obtain data on the use of specific chemicals by country, as the production companies are highly reluctant to provide this information. However, it is known that exposure to some of

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TABLE I. Regulatory Status of Some Organochlorine Pesticides in Different Countries*

	USA	China	India	Mexico	UK	Canada
DDT[a]	Banned	Restricted	Restricted	Restricted	Banned	Not registered
Aldrin	Banned	Not banned	Not banned	Banned	Banned	Not registered
Dieldrin	Banned	Not banned	Restricted	Banned	Banned	Not registered
Endrin	Banned	Not banned	Not registered	Banned	Banned	Not registered
Heptachlor	Restricted	Not banned	Not banned	Not registered	Banned	Not registered
HCB[b]	Banned				Banned	Not registered
Mirex	Banned	Restricted		Restricted		Banned
Toxaphene	Banned	Not banned	Banned	Banned	Banned	Not registered

Source: Physicians for Social Responsibility (PSR) [1998].
*Blanks indicate no available data.
[a]Dichlorodiphenyltrichloroethane.
[b]Hexachlorobenzene.

the more dangerous pesticides can greatly vary in developed and developing countries, as regulations and bans in the latter are usually less exigent (Table I).

Environmental contamination by persistent pesticides has been shown to present major differences among countries as well. Simonich and Hites [1995] investigated the global distribution of 22 potentially harmful organochlorine compounds, including several pesticides, measuring their levels in tree bark samples from 90 sites worldwide. Table II presents data from this study for dichlorodiphenyltrichloroethane (DDT) and lindane (γ-HCH) in a selection of countries. The levels of these pesticides differ among countries by several orders of magnitude, and reflects the different volatility of the compounds and their capacity to move through the atmosphere from warm regions to colder, higher latitudes.

Many of the effects of pesticides in human health will be the same for males and females, but sex-related biological differences strongly support a distinct susceptibility to the toxic action of these chemicals. This difference is expected to be observed in connection with hormone-related processes, with patterns of storage of lipophilic pesticides such as organochlorine insecticides because of the higher levels of adipose tissue in women, or with women's life events, such as pregnancy, lactation, or menopause. Experimental studies have shown different biological responses in male and female animals to pesticide exposure. For example, induction of some hepatic P-450 isozymes by insecticide DDT was shown to be much higher in female than in male rats [Sierra-Santoyo et al., 2000]. Epidemiological research has also provided some data supporting a different response to pesticide toxicity by sex. Besides well-known differences in sex-specific tumors, men and women experience different cancer risks from the same environmental agricultural exposures [McDuffie, 1994]. In a study of multiple myeloma in Nebraska farmers, Zahm and Blair [1992] found increased risks only for females. The authors pointed out the necessity to investigate in depth cancer risks by sex in order to explain these differences.

TABLE II. DDT and Lindane (γ-HCH) Levels in Tree Bark Samples From Different Countries

	DDT (ng/g lipid)		γ-HCH (ng/g lipid)
Romania	27,136.40	Romania	13,373.80
India	5,558.67	Belgium	2,036.85
Brazil	1,120.20	Denmark	923.65
Venezuela	307.60	Germany	483.20
Germany	187.00	India	321.25
Canada	10.30	Spain	186.70
Spain	5.73	Venezuela	29.10
Norway	5.10	China	28.70
United Kingdom	4.60	Argentina	17.50

Source: Simonich and Hites [1995].

WOMEN'S EXPOSURE TO PESTICIDES

It can be argued that the prevalence of exposure to pesticides is much higher in men than in women, particularly in occupational settings. However, according to recent data from the Food and Agriculture Organization of the United Nations (FAO) [2002], 44% of the total agricultural labor force in developing countries is female. Some studies provide data showing that the proportion of women involved in agricultural work in developing countries can be much higher. London et al. [2002] estimated that women do at least 75% of the agricultural work in Africa. In a study carried out in pesticide applicators in a coffee plantation in South Africa [Jaga et al., 1994], the majority of the exposed population were females—in fact, the number of males was so low that they were excluded from the study.

In other parts of the world, the proportion of women involved in agricultural work and applying pesticides may be

lower, but not negligible. Women are estimated to account for 36% of the total agricultural labor force in developed countries [Food and Agriculture Organization of the United Nations (FAO), 2002]. Data from the Agricultural Health Study [Alavanja et al., 1996], a large cohort study of pesticide applicators in Iowa and North Carolina, show that about one-third of farm spouses apply pesticides. In two evaluations of the Training Program for Pesticide Applicators of Valencia (Spain), the number of women directly handling pesticides in this agricultural Mediterranean area showed a clear increase from 5% at the beginning of the Program in the 1990s to 13% when approaching the new century [Martí et al., 1993; Ronda et al., 1998]. This last proportion of female applicators was the same found in a cohort of pesticide applicators in Iceland [Zhong and Rafnsson, 1996].

There are a number of major gender-related working conditions that may aggravate female occupational exposure to agricultural pesticides. As compared to men, women working in agriculture are typically found in lower-paid and lower-status jobs, with less access to promotion, information, and safety measures [London et al., 2002]. In a survey of 582 farmers in Thailand [Kunstadter et al., 2001], in which almost all farmers, both men and women, applied pesticides, 53% of the women were not able to read, compared to 29% of the men, decreasing their ability to heed the safety warnings offered on the labels of pesticides. The knowledge and attitudes of female farmers regarding pesticides risks were significantly different from men: for example, 35% of women versus 15% of men did not know any harmful consequences of using pesticides, while 54% of women versus 32% of men, and 43% of women versus 18% of men, respectively, never wore gloves or a cloth over mouth and nose when applying pesticides.

Besides exposure from application of agricultural pesticides, potential of exposure to these chemicals in women involved in agricultural tasks can be high. It has been observed that re-entry to areas in which crops were recently treated for harvesting, can be a major source of exposure, as residues are present in foliage and soil after spraying. Exposure can be also substantial as re-entry is a frequent activity and usually involves many more hours than pesticide application [De Cock, 1995]. There is also a potential exposure to farmers' wives and other family members through home contamination. Pesticides can be carried home through contaminated clothes, working equipment, or pesticide containers. Reutilization of pesticide containers for domestic uses is a frequent practice in many poor countries [London et al., 2002]. Children of applicators showed urine levels for metabolites of organophosphorus pesticides which are significantly higher than reference children in a study carried out in families from an agricultural region of Washington [Loewenherz et al., 1997].

There are other occupational sources of exposure to pesticides. Workers in production factories and formulation plants or structural pest control operators can be substantially exposed to pesticides, but in general the number of studies on these populations is limited. A remarkable exception is the International Register of Workers Exposed to Phenoxyherbicides and Contaminants, including 699 women in production plants [Kogevinas et al., 1993]. An overall increase in cancer occurrence among exposed women was observed. The interest in health effects of phenoxyherbicides is directly related to their massive use during the Vietnam War as a chemical weapon, Agent Orange [Sterling and Arundel, 1986]. Data on pesticide production workers exposed to other pesticides classes are extremely limited, and particularly for women.

A singular high exposure to structural pesticides in workers, mostly females, has been recently described in Barcelona, Spain [Obiols and López, 2000]. A substantial number of women working in hotels, hospitals, or offices buildings exhibited acute symptoms following structural treatments of their workplaces with pesticides which was mostly a mixture of organophosphates and pyrethroids. The follow-up of 114 severely affected women showed several long-term alterations, including neurophysiological disturbances and menstrual disorders [Valls-Llobet et al., 2002].

Environmental exposure to pesticides in ambient air has been also investigated. Beard et al. [1995] monitored outdoor and indoor ambient air in residential areas bounded by banana plantations in Australia on a daily basis for several pesticides. Chlorpyriphos is an organophosphorus pesticide frequently used for agricultural and domestic applications. Estimated mean indoor exposure levels were substantially higher than outdoor levels. Exposure levels were comparatively higher for infants and children than for adults, although in every case, even for the maximum outdoor levels detected, it accounted only for a small part of the acceptable reference dose established by the US Environmental Protection Agency for chlorpyriphos.

Effects of domestic exposure to wood-preserving pesticides were investigated in a reduced sample of 15 long-term exposed women, compared with a matched control group [Peper et al., 1999]. Blood levels of pentachlorophenol and γ-HCH were significantly higher in the exposed group, and exposed women manifested significantly worse self-reported attention level and mood state, learning and memory functions, and psychomotor speed.

Residence in areas where pesticides are sprayed is also a potential route for pesticide exposure in women. Research on this has frequently focused on the effects of maternal exposure on pregnancy outcome [e.g., Shaw et al., 1992; Thomas et al., 1992; Spagnolo et al., 1994; García-Rodríguez et al., 1996]. Results from these studies are generally not consistent, although some increased risks are observed for congenital anomalies and other negative outcomes of pregnancy. In a recent case-control study, the investigators observed an increased risk of fetal death due to congenital

anomalies in pregnancies with maternal residential proximity to pesticide application areas in California [Bell et al., 2001]. Interestingly, in this study the risks further increased as the definition of exposure and the relevant window of exposure were more restrictive.

For the majority of usual situations, food contamination will be the main route of pesticide exposure in the general population. Some countries have developed surveillance programs involving periodical monitoring of pesticides residues in foodstuffs. For example, the US Food and Drug Administration's Total Diet Study, includes the measurement of several contaminants in food items [MacIntosh et al., 1996]. Table III shows selected results from this survey. Although the proportion of food samples with residues for some pesticides is frequently high, according to available reference levels, exposure through this route is estimated to be without risk for the investigated population. In general, the levels of pesticide exposure for adult women were estimated as similar or slightly lower than for adult men.

Pesticide contamination of water is another potential source of exposure. Systematic monitoring of pesticide residues in drinking water is not usual in most countries of the world. In a 1996 press release in the United Kingdom, Friends of the Earth (FoE), a non-governmental organization, estimated that in 1992 around 14.3 million consumers in England received drinking water containing levels of pesticides above the legal standard at that time. In the same report, it was stated that nearly 50 different pesticides were detected in drinking water in England between 1990 and 1993 [Friends of the Earth (FoE), 2002]. Triazines were the main pesticides detected in rivers providing the water supply to the city of Barcelona, Spain [Quintana et al., 2001]. Triazines are the predominant herbicides (used according to pounds applied) in the United States and are frequently found with elevated concentrations in drinking water [Hopenhayn-Rich et al., 2002]. Exposure to triazines through contaminated water and other sources has been related to ovarian cancer [Donna et al., 1989; Kettles et al., 1997], but the association has not always been observed [Hopenhayn-Rich et al., 2002]. In an ecological study, Munger et al. [1992] observed an increased risk of birth defects in relation to pesticide-contaminated water supplies in Iowa, including triazines and other pesticides.

The potential for occupational and environmental exposure to pesticides in women is important, and it can be even higher than for men in some situations, as there are a substantial number of women working in agriculture in many parts of the world. However, comprehensive data on the prevalence of women's exposure to pesticides and on its impact on women's health are still lacking.

In order to illustrate common features in the research of pesticide effects on women's health, cancer and developmental and reproductive effects are used as examples. Both areas account for a majority of available epidemiological information in this field.

Example 1: Cancer

A substantial number of pesticides have been shown to be carcinogenic in experimental studies [Zahm et al., 1997], including several chemical classes (e.g., phenoxyacetic acids, triazines, and arsenical, organochlorine or organophosphate insecticides) and active ingredients (e.g., (2-4-dichlorophenoxyacetic acid (2,4-D), atrazine, DDT, γ-HCH, diazinon, and malathion). Zahm et al. [1997] pointed out that female farmers and female members of farm families have not been evaluated as extensively as male farmers regarding cancer risks. These researchers postulate different mechanisms for the carcinogenic effect of pesticides, including genotoxicity, hormonal action, tumor promotion, or immunotoxicity. As the authors stated, in the absence of genotoxicity a carcinogenic substance is much less likely to be detected and subsequently regulated than a genotoxic substance.

Epidemiological research has identified increased risks for some human cancers in association with pesticide exposure (Table IV). The lists for men and women are very

TABLE III. Residues of Selected Pesticides Measured in 234 Food Items in the Total Diet Study (United States) and Mean Estimated Dietary Exposure Levels for Adult Females

Compound (main food source)	Samples with residues (%)	Mean dietary exposure (range) (μg/day)	% RfD[a]
Chlorpyriphos (apples)	47	0.8 (0.12–5.6)	0.41 (0.06–2.9)
Diazinon (wheat-based products)	52	0.5 (0.10–2.0)	—
Malathion (wheat-based products)	41	5.5 (0.15–50.8)	0.04 (0.01–3.9)
p,*p*′-DDE[b] (beef, whole milk)	54	1.2 (0.15–16.7)	—
γ-HCH[c] (chocolate)	26	0.2 (0.03–3.2)	1.0 (0.15–16.4)

Source: MacIntosh et al. [1996].
[a]Percentage of the US Environmental Protection Agency reference dose for chlorpyriphos (body weight = 65 kg).
[b]*p*, *p*′ -dichlorophenyldichloroethylene.
[c]Lindane.

TABLE IV. Examples of Cancers With Observed Increased Risks From Pesticide Exposure in Epidemiological Studies

Women	Men
Non-Hodgkin's lymphoma	Non-Hodgkin's lymphoma
Multiple myeloma	Multiple myeloma
Leukemia	Leukemia
Soft-tissue sarcoma	Soft-tissue sarcoma
Lung cancer	Lung cancer
Bladder cancer	Bladder cancer
Lip	Lip
Stomach	Stomach
Sinonasal cancer	Hodgkin's disease
	Brain cancer
Breast cancer	Melanoma
Ovary cancer	Other skin
Cervical cancer	Prostate
	Testis

Source: Adapted from McDuffie [1994] and Zahm et al. [1997].

similar. Some studies have found an association of phenoxy-herbicides with increased risk of non-Hodgkin's lymphoma, soft tissue sarcoma, and other cancers [Dich et al., 1997]. Breast cancer has also been extensively investigated mostly in relation to organochlorinated pesticides. Less attention has been paid to other cancers (e.g., endometrial) or other chemical classes (e.g., triazines).

Results from cohort studies on cancer and pesticides are not always consistent [Dich et al., 1997]. It should be noted that exposure patterns to pesticides can be very diverse for different populations and study periods. In a Spanish survey of pesticide applicators in an agricultural Mediterranean area, the applicators reported the use of 78 different pesticide compounds during the 2 years of the survey [García et al., 2002]. The number of women included in cohort studies is also frequently low. For example, Wesseling et al. [1996] found increased risks for leukemia (standardized incidence ratio, SIR = 274, 95% confidence interval (95% CI) 89–639) and cervical cancer (SIR = 182, 95% CI 122–241) in women working in a banana plantation in Costa Rica. Zhong and Rafnsson [1996], in a cohort of Icelandic pesticide users, also observed significantly increased risks in women for lymphatic and hematopoietic tissue cancers, but only three cases were observed in women (SIR = 556, 95% CI 112–1,623). As stated by the authors, in Costa Rica the main pesticides used on banana plantations were dibromochloropropane (DBCP), maneb, mancozeb, and benomyl, while in Iceland the main pesticides used during the study period were 2,4-D, parathion, γ-HCH, chlorfenvinphos, and chlormequachlorid. These pesticides are quite different, pertaining to different chemical classes with diverse biological actions. Increased risk for cervical cancer was also observed in a cohort of licensed pesticide applicators in Florida [Fleming et al., 1999], exposed females showing a SIR = 369 (95% CI 184–661). Data from these studies cannot exclude other exposures related to pesticides use being responsible for the observed associations.

The International Agency for Research on Cancer (IARC) has evaluated some 885 agents to date (chemicals, groups of chemicals, complex mixtures, occupational exposures, cultural habits, and biological or physical agents), including several pesticides classes and compounds [International Agency for Research on Cancer (IARC), 2003]. Arsenical pesticides are the only pesticide class included in Group 1 (carcinogenic to humans). Some pesticides contaminants, such as 2,3,7,8-tetrachlorodibenzo-para-dioxin, are also found in this group. Group 2A (probably carcinogenic to humans) includes some other pesticides, such as the fungicide captafol or ''non-arsenical insecticides''—a highly uncertain category—in the group of ''mixtures.'' Chlordane, chlordecone, or DDT are examples of organochlorinated pesticides classified in Group 2B (probably carcinogenic to humans), including also organophosphorus insecticide dichlorvos.

A major area of interest in relation to pesticides and cancer has concentrated on pesticides acting as endocrine disrupters, mostly organochlorinated insecticides, and hormone-related cancers. Hormone-related cancers affecting women include breast, endometrium, ovary, bone, and thyroid tumors. Although the list of pesticides acting as endocrine disrupters is quite extensive and includes a number of different pesticide classes and compounds (Table V), research has largely been focused on the association between breast cancer and exposure to DDT and its metabolites.

Ahlborg et al. [1995] and Cocco [2002] review the association of exposure to DDT and other chlorinated pesticides and breast cancer. Ahlborg et al. reported negative ecological evidence of an association between DDT and breast cancer, as US time trends in breast cancer do not follow trends of DDT use in this country. Also Ahlborg et al. [1995] note that Japanese and black populations usually show higher levels of DDT and its metabolites in biological fluids but lower rates of breast cancer than other population. Summary odds ratio from reviewed case-control studies for DDE (DDT metabolite: 1,1,dichloro-2,2,bis(*p*-chlorophenyl)ethylene) was 1.27 (95% CI 0.95–1.69). Cocco [2002] reviewed 29 case-control studies assessing internal doses of exposure to DDT in relation to breast cancer. A majority of these studies were published after the review by Ahlborg et al., who concluded that ''*at the levels they are currently encountered these compounds are too weak to show any effect.*'' However, the conclusion of Cocco's review is slightly different: ''*We cannot exclude a role for high exposure to o,p′-DDE, particularly in post-menopausal estrogen receptor positive breast cancer.*'' A recent study carried out in India [Mathur et al., 2002], a country in which exposure to organochlorinated pesticides is expected to be higher and more recent than

TABLE V. Examples of Pesticides Acting as Endocrine-Disruptors

Organochlorine compounds
Aldrin
DDT[a]
Dicofol
Endosulfan
Endrin
γ-HCH[b]
Organophosphorus compounds
Chlorpyriphos
Dimethoate
Fenithrotion
Malathion
Parathion
Phenoxy herbicides
2,4-D[c]
2,4,5-T[d]
Carbamates
Aldicarb
Carbaryl
Carbofuran
Methomyl
Benzimidazole derivatives
Benomyl
Triazines
Atrazine
Simazine
Dithiocarbamates
Mancozeb
Maneb
Zineb

[a]Dichlorodiphenyltrichloroethylene.
[b]Lindane.
[c]2,4-dichlorophenoxyacetic acid.
[d]Trichlorophenoxyacetic acid.

in populations from developed countries, found significantly higher levels of organochlorinated pesticides (DDT and its metabolites and others) in the blood of women with breast cancer as compared to reference women. In a Danish cohort-nested case-control study [Hoyer et al., 2002], a modifying effect of p53 mutations on the breast cancer risk associated with exposures to organochlorines was observed suggesting a potential for gene–environment interactions still scarcely investigated in this field.

Several limitations have been noted in studies of endocrine-disrupting chemicals and breast cancer. Sample sizes are often small, and known risk factors for breast cancer are not always properly controlled. Biological samples and measurement methods can greatly vary among studies, making comparisons difficult. Although exposure levels are expected to be much higher in exposed populations in developing countries where DDT is still in use (see Table I), data arrive mainly from industrialized countries, where DDT use was banned some decades ago and current environmental exposure is expected to be much lower. Additionally, there are different DDT and DDE compounds with different levels of hormonal action: o,p'-DDT and o,p'-DDE show the highest estrogenic action, but they are present at much lower concentrations than other primary compounds and metabolites of the DDT formulation with slight or no estrogenic action [Longnecker et al., 1997].

Some researchers have noted that endometrial cancer is a natural focus to study estrogenic activity-cancer related to organochlorines, as estrogenic exposures have been consistently associated with increased risk of endometrial cancer, much more clearly than for breast cancer [Ahlborg et al., 1995; Adami et al., 1995]. However, the number of studies on endometrial cancer and endocrine-disrupting pesticides is very limited. In general, evidence of an association between exposure to DDT and metabolites and endometrial cancer is considered negative [Ahlborg et al., 1995; Sturgeon et al., 1998].

In an Italian case-control study, Donna et al. [1989] observed a significantly increased risk for ovarian cancer in women exposed to triazines, a class of herbicides including the frequently used atrazine, simazine, and others. The association was replicated in a study carried out in Kentucky in which exposure was not measured on an individual basis [Kettles et al., 1997]. A more recent study by Hopenhayn-Rich et al. [2002], assessed exposure level through a composite index based on public drinking water atrazine levels, atrazine sales, and acreage of corn planted in the study area, but did not find an association between exposure and ovarian or breast cancer in women.

Atrazine was considered a suspected human carcinogen [Dich et al., 1997], although there was only limited evidence of atrazine carcinogenicity in animals [Zahm et al., 1997]. However, in the IARC evaluation of the carcinogenicity of this pesticide in 1999 [International Agency for Research on Cancer (IARC), 1999], atrazine was considered not classifiable as to its carcinogenicity in humans (Group 3). Triazines are also included in the list of pesticides acting as endocrine disruptors (Table V). Atrazine was among the more frequently used pesticides in the Agricultural Health Study [Alavanja et al., 1999]. As stated before, triazines are frequently found as contaminants in drinking water. Levels of atrazine in some vegetables were also found to exceed European recommendable limits in a Spanish national survey of pesticide residues in foods [Ministerio de Agricultura, Pesca y Alimentación (MAPA), 1998]. More data on triazines' impact on human health are needed, because of the frequent use of these pesticides, their frequent detection as contaminants in water and foods for human consumption and the available evidence on their effects as endocrine-disruptors.

Example 2: Reproductive and Developmental Effects

Several negative reproductive and developmental endpoints could be related to women's exposure to pesticides, including infertility, time to pregnancy, early menopause, early pregnancy loss, spontaneous abortion, fetal death, congenital malformations, intrauterine growth retardation, and childhood or adult diseases. Again, some endpoints have received a more attention than others.

A large number of pesticides have been shown to be teratogenic in experimental studies (Table VI). Experimental research is necessary and can provide major clues, but does not exclude the need for epidemiological studies. In a list of 2,200 agents listed in a catalogue of teratogenic agents that is periodically revised [Shepard, 1992], 1,200 were proven teratogens for animals and only 30 were known teratogens for human beings. Paternal and maternal exposure to pesticides and congenital malformations has been a frequent area of research.

Several studies have found increased risks for different defects related to agricultural activity or exposure to pesticides, but until now, for common levels of exposure, there is not any specific pesticide related to increased risk for congenital anomalies in human beings. Research in this area has mostly failed to assess an hypothesis concerning specific exposures and outcomes. Figure 1 summarizes approaches for exposure and outcome measurement in a review of epidemiological studies on maternal exposure to pesticides and congenital defects [García, 1998, 1999]. The outcome considered by the different studies varies, from any congenital malformation, to groups of anomalies by affected organ system or specific defects. The approaches for exposure measurement vary as well from more generic to more specific. Exposure can be defined through job title, as agricultural worker or applicator, or identifying exposure to

TABLE VI. Examples of Pesticides That Have Been Found to Act as Teratogens for Animals

Classes and active ingredients	Main birth defects described
Phenoxy herbicides	
2,4,5-T	Cleft palate, renal, skeletal anomalies
2,4-D	Cleft palate, skeletal anomalies
Ureas and guanidines herbicides	
Buturon, diuron, linuron	Skeletal anomalies
Halophenol herbicides	
Pentachlorophenol	Skeletal, urogenital tract anomalies
Pyridil derivatives	
Paraquat	Skeletal anomalies
Organic chlorinated insecticides	
Chlordecone	Clubfoot, estrogen-like effects
Dieldrin	Skeletal anomalies
Endrin	Cleft palate, nervous system defects
Mirex	Cataracts
Toxaphene	Nervous system defects
Organic phosphorus compounds	
Dialifos	Limb defects, skeletal anomalies
Diazinon	Skeletal anomalies
Dimethoate	Polydactyly, skeletal, urogenital anomalies
Parathion-methyl	Cleft palate
Carbamates	
Carbaryl	Skeletal anomalies
Propoxur	Skeletal anomalies
Arsenical pesticides	Urogenital tract, cleft palate, skeletal eye, and nervous system anomalies
Fungicides	
Benomyl	Nervous system, eye, skeletal anomalies
Thiram	Cleft palate, nervous system, renal, cardiovascular, limb, skeletal defects
Zineb	Skeletal anomalies
Ziram	Skeletal anomalies

Source: García [1997].

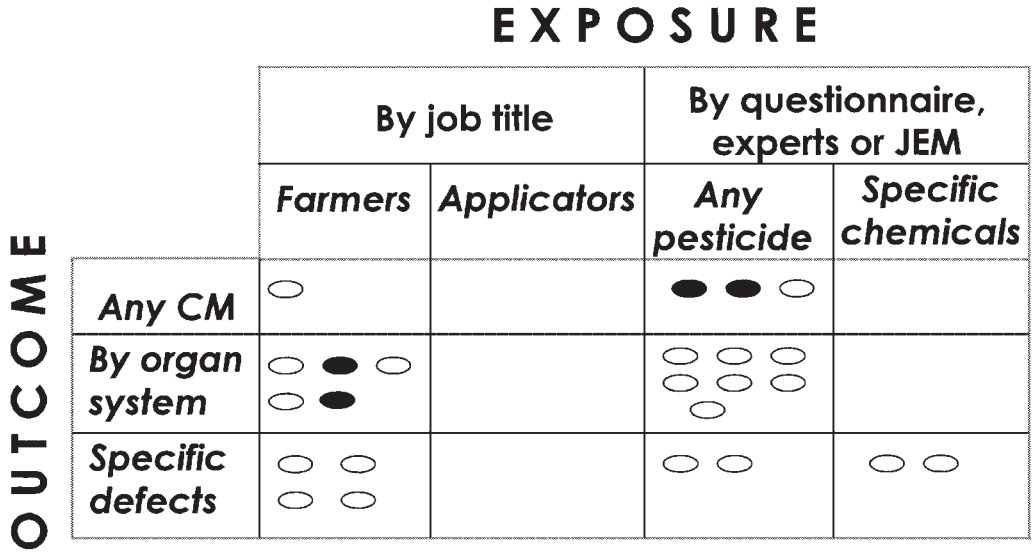

FIGURE 1. Distribution of 24 epidemiological studies (dots) on maternal exposure to pesticides and congenital defects according to the approach for exposure assessment and the definition of the outcome of interest. ⬭: Small epidemiological study (less than 30 exposed cases or discordant pairs). ⬬: Large epidemiological study (30 exposed cases or discordant pairs or more). CM, congenital malformation; JEM, job-exposure matrix. Source: Garcia [1998, 1999].

pesticides through questionnaires, job-exposure matrices or experts' assessment of exposure. Very few studies assessed the risks related to exposure to specific chemicals and/or defects. Sample size was limited. Often these studies can neither differentiate the risk due to pesticide exposure or to other exposures associated with farming or handling pesticides. In a case-control study carried out in an agricultural Mediterranean area in Spain [García et al., 1999], the adjusted risk of bearing a child with some specific congenital defects for maternal exposure to agricultural activities during the first trimester of pregnancy was 3.16 (99% CI 1.11–9.01). However, the number of mothers reporting direct handling of pesticides during this period was too low to permit further analysis.

Studies on fertility have mostly focused on men. In a recent attempt to provide some information on female fertility and exposure to specific pesticides, Curtis et al. [1999] measured time to pregnancy with data from the Ontario Farm Family Health Study in 1,048 couples and 2,012 pregnancies. Very detailed data on exposure to pesticides for men and women was collected with a questionnaire. Several confounders were accounted for. Conditional fecundability ratios, measuring fecundability conditional to pregnancy ultimately being achieved during the particular attempt, was only decreased when both men and women were engaged in pesticide activities. Several pesticide categories were related to a decreased risk. Because of the heterogenicity of the observed associations, the authors discussed other exposures related to pesticide exposure, such as solvents, heavy physical effort, or decrease in coital frequency during treatments, potentially acting as confounders.

Table VII summarizes the review by Nurminen [1995] on maternal pesticide exposure and spontaneous abortion and stillbirth. As noted by the author, none of the studies measures exposure to specific pesticides. Proper control of confounding and interactions is almost lacking. Some studies also lack adequate statistical power.

Although based on a small number of women, the study by Saxena et al. [1981] is one of the few in which exposure to specific pesticides is assessed. These investigators measured levels of organochlorine pesticides in maternal blood in pregnant women undergoing abortion ($n = 10$) or premature labor ($n = 15$) as compared with pregnant women in full term labor ($n = 25$) in a hospital in India. Higher levels of organochlorine pesticides were observed in women with negative outcomes of pregnancy. These results were recently re-

TABLE VII. Distribution of Epidemiological Studies Reviewed by Nurminen [1995] According to Their Support for an Association Between Maternal Pesticide Exposure and Spontaneous Abortion and Stillbirth

	Positive findings	Negative findings
Spontaneous abortion	Hemminki et al. [1980]	McDonald et al. [1987]
	Lindbohm et al. [1984]	Thomas et al. [1992]
	Heidam [1984]	
	Rita et al. [1987]	
	Restrepo et al. [1990]	
Stillbirth	McDonald et al. [1987]	Thomas et al. [1980]
	White et al. [1988]	Restrepo et al. [1990]
	Goulet et al. [1991]	
	Thomas et al. [1992]	

plicated by Korrick et al. [2001] in a Chinese study. Previous evidences on the association between DDT exposure and spontaneous abortion are not consistent. However, in these two studies, the levels of DDT and metabolites were particularly high and exposure to DDT in the population of both countries has a high potential to be much more direct or recent than in developed countries. As suggested by Korrick et al. [2001] these observations could suggests a potential threshold effect or other interesting mechanistic processes involved in increased risk.

Some researchers have pointed out that markers of current or relatively recent exposure to pesticides are not appropriate to assess some health effects. In a recent case-control study intended to investigate the association between endometriosis and plasma concentrations of some organochlorines in women, including metabolites of DDT and other pesticides, no differences among cases and controls were observed [Lebel et al., 1998]. As stated by the authors, this was the first case-control study on this subject. And as they noted, levels measured may not reflect exposure during the crucial period for induction of endometriosis—for example, puberty, early infancy, or in utero. Life course epidemiology is intended to study long-term effects of chronic disease risks of exposures during gestation, childhood, adolescence, young adulthood, and later adult life [Ben-Shlomo and Kuh, 2002]. This would include the study of fetal origins of adult chronic disease [Gillman, 2002], an approach that could be particularly of interest for hormone-related processes and endocrine-disrupting pesticides.

OTHER HEALTH EFFECTS OF PESTICIDES AND FINAL REMARKS

Acute effects from pesticide exposure have not been discussed, although it deserves a brief comment. In a report of the World Health Organization (WHO) [1990], the incidence of severe acute toxicity by pesticides, excluding intentional exposures, was estimated to exceed one million of cases per year, with a lethality rate between 0.4 and 1.9%. Seventy percent of these cases are of occupational origin. The rate of cases of intentional poisoning with pesticides was estimated at 2 million per year. In some countries pesticide ingestion has been claimed to be the most frequent method of suicide [Daisley and Hutchinson, 1998]. It is not easy to obtain proper estimates by sex, but data from developing countries suggest that women's exposure to pesticides and pesticide-related acute morbidity and mortality can be strongly underestimated in these countries [London et al., 2002].

Other chronic effects, such as pesticides neurotoxicity, are also of concern. Several pesticides show well-known acute toxicity on the nervous system, but data on delayed neurotoxicity is still scarce [Keifer and Mahurin, 1997]. Subtle neurobehavioral effects have only recently received epidemiological attention [Landrigan, 2001].

Gender-sensitive research is needed to properly address the study of women's pesticide exposures and related adverse outcomes. Occupational cohorts of highly exposed women (e.g., female applicators or workers in production plants) can provide valuable information. Epidemiological research should focus on individual pesticides or known combinations of pesticides, and exposure assessment methods should be refined. The assessment of gene–environmental and environmental–environmental interactions should also receive greater attention. For example, serum paraoxonase PON1 polimorphisms, related to the activity of the enzyme hydrolyzing the bioactive form of some organophosphorus pesticides in the organism, have been related to different sensitivities to the toxic action of these pesticides, with very wide variations [Furlong et al., 1998].

Besides environment–environment and gene–environment interactions, a better understanding of sex–environment (dealing with biological differences by sex in the response to pesticides) and gender–environment interactions (dealing with different social-related characteristics of pesticide exposure and case-ascertainment in pesticide exposed women and men) is highly needed to improve our knowledge of pesticide-related health effects in women.

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