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Original Contribution

Pesticide Use and Thyroid Disease Among Women in the Agricultural Health Study

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Thyroid disease is common, and evidence of an association between organochlorine exposure and thyroid disease is increasing. The authors examined the cross-sectional association between ever use of organochlorines and risk of hypothyroidism and hyperthyroidism among female spouses ($n = 16{,}529$) in Iowa and North Carolina enrolled in the Agricultural Health Study in 1993–1997. They also assessed risk of thyroid disease in relation to ever use of herbicides, insecticides, fungicides, and fumigants. Prevalence of self-reported clinically diagnosed thyroid disease was 12.5%, and prevalence of hypothyroidism and hyperthyroidism was 6.9% and 2.1%, respectively. There was an increased odds of hypothyroidism with ever use of organochlorine insecticides (adjusted odds ratio (OR_{adj}) = 1.2 (95% confidence interval (CI): 1.0, 1.6) and fungicides ($OR_{adj} = 1.4$ (95% CI: 1.1, 1.8) but no association with ever use of herbicides, fumigants, organophosphates, pyrethroids, or carbamates. Specifically, ever use of the organochlorine chlordane ($OR_{adj} = 1.3$ (95% CI: 0.99, 1.7), the fungicides benomyl ($OR_{adj} = 3.1$ (95% CI: 1.9, 5.1) and maneb/mancozeb ($OR_{adj} = 2.2$ (95% CI: 1.5, 3.3), and the herbicide paraquat ($OR_{adj} = 1.8$ (95% CI: 1.1, 2.8) was significantly associated with hypothyroidism. Maneb/mancozeb was the only pesticide associated with both hyperthyroidism ($OR_{adj} = 2.3$ (95% CI: 1.2, 4.4) and hypothyroidism. These data support a role of organochlorines, in addition to fungicides, in the etiology of thyroid disease among female spouses enrolled in the Agricultural Health Study.

agriculture; environmental exposure; hyperthyroidism; hypothyroidism; pesticides; thyroid gland

Abbreviations: CI, confidence interval; DDT, dichlorodiphenyltrichloroethane; OR_{adj}, adjusted odds ratio; TSH, thyroid-stimulating hormone.

Identifying modifiable risk factors for thyroid disease is important, given that an estimated 5%–9% of adults have subclinical thyroid disease and 0.8%–7.5% have clinical thyroid disease (1–3). Subclinical thyroid disease is defined by abnormal serum thyroid-stimulating hormone (TSH) but normal T4 and T3 levels and does not always require treatment, whereas persons with clinical thyroid disease have abnormal serum TSH, T4, and T3 levels *and* require treatment. Known risk factors for thyroid disease include autoimmunity, external irradiation of the head and neck, a biosynthetic defect in iodine organification, replacement of the thyroid gland by tumor, and use of certain drugs (4). Other factors associated with an increased risk of thyroid disease include female sex, increasing age, and iodine deficiency (5, 6).

There is increasing evidence that environmental exposures, specifically to pesticides, should also be considered potential risk factors for thyroid disease. Certain insecticides, herbicides, and fungicides have been previously reported to be endocrine disruptors and, more specifically, thyroid disruptors acting through diverse mechanisms (7–9) such as inhibition of thyroidal iodine uptake, interference at the thyroid hormone receptor, binding to transport proteins, interference with iodothyronine deiodinases, increased clearance of thyroid hormones, interference with cellular uptake of thyroid hormones, and interference with thyroid hormone gene expression (7, 9). Animal studies have shown that pesticide exposure to dichlorodiphenyltrichloroethane (DDT), amitrole, and chemicals from the

thiocarbamate family can serve as goitrogens (10, 11) and can cause decreased total T4, free T4, total T3, and free T3 levels as well as increased TSH levels (12).

Applicators of herbicides and fungicides in the Red River Valley in northwestern Minnesota were found to have a higher rate of subclinical hypothyroidism (using a definition of TSH >4.5 mIU/L), 3.4% versus 1% of the general population (13), and significant shifts in TSH levels were associated with seasonal fungicide use (13). Specific herbicides and fungicides causing this effect were not delineated in this study. Another study evaluating thyroid function in pesticide-exposed Danish greenhouse workers showed that the workers had a 32% increase in serum TSH and a 5%–9% decrease in T3 and T4 levels in the spring compared with the fall (14). The Danish greenhouse workers were exposed to approximately 60 chemicals, a combination of insecticides, fungicides, and growth regulators; however, the most common chemicals used included primicarb (87% of workers), benomyl and iprodione (both 53%), chlormequat (77%), and daminozide (57%). Other studies have shown that older women with environmental exposure to the organochlorines polychlorinated biphenyls and polychlorinated dibenzo-*p*-dioxines have decreased T4 levels compared with the general population without thyroid disease (15), and populations highly exposed to polychlorinated biphenyls have also been reported to have thyroid hormone alterations, change in thyroid volume, and elevated thyroid antibodies (16–20). Similarly, workers exposed to tetrachlorodibenzo-*p*-dioxin (20) and polychlorinated biphenyls (16) have been reported to have a higher incidence of thyroid disease. Interestingly, the group exposed to polychlorinated biphenyls had elevated TSH levels and thyroid antibodies but no change in T4 serum levels (16).

Given the high prevalence of thyroid disease among women and current data implicating pesticide exposure in thyroid disruption, specifically organochlorines, we hypothesized that the rates of self-reported history of physician-diagnosed thyroid disease would be higher among female spouses of pesticide applicators in the Agricultural Health Study with exposure to organochlorines compared with those unexposed. As part of an exploratory analysis, we also investigated rates of thyroid disease in relation to ever use of specific herbicides, insecticides, fungicides, and fumigants, since it is common to be exposed to multiple compounds in an agricultural setting.

MATERIALS AND METHODS

Study population

The Agricultural Health Study is a prospective study of licensed pesticide applicators and their spouses in Iowa and North Carolina. Study details have been reported previously (21), and questionnaires are available on the study website (www.aghealth.org/questionnaires.html). The institutional review boards of the National Institutes of Health (Bethesda, Maryland) and their contractors approved the study.

Pesticide applicators applying for certification to use restricted-use pesticides in Iowa and North Carolina were recruited between 1993 and 1997 (phase I). Male private applicators (mainly farmers) who were married were given 2 questionnaires, the Spouse Enrollment Questionnaire and the Female and Family Health Questionnaire to be completed by their spouse at home. Applicators and spouses were recontacted for a follow-up telephone interview approximately 5 years after enrollment (phase II, 1999–2003).

Questionnaires and exposure assessment

Pesticide exposure and thyroid disease were assessed by both the Spouse Enrollment Questionnaire (phase I) and a computer-assisted follow-up telephone interview (phase II), respectively. In phase I, spouses indicated their overall pesticide exposure by reporting ''years lived or worked on a farm,'' ''ever personally mixing or applying any pesticide during their lifetime,'' ''total years of personally mixing or applying pesticides,'' ''days per year of mixing or applying pesticides,'' and ever use of 50 itemized herbicides, insecticides, fumigants, and fungicides. This exposure information did not account for secondhand pesticide exposure of the spouse. In addition, demographics, smoking history, agricultural activity, and reproductive health and medical history were assessed. The phase II interview obtained detailed information about medical history, including thyroid disease and current reproductive health. The average time between phase I and phase II data collections for spouses was 4.7 years. Our analysis was limited to female spouses of private applicators who completed both phase I (pesticide use) and phase II (thyroid disease) data collections and had complete data on all covariates (Figure 1).

Study outcome

Our outcome was self-reported history of physician-diagnosed thyroid disease. This outcome was based on the spouse's answer to the phase II question, Has a doctor or other health professional ever told you that you had thyroid disease or thyroid problems? Thyroid disease was classified into 3 groups: hyperthyroid, hypothyroid, and other. A diagnosis of hyperthyroidism was established if the participant answered yes to any of the following questions: Were you ever told you had an overactive thyroid? Was it due to Graves disease? Was it due to thyrotoxicosis? Was there some other cause of overactive thyroid that was identified? Participants were considered to have hypothyroidism if they answered yes to least one of the following questions: Were you ever told you have an underactive thyroid? Was this due to thyroiditis, Hashimoto's, or autoimmune disease? Was there some other cause identified for underactive thyroid disease?

Participants were considered to have other thyroid disease if they did not report hyperthyroidism or hypothyroidism but reported any of the following—an enlarged thyroid, thyroid nodules, or goiter—or were told they had some type of thyroid problem or thyroid disease. Additionally, a small number of participants answered yes to having both hypothyroidism and hyperthyroidism. It is possible for persons to have both, such as in the case of thyroiditis or treatment of hyperthyroidism with surgery or radioactive iodine. However, for these participants, we did not have additional

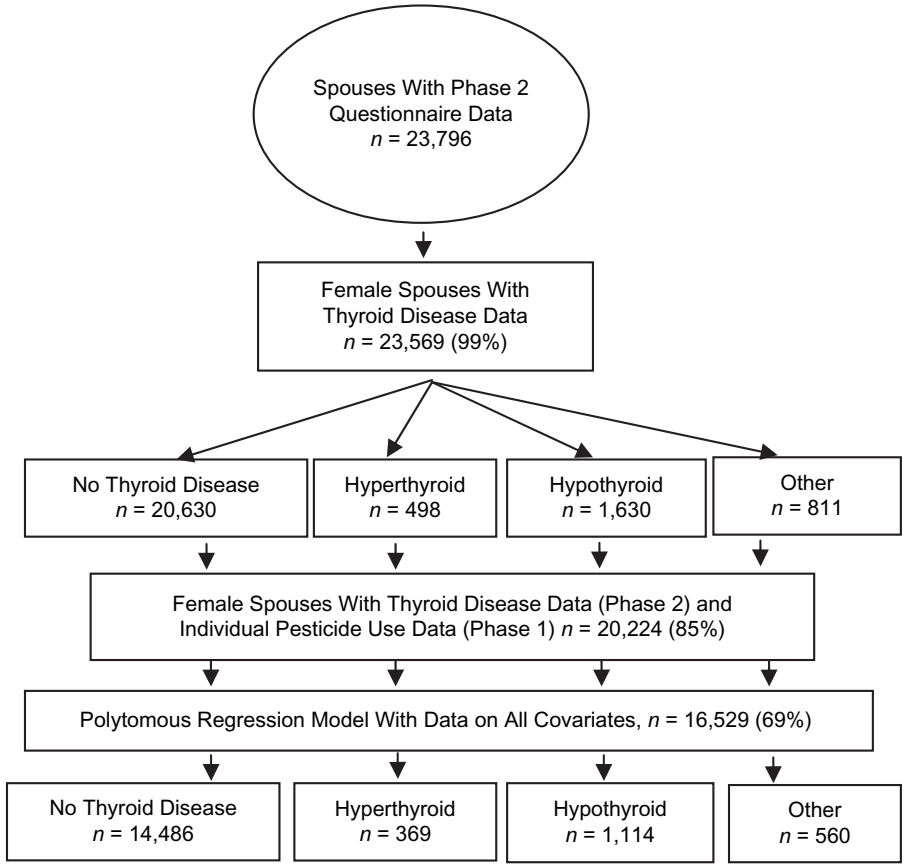

Figure 1. Selection of the study population, Agricultural Health Study, 1993–1997. Female spouses of licensed pesticide applicators in Iowa and North Carolina who were part of the Agricultural Health Study and who also had thyroid disease and pesticide use data were included. For further analysis, the population was then divided into 4 groups: no thyroid disease, hyperthyroid, hypothyroid, and other.

information to be able to determine the exact nature of their thyroid disease. Hence, all were combined to form the ''other thyroid disease'' category, a very heterogeneous group.

Overall lifetime history of thyroid disease in this population was calculated on the basis of those classified as having hyperthyroid, hypothyroid, and other thyroid disease (Figure 1). Furthermore, although age at diagnosis was sought at phase II, age was incompletely ascertained. Thus, our analysis was based on lifetime history of thyroid disease reported at phase II (Figure 1).

Statistical analyses

We examined pesticide exposures at enrollment (phase I) in relation to the outcome of thyroid disease reported in the phase II interview. Adjusted odds ratios and 95 percent confidence intervals were calculated from polytomous logistic regression models by using PROC Logistic software (version 9.1; SAS Institute, Inc., Cary, North Carolina). We categorized the spouses for whom thyroid data, pesticide use data, and all covariates were complete into mutually exclusive categories consisting of hyperthyroid disease, hypothyroid disease, other thyroid disease, and the referent category of no thyroid disease. Of the 50 possible pesticides, 6 (aluminum phosphide, ziram, aldicarb, toxaphane, trichlorfon, dieldrin) were excluded from our analysis because fewer than 5 cases were exposed.

All models were fit with adjustment for age at enrollment ($\leq$45, 46–55, 56–65, $\geq$66 years), education ($\leq$high school, $>$high school), smoking status (never, past, current), hormone replacement therapy (ever, never), and body mass index at enrollment ($<$25, 25–29.9, and $\geq$30 kg/m^2). Subjects were categorized as never smokers if they had never smoked 100 cigarettes in their lifetime. We chose to adjust for these risk factors since they were shown to be highly associated with thyroid disease (either hyperthyroidism or hypothyroidism) by the stepwise model selection criterion with $P = 0.05$ for entering and $P = 0.1$ for staying to determine what covariates were added to the model. Covariates added to the model were assessed for goodness of fit by the change in -2 log likelihood.

Variables for birth control therapy (phase I and II data; ever, never), state of residence (Iowa, North Carolina), and menopause status (phase I and II data; premenopausal, natural or age $>$55 years, surgical/other) were not significantly associated with hypothyroid or hyperthyroid disease and therefore were not included in the model

Table 1. Characteristics of Female Spouses by Thyroid Disease Status, Agricultural Health Study, 1993–2003

Characteristic	No Thyroid Disease (n = 14,486; 88%)		Hyperthyroid (n = 369; 2%)		Hypothyroid (n = 1,114; 7%)		Other (n = 560; 3%)	
	No.	%	No.	%	No.	%	No.	%
US State								
North Carolina	4,044	27.9	130	35.2	339	30.4	173	30.9
Iowa	10,442	72.1	239	64.8	775	69.6	387	69.1
Age at baseline, years								
≤45	5,453	37.7	73	19.8	251	22.5	109	19.5
46–55	3,930	27.1	98	26.5	313	28.1	135	24.1
56–65	3,217	22.2	125	33.9	343	30.8	178	31.8
≥66	1,886	13.0	73	19.8	207	18.6	138	24.6
Body mass index, kg/m^2								
<25	7,245	50.0	167	45.3	461	41.4	247	44.1
25–29.9	4,623	31.9	126	34.1	375	33.7	185	33.0
≥30	2,618	18.1	76	20.6	278	24.9	128	22.9
Race								
White	14,246	98.3	364	98.6	1,108	99.5	549	98.0
Nonwhite	240	1.7	5	1.4	6	0.5	11	2.0
Education								
≤High school	6,298	43.5	200	54.2	428	38.4	285	50.9
>High school	8,188	56.5	169	45.8	686	61.6	275	49.1
Smoking status								
Never	10,747	74.2	251	68.0	797	71.5	411	73.4
Past	2,326	16.0	72	19.5	247	22.2	107	19.1
Current	1,413	9.8	46	12.5	70	6.3	42	7.5
Menopausal status								
Premenopausal	7,583	53.2	122	33.9	399	36.2	170	31.0
Yes, natural or age >55 years	4,874	34.2	183	50.8	511	46.3	283	51.7
Yes, surgical/other	1,805	12.6	55	15.3	193	17.5	95	17.3
Birth control therapy								
Never	3,687	25.6	127	34.6	317	28.6	193	34.6
Ever[a]	10,731	74.4	240	65.4	793	71.4	365	65.4
Hormone replacement therapy								
Never	9,892	68.3	195	52.8	567	50.9	293	52.3
Ever	4,594	31.7	174	47.2	547	49.1	267	47.7

[a] Ever used birth control therapy was determined if the spouse answered yes or filled in a positive number to any one of the following questions in the phase I or II questionnaires: Have you ever taken birth control pills? Are you currently taking birth control pills? How old were you when you first began taking birth control pills? How many years altogether did you take or use birth control pills?

($P > 0.7$). Premenopausal status was identified when spouses answered no to the phase II question, Have you gone through menopause or had surgery that caused you to completely stop having menstrual periods? Natural menopause was defined by self-report of natural menopause in the phase I or II questionnaires or age greater than 55 years in phase II without another cause for menopause prior to age 55 years. Surgical menopause/other was defined as ever having bilateral oophorectomy, chemotherapy, radiation, or other conditions that resulted in menopause prior to age 55 years.

Given that participants may use different pesticides simultaneously, Spearman's correlation coefficients were calculated between each pair of pesticides showing a significant association with hyperthyroid or hypothyroid disease. When the correlation coefficients were larger than 0.3, we constructed polytomous models including both pesticides (22).

This analysis used the P1REL0506.03, AHSREL0506.03, AHSREL0612.01, and P2REL0612.03 data release from the Agricultural Health Study. Inquiries regarding the data used in this analysis should reference these data releases.

Table 2. General Farm Characteristics and Pesticide Use Among Female Spouses by Thyroid Disease Status, Agricultural Health Study, 1993–2003[a]

Exposure	No Thyroid Disease (n = 14,486; 88%)		Hyperthyroid (n = 369; 2%)				Hypothyroid (n = 1,114; 7%)				Other (n = 560; 3%)			
	No.	% Exposed	No.	% Exposed	OR	95% CI	No.	% Exposed	OR	95% CI	No.	% Exposed	OR	95% CI
Worked/lived on a farm, years														
Never	460	3.2	13	3.6	1.0		25	2.3	1.0		17	3.1	1.0	
≤25	5,352	37.3	111	30.7	0.87	0.49, 1.6	357	32.4	1.5	0.95, 2.2	155	27.9	0.95	0.57, 1.6
26–40	4,111	28.7	94	26.1	0.78	0.43, 1.4	299	27.1	1.4	0.89, 2.1	145	26.1	0.93	0.56, 1.6
>40	4,416	30.8	143	39.6	0.76	0.42, 1.4	422	38.2	1.3	0.87, 2.0	238	42.9	0.92	0.55, 1.5
Lifetime pesticide application, years														
Never	6,983	56.0	178	56.2	1.0		530	54.4	1.0		267	55.7	1.0	
≤5	2,064	16.6	50	15.8	1.1	0.79, 1.5	149	15.3	0.99	0.82, 1.2	72	15.0	1.1	0.82, 1.4
6–16	2,385	19.1	47	14.8	0.80	0.58, 1.1	188	19.3	1.0	0.84, 1.2	86	18.0	0.99	0.77, 1.3
≥17	1,032	8.3	42	13.2	1.2	0.85, 1.7	107	11.0	1.0	0.82, 1.3	54	11.3	1.0	0.75, 1.4
Mixed/applied pesticides, days/year														
Never	6,983	56.0	178	56.5	1.0		530	54.3	1.0		267	55.5	1.0	
≤3	2,824	22.7	63	20.0	0.91	0.68, 1.2	210	21.5	0.95	0.80, 1.1	92	19.1	0.89	0.70, 1.1
4–7	1,228	9.9	40	12.7	1.2	0.87, 1.8	114	11.7	1.1	0.91, 1.4	50	10.4	1.0	0.76, 1.4
≥8	1,429	11.4	34	10.8	0.89	0.61, 1.3	122	12.5	1.0	0.84, 1.3	72	15.0	1.3	0.98, 1.7

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] For each exposure, odds ratios were calculated by using polytomous logistic regression and were adjusted for education (≤high school, >high school), age at baseline (≤45, 46–55, 56–65, ≥66 years), smoking status (never, past, current), body mass index (<25, 25–29.9, ≥30 kg/m^2), and hormone replacement therapy (never, ever).

RESULTS

Study demographics

In phase II, 23,569 spouses were evaluated, and 12.5% reported a history of physician-diagnosed thyroid disease (Figure 1). The prevalence of hypothyroidism and hyperthyroidism was 6.9% and 2.1%, respectively. Participants having other thyroid disease included 0.7% with both overactive and underactive thyroid disease and 1.8% with goiter, enlarged thyroid, or thyroid nodules; the rest reported unspecified thyroid disease (0.9%). Spouses in the Agricultural Health Study were predominantly white women with an average age at enrollment of 47.2 years (range, 17–88) (Table 1). Compared with spouses without thyroid disease, those in all outcome categories were more likely to be older, to have a higher body mass index, to have experienced menopause, to be past or current smokers, and to have used hormone replacement therapy (Table 1). No clear associations were found with level of education or birth control therapy (Table 1).

Association between pesticide use and thyroid disease

There were 16,529 spouses who had thyroid data, pesticide use data, and all covariate data; 2.2% were classified as hyperthyroid, 6.7% as hypothyroid, 3.4% as having other thyroid disease, and 87.6% as having no thyroid disease. Using multivariate analysis adjusted for education, age at baseline, smoking status, body mass index, and hormone replacement therapy, we found no association between lifetime pesticide application (years) or number of days per year mixing/applying pesticides and the risk of having either hyperthyroidism or hypothyroidism (Table 2). Of note, odds of hypothyroid disease increased if the spouse ever worked or lived on a farm, although it was not statistically significant, suggesting the influence of farm exposures on thyroid disease.

We found no significant association between ever use of any herbicide or ever use of the specific herbicides listed and thyroid disease, except for dichlorophenoxyacetic acid and paraquat (Table 3). Spouses who ever used paraquat, compared with those who never used paraquat, had an increased odds of hypothyroid disease (adjusted odds ratio (OR_{adj}) = 1.8 (95% confidence interval (CI): 1.1, 2.8). For the organochlorine insecticides, hypothyroidism was significantly associated with ever use of any organochlorine insecticide (OR_{adj} = 1.2 (95% CI: 1.0, 1.6)), and elevated odds ratios were observed for ever use of the organochlorines aldrin (OR_{adj} = 1.3 (95% CI: 0.64, 2.4)), chlordane (OR_{adj} = 1.3 (95% CI: 0.99, 1.7)), DDT (OR_{adj} = 1.2 (95% CI: 0.85, 1.6)), heptachlor (OR_{adj} = 1.2 (95% CI: 0.66, 2.3)), and lindane (OR_{adj} = 1.5 (95% CI: 0.93, 2.4)) (Table 4). Strikingly, ever use of any fungicide (OR_{adj} = 1.4 (95% CI: 1.1, 1.8)) or the specific use of benomyl (OR_{adj} = 3.1 (95% CI: 1.9, 5.1)) or maneb/mancozeb (OR_{adj} = 2.2 (95% CI: 1.5, 3.3) was associated with a very high odds of hypothyroid

Table 3. Herbicide Use and Odds of Thyroid Disease Among Female Spouses, Agricultural Health Study, 1993–2003[a]

Herbicide	No Thyroid Disease (n = 14,486; 88%)		Hyperthyroid (n = 369; 2%)				Hypothyroid (n = 1,114; 7%)				Other (n = 560; 3%)			
	No.	% Exposed	No.	% Exposed	OR	95% CI	No.	% Exposed	OR	95% CI	No.	% Exposed	OR	95% CI
Any	4,894	33.8	117	31.7	0.94	0.75, 1.2	390	35	1.0	0.91, 1.2	190	33.9	1.1	0.88, 1.3
2,4-D	1,887	13.0	46	12.5	0.93	0.68, 1.3	147	13.2	0.96	0.80, 1.1	87	15.5	1.2	0.95, 1.5
2,4,5-T	77	0.5	3	0.8	—[b]		7	0.6	1.01	0.46, 2.2	4	0.7	—[b]	
Alachlor	521	3.6	13	3.5	0.93	0.53, 1.6	36	3.2	0.83	0.59, 1.2	21	3.8	1.0	0.64, 1.6
Atrazine	539	3.7	10	2.7	0.67	0.35, 1.3	39	3.5	0.84	0.61, 1.2	27	4.8	1.2	0.82, 1.8
Butylate	161	1.1	4	1.1	—[b]		14	1.3	0.98	0.56, 1.7	6	1.1	0.83	0.36, 1.9
Chlorimuron-ethyl	221	1.5	7	1.9	1.2	0.57, 2.6	18	1.6	1.0	0.63, 1.7	10	1.8	1.2	0.61, 2.2
Cyanazine	367	2.5	10	2.7	1.0	0.54, 1.9	21	1.9	0.69	0.44, 1.1	16	2.9	1.1	0.65, 1.8
Dicamba	500	3.5	17	4.6	1.3	0.79, 2.1	27	2.4	0.66	0.45, 0.98	19	3.4	0.96	0.60, 1.5
EPTC	172	1.2	4	1.1	—[b]		11	1.0	0.75	0.40, 1.4	9	1.6	1.3	0.65, 2.5
Glyphosate	4,449	30.7	108	29.3	0.98	0.78, 1.2	353	31.7	1.0	0.91, 1.2	161	28.8	0.97	0.81, 1.2
Imazethapyr	368	2.5	12	3.3	1.3	0.72, 2.3	24	2.2	0.84	0.55, 1.3	14	2.5	1.0	0.59, 1.7
Metolachlor	422	2.9	13	3.5	1.2	0.68, 2.1	23	2.1	0.66	0.43, 1.0	21	3.8	1.3	0.82, 2.0
Metribuzin	209	1.4	6	1.6	1.0	0.44, 2.3	20	1.8	1.1	0.69, 1.7	9	1.6	0.99	0.50, 1.9
Paraquat	135	0.9	5	1.4	—[b]		21	1.9	1.8	1.1, 2.8	8	1.4	1.5	0.73, 3.1
Pendimethalin	289	2.0	9	2.4	1.2	0.59, 2.3	21	1.9	0.93	0.59, 1.5	13	2.3	1.2	0.66, 2.1
Petroleum oil	426	2.9	12	3.3	1.1	0.60, 1.9	38	3.4	1.1	0.76, 1.5	18	3.2	1.1	0.66, 1.7
Trifluralin	658	4.5	17	4.6	0.97	0.59, 1.6	58	5.2	1.1	0.80, 1.4	23	4.1	0.86	0.56, 1.3

Abbreviations: CI, confidence interval; EPTC, *s*-ethyl dipropylcarbamothioate; OR, odds ratio; 2,4-D, dichlorophenoxyacetic acid; 2,4,5-T, trichlorophenoxyacetic acid.

[a] Odds ratios were calculated by using polytomous logistic regression and were adjusted for education (≤high school, >high school), age at baseline (≤45, 46–55, 56–65, ≥66 years), smoking status (never, past, current), body mass index (<25, 25–29.9, ≥30 kg/m^2), and hormone replacement therapy (never, ever). Relative to 1.0 for the reference category of unexposed.

[b] Cell with counts ≤5. No appropriate inference can be made based on the odds ratio and its confidence interval.

disease (Table 5). Maneb/mancozeb was the only pesticide found to be associated with both hyperthyroidism (OR_{adj} = 2.3 (95% CI: 1.2, 4.4)) and hypothyroidism (OR_{adj} = 2.2 (95% CI: 1.5, 3.3)). We examined possible effect modification of the association between pesticide use and thyroid disease by race and menopause status. No appreciable differences were found (data not shown).

We evaluated the role of correlated use of pesticides as an explanation for our findings with hypothyroidism. We found that both fungicides benomyl (OR_{adj} = 2.7 (95% CI: 1.4, 5.2)) and maneb/mancozeb (OR_{adj} = 1.8 (95% CI: 1.1, 2.9)) were associated with hypothyroid disease.

DISCUSSION

In this study, we examined the association between 5 organochlorine insecticides, 39 other pesticides, and self-reported history of physician-diagnosed thyroid disease in female spouses of pesticide applicators. The population of female spouses in the Agricultural Health Study is large, and these data support the role of the organochlorines aldrin, DDT, heptachlor, lindane, and chlordane; the fungicides benomyl and maneb/mancozeb; and the herbicide paraquat in the etiology of thyroid disease.

We found the prevalence of self-reported, clinically diagnosed thyroid disease in female spouses in the Agricultural Health Study to be 12.5%. This prevalence is higher than previously reported in the Third National Health and Nutrition Examination Survey (2) and the Colorado Health Study (1) for both clinical (abnormal TSH and abnormal T4 and/or T3 levels) and subclinical (abnormal TSH but normal T4 and T3 levels) thyroid disease in the general population. Clinical thyroid disease was estimated at 0.8%–7.5% (1, 2, 23) and subclinical thyroid disease at 5%–9.4% in these populations (1, 2). Ethnicity in the Colorado thyroid disease prevalence study was similar to that for spouses in the Agricultural Health Study; both populations were predominantly white (94% for the Colorado Health Study vs. 98% for the Agricultural Health Study). Agricultural Health Study participants were slightly younger than the Colorado population: 39% were aged >55 years and 52.5% were aged >54 years (1), respectively. Thyroid disease is more prevalent with increasing age, but given that the Agricultural Health Study population is slightly younger than the Colorado study population, differences in age are unlikely to explain differences in thyroid disease prevalence between the 2 studies. Note, however, that the Agricultural Health Study is assessing only women with thyroid disease, and other studies evaluate both men and women. The fact that women have a higher rate of thyroid disease could contribute to higher overall reported rates of thyroid disease in this population. Because this study assessed self-reported, physician-

Table 4. Insecticide Use and Odds of Thyroid Disease Among Female Spouses, Agricultural Health Study, 1993–2003[a]

Insecticide	No Thyroid Disease (n = 14,486; 88%)		Hyperthyroid (n = 369; 2%)				Hypothyroid (n = 1,114; 7%)				Other (n = 560; 3%)			
	No.	% Exposed	No.	% Exposed	OR	95% CI	No.	% Exposed	OR	95% CI	No.	% Exposed	OR	95% CI
Organochlorines														
Any	862	6.0	27	7.3	1.0	0.68, 1.5	101	9.1	1.2	1.0, 1.6	51	9.1	1.3	0.93, 1.7
Aldrin	87	0.6	6	1.6	2.1	0.93, 5.0	10	0.9	1.3	0.64, 2.4	5	0.9	—[b]	
Chlordane	474	3.3	18	4.9	1.3	0.78, 2.1	58	5.2	1.3	0.99, 1.7	30	5.4	1.4	0.94, 2.0
DDT	386	2.7	15	4.1	1.1	0.65, 1.9	48	4.3	1.2	0.85, 1.6	24	4.3	1.1	0.74, 1.7
Heptachlor	98	0.7	6	1.6	1.9	0.84, 4.5	11	1.0	1.2	0.66, 2.3	2	0.4	—[b]	
Lindane	162	1.1	3	0.8	—[b]		21	1.9	1.5	0.93, 2.4	10	1.8	1.5	0.78, 2.8
Organophosphates														
Any	3,248	22.4	88	23.8	1.0	0.81, 1.3	285	25.6	1.1	0.94, 1.2	126	22.5	1.0	0.78, 1.2
Chlorpyrifos	495	3.4	16	4.3	1.2	0.74, 2.1	40	3.6	1.0	0.74, 1.4	26	4.6	1.4	0.92, 2.1
Coumaphos	148	1	5	1.4	—[b]		12	1.1	1.0	0.57, 1.9	9	1.6	1.6	0.80, 3.1
Diazinon	1,251	8.6	36	9.8	1.1	0.79, 1.6	108	9.7	1.1	0.86, 1.3	45	8.0	0.92	0.67, 1.3
Dichlorvos	343	2.4	6	1.6	0.62	0.27, 1.4	18	1.6	0.60	0.37, 0.97	11	2.0	0.73	0.40, 1.3
Fonofos	209	1.4	8	2.2	1.4	0.66, 2.8	17	1.5	0.99	0.60, 1.6	8	1.4	0.91	0.45, 1.9
Malathion	2,426	16.7	64	17.3	0.97	0.73, 1.3	220	19.7	1.1	0.92, 1.3	98	17.5	0.97	0.77, 1.2
Phorate	216	1.5	4	1.1	—[b]		16	1.4	0.86	0.51, 1.4	12	2.1	1.3	0.72, 2.4
Parathion	108	0.7	6	1.6	2.1	0.91, 4.8	10	0.9	1.0	0.53, 2.0	8	1.4	1.8	0.89, 3.8
Terbufos	370	2.6	8	2.2	0.81	0.40, 1.7	30	2.7	1.0	0.70, 1.5	14	2.5	0.96	0.56, 1.7
Carbamates														
Any	4,082	28.2	100	27.1	0.88	0.70, 1.1	339	30.4	1.0	0.88, 1.1	151	27.0	0.87	0.72, 1.1
Carbaryl	3,988	27.5	97	26.3	0.88	0.69, 1.1	333	29.9	1.0	0.88, 1.2	148	26.4	0.88	0.72, 1.1
Carbofuran	216	1.5	5	1.4	—[b]		18	1.6	1.0	0.59, 1.6	12	2.1	1.3	0.71, 2.3
Pyrethroids														
Permethrin/crops	253	1.7	5	1.4	—[b]		13	1.2	0.6	0.4, 1.1	5	0.9	—[b]	

Abbreviations: CI, confidence interval; DDT, dichlorodiphenyltrichloroethane; OR, odds ratio.

[a] Odds ratios were calculated by using polytomous logistic regression and were adjusted for education (≤high school, >high school), age at baseline (≤45, 46–55, 56–65, ≥66 years), smoking status (never, past, current), body mass index (<25, 25–29.9, ≥30 kg/m^2), and hormone replacement therapy (never, ever). Relative to 1.0 for the reference category of unexposed.

[b] Cell with counts ≤5. No appropriate inference can be made based on the odds ratio and its confidence interval.

diagnosed thyroid disease rather than actual medical records, the definition of thyroid disease is very heterogeneous, which may limit our interpretation regarding the different categories of thyroid disease represented in this study.

We found elevated odds of hypothyroid disease for all of the organochlorine insecticides assessed—aldrin, chlordane, DDT, heptachlor, and lindane—as well as the organochlorine fungicide chlorothalonil. Lindane and chlordane are both organochlorine insecticides, which have been reported to affect thyroid hormone levels in humans (17, 19). Elevated chlordane levels in breast milk have been associated with higher levels of congenital hypothyroidism (24). A study assessing formulators of both organochlorines, specifically lindane, and organophosphate insecticides showed an increase in TSH levels and a decrease in T3 levels in workers compared with controls (25). Malathion is an organophosphate insecticide and has been reported to affect thyroid hormone levels in freshwater catfish and bullfrog tadpoles (26, 27), but it was not associated with thyroid disease in our study. Consistent with our hypothesis, the organochlorine chlordane was associated with hypothyroidism, and, even though not all associations were statistically significant, the remainder of the organochlorines were all associated with an elevated odds of developing hypothyroidism.

We found that the fungicides benomyl and maneb/mancozeb were both strongly associated with increased odds of thyroid disease. Benomyl and maneb/mancozeb are both fungicides with carbamate groups. The dithiocarbamate pesticides ethylenebisdithiocarbamate and ethylenethiourea have been associated with thyroid dysfunction. Maneb/mancozeb has been shown to cause hypothyroidism in rabbits (28), and human workers exposed to ethylenethiourea showed significantly lower levels of total T4 compared with unexposed controls (29). In another study of unprotected workers heavily exposed to ethylenebisdithiocarbamate, TSH levels were elevated, but T4 levels were no different from those of controls (30). In this study, maneb/mancozeb

Table 5. Fungicide and Fumigant Use and Odds of Thyroid Disease Among Female Spouses, Agricultural Health Study, 1993–2003[a]

Chemical	No Thyroid Disease (n = 14,486; 88%)		Hyperthyroid (n = 369; 2%)				Hypothyroid (n = 1,114; 7%)				Other (n = 560; 3%)			
	No.	% Exposed	No.	% Exposed	OR	95% CI	No.	% Exposed	OR	95% CI	No.	% Exposed	OR	95% CI
Fungicide														
Any	535	3.7	17	4.6	1.2	0.72, 1.9	61	5.5	1.4	1.1, 1.8	24	4.3	1.1	0.72, 1.7
Benomyl	82	0.6	5	1.4	—[b]		21	1.9	3.1	1.9, 5.1	7	1.3	2.1	0.97, 4.6
Captan	247	1.7	3	0.8	—[b]		24	2.2	1.1	0.73, 1.7	11	2	1.1	0.59, 2.0
Chlorothalonil	108	0.7	2	0.5	—[b]		14	1.3	1.6	0.92, 2.9	4	0.7	—[b]	
Maneb/mancozeb	153	1.1	10	2.7	2.3	1.2, 4.4	30	2.7	2.2	1.5, 3.3	12	2.1	1.8	0.98, 3.3
Metalaxyl	160	1.1	4	1.1	—[b]		17	1.5	1.4	0.83, 2.3	7	1.3	1.1	0.52, 2.4
Fumigant														
Any	195	1.3	2	0.5	—[b]		24	2.2	1.4	0.93, 2.2	9	1.6	1.1	0.55, 2.1
Carbon tetrachoride/ carbon disulfide	62	0.4	0	0.0	—[b]		9	0.8	1.3	0.65, 2.7	3	0.5	—[b]	
Methylbromide	126	0.9	2	0.5	—[b]		15	1.3	1.6	0.92, 2.8	6	1.1	1.3	0.55, 2.9

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Odds ratios were calculated by using polytomous logistic regression and were adjusted for education (≤high school, >high school), age at baseline (≤45, 46–55, 56–65, ≥66 years), smoking status (never, past, current), body mass index (<25, 25–29.9, ≥30 kg/m^2), and hormone replacement therapy (never, ever). Relative to 1.0 for the reference category of unexposed.

[b] Cell with counts ≤5. No appropriate inference can be made based on the odds ratio and its confidence interval.

was found to be associated with both hyperthyroidism and hypothyroidism. A potential mechanism to explain its association with both types could be via a direct toxic effect on the thyroid gland, resulting in inflammation of the thyroid gland, thyroiditis, release of preformed thyroid hormone, and hyperthyroidism. This process may then result in transient or permanent hypothyroidism, similar to the mechanism of action for other medications known to cause direct toxic effects on the thyroid. To our knowledge, the observed increased risk of hyperthyroidism with use of maneb/mancozeb is novel. Overall, it is unknown whether the effect of pesticides on human thyroid function is transient, associated with contemporaneous pesticide exposure, or sustained.

We found an increased odds of hypothyroidism with ever use of chlorothalonil, an organochlorine fungicide. Chlorothalonil has not previously been reported to cause hypothyroidism, but it has been shown to increase the size of thyroid glands in animals (31).

We also found an association between the herbicide paraquat and hypothyroidism. Paraquat is a quaternary nitrogen herbicide commonly used for broadleaf control. Paraquat has not been reported to be associated with altered thyroid function; however, the US Environmental Protection Agency website (http://www.epa.gov/iris/subst/0183.htm) reports that thyroid adenomas were observed in Fischer rats exposed to increasing concentrations of paraquat, yet the thyroid adenomas were not thought to be attributable to the paraquat administration. Postmortem analysis of humans with paraquat poisoning revealed detectable amounts of paraquat in the thyroid gland, higher for women than for men (32), suggesting that the thyroid could be susceptible to the effects of paraquat when exposed. We are not aware of a previously published association between paraquat and hypothyroidism in humans, making this finding also novel.

Although we have the advantage of a large sample size, our results are based on self-report of diagnosed thyroid disease and not physician confirmation. In addition, when evaluating 44 pesticides and 3 outcomes, it is possible that by chance alone we would find approximately 7 statistically significant associations; we found 4. Our finding of a higher prevalence of thyroid disease may reflect increased risk associated with pesticides or may indicate overreporting given that the population was entirely women. It is also possible that the higher prevalence may be associated with other farm-related exposures not assessed. Because the Agricultural Health Study did not focus specifically on thyroid disease, and because only selected chemicals were associated with hypothyroidism, we have no reason to think that any such overreporting was related to pesticide use.

We could not distinguish between prevalent and incident disease, and our exposure measure—ever use of pesticides—may not always reflect an exposure that antedated disease onset. Furthermore, we did not have information on timing or level of exposure, and some of the associations were based on small numbers of exposed women.

We found an association of organochlorines and fungicides with hypothyroidism. Exposure to these classes of pesticides and thyroid dysfunction is plausible given that the main effects of these compounds are thought to be elevation of TSH levels and reduction of circulating thyroid hormone (T3 and T4). However, we do not know why this does not occur for the entire class of fungicides or whether these specific compounds cause a combination of goiter and biochemical thyroid dysfunction or just biochemical dysfunction alone. Unfortunately, we did not have access to blood samples in this study to evaluate the prevalence of subclinical thyroid disease. Finally, although we focused on self-reported use of pesticides by the female spouses of

pesticide applicators, spouses who do not apply pesticides may also be indirectly exposed to these same and other pesticides by virtue of living on the farm. Thus, there is the possibility of exposure misclassification that might lead to bias toward the null.

In conclusion, we found that the prevalence of self-reported clinical thyroid disease in female spouses of pesticide applicators is 12.5%, higher than in the general population. Hypothyroidism is the most common abnormality and is associated with the use of benomyl, maneb/mancozeb, and paraquat in addition to the class of organochlorines that includes aldrin, DDT, heptachlor, lindane, and chlordane. Maneb/mancozeb was also found to be associated with hyperthyroidism. Further studies are needed to confirm these novel findings, to determine whether pesticide exposure is also associated with thyroid disease in male pesticide applicators, and to evaluate mechanisms of action.

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