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ORIGINAL ARTICLE

Occupational pesticide exposure and subclinical hypothyroidism among male pesticide applicators

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ABSTRACT

Objectives Animal studies suggest that exposure to pesticides may alter thyroid function; however, few epidemiologic studies have examined this association. We evaluated the relationship between individual pesticides and thyroid function in 679 men enrolled in a substudy of the Agricultural Health Study, a cohort of licensed pesticide applicators.

Methods Self-reported lifetime pesticide use was obtained at cohort enrolment (1993-1997). Intensity-weighted lifetime days were computed for 33 pesticides, which adjusts cumulative days of pesticide use for factors that modify exposure (eg, use of personal protective equipment). Thyroid-stimulating hormone (TSH), thyroxine (T4), triiodothyronine (T3) and antithyroid peroxidase (anti-TPO) autoantibodies were measured in serum collected in 2010-2013. We used multivariate logistic regression to estimate ORs and 95% CIs for subclinical hypothyroidism (TSH >4.5 mIU/L) compared with normal TSH (0.4-≤4.5 mIU/L) and for anti-TPO positivity. We also examined pesticide associations with TSH, T4 and T3 in multivariate linear regression models.

Results Higher exposure to the insecticide aldrin (third and fourth quartiles of intensity-weighted days vs no exposure) was positively associated with subclinical hypothyroidism (OR_{Q3}=4.15, 95% CI 1.56 to 11.01, OR_{Q4}=4.76, 95% CI 1.53 to 14.82, p_{trend} <0.01), higher TSH (p_{trend}=0.01) and lower T4 (p_{trend}=0.04). Higher exposure to the herbicide pendimethalin was associated with subclinical hypothyroidism (fourth quartile vs no exposure: OR_{Q4}=2.78, 95% CI 1.30 to 5.95, p_{trend}=0.02), higher TSH (p_{trend}=0.04) and anti-TPO positivity (p_{trend}=0.01). The fumigant methyl bromide was inversely associated with TSH (p_{trend}=0.02) and positively associated with T4 (p_{trend}=0.01).

Conclusions Our results suggest that long-term exposure to aldrin, pendimethalin and methyl bromide may alter thyroid function among male pesticide applicators.

What this paper adds?

- Studies in laboratory animals have suggested that occupational exposure to individual pesticides may alter thyroid function.
- Posited mechanisms include competitive binding to thyroid hormone receptors and interference with thyroid enzymes; however, few epidemiologic studies have examined this association.
- In a large study of US male pesticide applicators, we observed associations between long-term occupational exposure to certain pesticides with thyroid hormone levels and subclinical hypothyroidism.
- For many of the pesticides examined, this is the first report in a human population; thus, there are no immediate implications for clinical practice.
- Future studies are needed to confirm these findings.

BACKGROUND

Thyroid dysfunction is relatively common in the US adult population. Approximately 5%, or 10.4 million, adults self-reported thyroid disease in a survey conducted in 1988–1994,[1] though prevalence estimates vary depending on population characteristics and diagnostic criteria.[2 3] Thyroid disease includes both hypothyroidism (ie, thyroid gland fails to secrete adequate thyroid hormone) and hyperthyroidism (ie, elevated blood levels of thyroid hormones);[4] diagnosis of hypothyroidism is more common.[2 5] Established risk factors for thyroid disease include female sex, increasing age, prior benign thyroid nodules or goitre, autoimmunity, iodine deficiency, and ionising radiation exposure.[6] If untreated, thyroid disease may result in increased risk for atrial fibrillation, bone loss and elevated cholesterol.[3]

Thyroid function is assessed by measurement of thyroid-stimulating hormone (TSH) and the thyroid hormones triiodothyronine (T3) and thyroxine (T4). TSH regulates thyroid hormone secretion and promotes thyroid gland growth. TSH is also regulated by T4 and T3 through negative feedback mechanisms. Antithyroid peroxidase (anti-TPO) autoantibodies are the most common autoantibodies present in the sera of individuals with autoimmune thyroid disease.[7]

Subclinical hypothyroidism is a subset of hypothyroid disease where laboratory evidence of thyroid dysfunction is present without symptoms characteristic of overt disease.[8] It is characterised by TSH concentrations above the upper limit of the reference range (0.4–4.5 mIU/L) with normal free

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T4 levels. Occurring in approximately 3.9% of US adults who do not report being diagnosed with thyroid disease, subclinical hypothyroidism represents early, mild thyroid failure that can progress to more clinically significant disease.[1 6]

There is growing evidence that environmental exposures, including certain pesticides, have biological properties that may influence thyroid function. For example, dichlorodiphenyltrichloroethane (DDT) is structurally similar to thyroid hormones[9] and can competitively bind to thyroid hormone receptors.[10] Also, fungicides belonging to the ethylenebis(dithiocarbamate) (EBDC) class are metabolised to ethylene thiourea, a chemical known to inhibit TPO. Additional posited mechanisms of pesticide-induced thyroid disruption include inhibition of iodine uptake, binding to transport proteins, interference with iodothyronine deiodinases, increased clearance of thyroid hormones, interference with cellular uptake of thyroid hormones and interference with thyroid gene expression.[11 12]

Few epidemiologic studies have evaluated thyroid disease and long-term occupational exposure to pesticides. A large study conducted among male pesticide applicators in the Agricultural Health Study (AHS) found higher occupational use of the pesticides aldrin, chlordane, DDT, lindane, parathion, alachlor and 2,4-dichlorophenoxyacetic acid (2,4-D) was associated with self-reported hypothyroidism.[13] Among female spouses of AHS applicators, use of chlordane, paraquat, benomyl and maneb/mancozeb was associated with self-reported hypothyroidism; maneb/mancozeb use was also associated with hyperthyroidism.[14] Several epidemiologic studies have evaluated occupational pesticide exposure and subclinical thyroid function. EBDC fungicide-exposed pesticide applicators in Mexico demonstrated higher TSH compared with unexposed controls.[15] Several epidemiologic studies have found changes in TSH, T3 and/or T4 to be associated with self-reported pesticide use.[16–18] However, a common limitation of these studies was their inability to examine associations with individual pesticides, instead examining overall pesticide use or broad chemical groupings (eg, herbicides, fungicides).

These previous studies of occupational pesticide exposures and thyroid function have been limited by low power, lack of information on specific pesticides or reliance on self-reported thyroid disease. In the present study, we examine whether subclinical hypothyroidism, TSH, T3 and T4 levels, and thyroid autoantibodies are associated with occupational exposures to pesticides among male pesticide applicators without self-reported thyroid disease in Iowa and North Carolina.

METHODS

Study design

We evaluated thyroid dysfunction in a subset of AHS participants who enrolled in the Biomarkers of Exposure and Effect in Agriculture (BEEA) Study between June 2010 and September 2013; the design and enrolment methods of the BEEA Study have been described.[19] Briefly, BEEA Study participants were selected from among male pesticide applicators with a private licence in the AHS cohort.[20] Those who continuously resided in Iowa or North Carolina, were over 50 years of age at the time of BEEA Study enrolment, had never been diagnosed with any type of cancer other than non-melanoma skin cancer, and had completed the enrolment AHS questionnaire (1993–1997), as well as two follow-up interviews (1999–2003 and 2005–2010) were eligible for the BEEA Study. All participants provided written informed consent at BEEA Study enrolment. A trained phlebotomist conducted a computer-assisted personal interview and collected a non-fasting blood sample. Samples were shipped in temperature-controlled containers overnight to a central processing facility, where serum was isolated, aliquoted and stored at −80°C. We sampled 684 of 955 eligible BEEA Study participants who had provided a blood sample, did not have a history of clinical thyroid disease (as reported on previous AHS questionnaires) and were not taking thyroid medications at the time of phlebotomy. Among the selected participants, we excluded five with laboratory results indicative of subclinical hyperthyroidism (TSH <0.4 mIU/L), leaving 679 participants for analysis.

TSH, thyroid hormones and anti-TPO autoantibodies

TSH was measured using a multiplexing kit from Millipore (The Human Pituitary Panel, Cat no. STTHMAG-21K). Total T4 and T3 were measured using another multiplexing kit from the same manufacturer (Steroid/Thyroid Hormone Magnetic Bead Panel, Cat no. STTHMAG-21K). Coefficients of variation for blinded duplicate quality control (QC) samples (n=30) were 9.5%, 11.7% and 15.8% for TSH, T4 and T3, respectively. Anti-TPO autoantibodies were measured using a Luminex-based kit from Applied Biosystems (Cat no. PP1000). We categorised results as negative or positive based on the raw Luminex median fluorescence intensity (MFI), with MFI 10–55 times higher than the median indicating anti-TPO positivity. In QC analyses of blind duplicate samples (n=30), we found 100% agreement.

For a subset of the QC samples with adequate serum (n=23) we compared the multiplex assay results with measurements from standard clinical laboratory immunoassays for TSH (Roche Diagnostics, Cat no. 11731459122) and T4 (Roche Diagnostics, Cat no. 20739006322). The assay results were highly correlated (TSH Spearman's ρ=0.76, T4 Spearman's ρ=0.71).

We defined normal thyroid function as having TSH levels of 0.4–4.5 mIU/L and subclinical hypothyroidism as TSH >4.5 mIU/L.[21] We evaluated pesticide associations comparing those with subclinical hypothyroidism to those with normal TSH levels. We also evaluated TSH, T4, and T3 as continuous outcomes, and anti-TPO as a binary outcome (negative or positive).

Exposure assessment

Information on use of individual pesticides came from two AHS cohort study questionnaires that were completed at enrolment (http://www.aghealth.nih.gov/collaboration/questionnaires.html). All applicators completed the first enrolment questionnaire, and provided information about ever/never use of 50 pesticides, as well as duration (years) and frequency (average days/year) of use for a subset of 22 pesticides. In addition, 63% of the applicators in this analysis returned the second (take-home) enrolment questionnaire, and provided information about duration and frequency of use for the remaining 28 pesticides. On average, there were 17 years of follow-up from enrolment to specimen collection.

For each pesticide, the number of cumulative days of use was calculated by multiplying the number of days the pesticide was used per year by total years of use. Intensity-weighted lifetime exposure days were computed by multiplying an intensity-weighting factor by lifetime exposure days. The intensity-weighting factor incorporates information that may influence exposure, that is, the repair and cleaning of equipment, application method, whether the applicator mixed pesticides and the use of personal protective equipment.[22] For herbicides and insecticides, we examined agents with ≥20 exposed cases

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of subclinical hypothyroidism. Because use of fumigants and fungicides was less prevalent, we examined agents with more than five exposed cases of subclinical hypothyroidism. Herbicides and insecticides were classified as unexposed (no reported use) and quartiles of intensity-weighted exposure days among all applicators, fungicides and fumigants were classified as unexposed (no reported use), low (≤ median) or high exposure based on the intensity-weighted exposure days among all applicators. Similarly, for analyses of anti-TPO positivity, we classified pesticide intensity-weighted days as unexposed, low or high exposed based on the median among all applicators reporting use. Applicators with missing information for a particular pesticide were excluded from that analysis. We evaluated a total of 33 pesticides (16 herbicides, 13 insecticides, two fungicides, two fumigants).

Statistical analysis

We compared sociodemographic, farming, and other health and behavioural characteristics for persons with normal TSH and those with subclinical hypothyroidism. We used logistic regression models to estimate ORs and 95% CIs for the association of each pesticide with subclinical hypothyroidism and anti-TPO positivity. To evaluate the relationship between each pesticide active ingredient and TSH, T4 and T3 levels modelled continuously, we estimated β coefficients and 95% CIs using multivariate linear regression models. TSH, T4 and T3 levels were natural log (ln) transformed to satisfy the assumptions of our statistical models. We exponentiated the resulting β coefficients, which reflect the ratio of the geometric mean for individuals in each exposure category relative to the geometric mean for unexposed individuals. Tests for trend used the median of each exposure category treated as a continuous variable. All models were adjusted for age at sample collection (continuous), state of residence (Iowa or North Carolina), body mass index at sample collection (BMI, continuous) and smoking status (current, former, never). Models were also adjusted for use of correlated pesticides (no exposure, quartiles of exposure, missing) at AHS enrolment (Spearman's ρ >0.40 calculated using continuous intensity-weighted lifetime days; see online supplementary table S1). Other variables considered as potential confounders included month and time of day of blood draw (modelled as cubic terms), alcohol consumption, educational attainment and race. These variables were ultimately not included in the final models because they did not impact the observed associations (<20% change in main effect). We also examined pesticide use reported during follow-up interviews conducted after AHS enrolment up to time of BEEA sample collection. For the pesticides queried at enrolment, pesticide use had either stopped completely (ie, ingredient registration was cancelled) or was markedly lower, the one exception being the commonly used herbicide glyphosate. However, including additional recent exposure to these pesticides (ie, exposure at follow-up interviews) did not substantively alter our findings (<20% change in main effect). To evaluate pesticide associations with subclinical hypothyroidism, TSH and thyroid hormones among those without evidence of an autoimmune aetiology, we performed analyses excluding anti-TPO positive participants.

Analyses were conducted using SAS V.9.3 (SAS Institute, Cary, North Carolina, USA). All tests were two-sided with $\alpha=0.05$.

RESULTS

Among the 679 pesticide applicators in our analysis, 127 (19%) met our definition for subclinical hypothyroidism (table 1). The prevalence increased with age: 17%, 16%, 21% and 32% of men ages 50–59 years, 60–69 years, 70–79 years and 80+ years had subclinical hypothyroidism, respectively. Men with subclinical hypothyroidism were more likely to be positive for anti-TPO ($p<0.01$). Age, race, state, BMI, smoking status, alcohol consumption and education did not vary substantially by subclinical hypothyroidism status. Men with subclinical hypothyroidism were less likely to have raised animals or to have applied pesticides in the last 12 months, although these differences were not statistically significant.

Among the insecticides (table 2), aldrin use was positively associated with subclinical hypothyroidism (fourth quartile of intensity-weighted lifetime days of use vs no use: $OR_{Q4}=4.76$, 95% CI 1.53 to 14.82, $p_{trend}<0.01$) and TSH ($p_{trend}=0.01$). Increasing use of aldrin was also associated with lower T4 ($p_{trend}=0.04$) and T3 ($p_{trend}=0.08$). Diazinon use was associated with elevated odds of subclinical hypothyroidism (third quartile vs no use: $OR_{Q3}=2.64$, 95% CI 1.00 to 6.98, $p_{trend}=0.10$) and higher TSH levels ($p_{trend}=0.07$), with no significant monotonic trend. Terbufos use in all quartiles was associated with elevated T3, though we observed no significant exposure-response trend ($p_{trend}=0.10$), and no association with TSH or T4.

Applicators reporting use of pendimethalin had increased odds of subclinical hypothyroidism (fourth quartile of intensity-weighted lifetime days of use vs no use: $OR_{Q4}=2.78$, 95% CI 1.30 to 5.95, $p_{trend}=0.02$) and significantly increased TSH with increasing use ($p_{trend}=0.04$) (table 3). Higher use of S-ethyl dipropylthiocarbamate (EPTC) was statistically significantly associated with increased TSH (fourth quartile vs no use: $\exp(\beta)_{Q4}=1.24$, 95% CI 1.00 to 1.54, $p_{trend}=0.04$), and was non-significantly associated with subclinical hypothyroidism (fourth quartile vs no use: $OR_{Q4}=2.05$, 95% CI 0.91 to 4.63, $p_{trend}=0.05$). Increasing 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) intensity-weighted lifetime days of use was associated with significantly decreased T4 ($p_{trend}=0.03$). Cyanazine was associated with elevated odds of subclinical hypothyroidism (third quartile vs no use: $OR_{Q3}=2.53$, 95% CI 1.34 to 4.78, $p_{trend}=0.35$) and increased TSH (third quartile vs no use: $\exp(\beta)_{Q3}=1.19$, 95% CI 1.02 to 1.39, $p_{trend}=0.11$) without evidence for a monotonic trend. Increasing use of petroleum distillates was associated with significantly decreased T3 ($p_{trend}=0.045$) and non-significantly elevated TSH ($p_{trend}=0.09$).

No evaluated fumigant or fungicide was significantly associated with subclinical hypothyroidism (table 4). However, methyl bromide use was associated with significantly lower TSH (>median vs unexposed: $\exp(\beta)_{high}=0.75$, 95% CI 0.56 to 1.00, $p_{trend}=0.02$), higher T4 ($p_{trend}=0.01$) and higher T3 ($p_{trend}=0.06$). In contrast, captan intensity-weighted lifetime days of use above the median was associated with borderline significantly higher TSH levels ($\exp(\beta)_{high}=1.23$, 95% CI 1.00 to 1.52, $p_{trend}=0.05$) compared with unexposed.

Results for pesticide use and anti-TPO positivity are shown in online supplementary table S2. Compared with men with no exposure, intensity-weighted lifetime days of pendimethalin use above the median was significantly associated with anti-TPO positivity ($OR_{high}=2.69$, 95% CI 1.29 to 5.60, $P_{trend}=0.01$) compared with unexposed applicators. A few additional pesticides had non-significantly elevated associations at exposure greater than the median intensity-weighted days, including aldrin ($OR_{high}=2.31$, 95% CI 0.79 to 6.73, $P_{trend}=0.12$), DDT ($OR_{high}=2.28$, 95% CI 0.73 to 7.15, $p_{trend}=0.09$) and atrazine ($OR_{high}=2.15$, 95% CI 0.75 to 4.88, $p_{trend}=0.29$).

Excluding individuals with anti-TPO positivity (n=65), we generally observed weaker associations for subclinical hypothyroidism, TSH, T4 and T3 with pesticide exposures that were in the same direction as those among all subjects

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Table 1 Selected characteristics of pesticide applicators at the BEEA Study sample collection (unless noted) stratified by subclinical hypothyroidism (TSH 0.4–4.5 mIU/L or >4.5 mIU/L)

		Subclinical hypothyroidism		
	Totaln=679N (%)	Non=552N (%)	Yesn=127N (%)	p Value*
Age, years				
50–59	254 (37.41)	210 (38.04)	44 (34.65)	0.12
60–69	231 (34.02)	193 (34.96)	38 (29.92)	
70–79	156 (22.97)	123 (22.28)	33 (25.98)	
80+	38 (5.60)	26 (4.71)	12 (9.45)	
Race†				
Non-Hispanic white	664 (97.80)	540 (97.80)	124 (97.60)	0.90
Other	15 (2.20)	12 (2.20)	3 (2.40)	
State†				
Iowa	582 (85.71)	474 (85.87)	108 (85.04)	0.81
North Carolina	97 (14.29)	78 (14.13)	19 (14.96)	
Body mass index				
Normal (<25)	118 (17.38)	97 (17.57)	21 (16.54)	0.86
Overweight (25–29.9)	301 (44.33)	242 (43.84)	59 (46.46)	
Obese (30+)	260 (38.29)	213 (38.59)	47 (37.01)	
Tobacco smoking‡				
Never	407 (59.94)	325 (58.88)	82 (64.57)	0.46
Former	230 (33.87)	191 (34.6)	39 (30.71)	
Current	42 (6.19)	36 (6.52)	6 (4.72)	
Alcohol consumption (last 7 days)				
None	322 (47.42)	257 (46.56)	65 (51.18)	0.63
<5 drinks	206 (30.34)	171 (30.98)	35 (27.56)	
5+ drinks	151 (22.24)	124 (22.46)	27 (21.26)	
Education†				
Less than high school	26 (3.83)	18 (3.26)	8 (6.3)	0.29
High school graduate	321 (47.28)	260 (47.1)	61 (48.03)	
Vocational school/some college	157 (23.12)	133 (24.09)	24 (18.9)	
College grad	162 (23.86)	132 (23.91)	30 (23.62)	
Missing/don't know	13 (1.91)	9 (1.63)	4 (3.15)	
Raised farm animals in the last 12 months				
Did not farm	104 (15.32)	79 (14.31)	25 (19.69)	0.06
No	274 (40.35)	217 (39.31)	57 (44.88)	
Yes	301 (44.33)	256 (46.38)	45 (35.43)	
Applied pesticides occupationally in the last 12 months				
No	192 (28.28)	148 (26.81)	44 (34.65)	0.08
Yes	487 (71.72)	404 (73.19)	83 (65.35)	
Off-farm job in the last 12 months				
No	446 (65.68)	365 (66.12)	81 (63.78)	0.62
Yes	233 (34.32)	187 (33.88)	46 (36.22)	
Anti-TPO antibodies				
Negative	614 (90.43)	516 (93.48)	98 (77.17)	<0.01
Positive	65 (9.57)	36 (6.52)	29 (22.83)	

*χ^2 Test for homogeneity
†Collected at AHS enrolment
‡Collected at the second AHS follow-up
BEEA, Biomarkers of Exposure and Effect in Agriculture; TSH, thyroid stimulating hormone; TPO, thyroid peroxidase.

(see online supplementary table S3). The associations between aldrin and cyanazine with subclinical hypothyroidism, methyl bromide with TSH and terbufos with T3 remained statistically significant; however, other reported associations were substantially attenuated including pendimethalin with hypothyroidism (fourth quartile of intensity-weighted days vs no exposure: OR_{Q4}=1.86, 95% CI 0.73 to 4.73, p_{trend}=0.25) and EPTC with TSH (fourth quartile vs no exposure: $\exp(\beta)_{Q4}$=1.07, 95% CI 0.86 to 1.32, p_{trend}=0.45).

DISCUSSION

Our study is the first to comprehensively examine occupational use of a wide range of pesticide active ingredients and the prevalence of subclinical hypothyroidism, TSH, thyroid hormones and thyroid autoantibodies. The insecticide aldrin and the herbicide pendimethalin were associated with subclinical hypothyroidism and higher TSH levels. Pendimethalin was also significantly associated with anti-TPO positivity, suggesting that it may influence TSH through an autoimmune pathway. The prevalence

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Table 2 Multivariate regression models examining association between intensity-weighted days of specific insecticides and subclinical hypothyroidism (TSH >4.5 mIU/L) and natural log of TSH, T4 and T3

				TSH and thyroid hormones			
	Intensity- weighted days	Subclinical hypothyroidism			TSH	T4	T3
		N†	OR (95% CI)	N‡	Expβ (95% CI)	Expβ (95% CI)	Expβ (95% CI)
Organochlorine							
Aldrin§	0	85	1.00 (ref)	533	1.00 (ref)	1.00 (ref)	1.00 (ref)
	26–210	5	0.99 (0.31 to 3.18)	25	1.10 (0.84 to 1.45)	1.07 (0.96 to 1.20)	1.09 (0.97 to 1.23)
	>210–392	5	1.53 (0.44 to 5.28)	19	0.89 (0.65 to 1.22)	1.01 (0.89 to 1.15)	0.97 (0.84 to 1.11)
	>392–1117	9	4.15 (1.56 to 11.0)¶	20	1.53 (1.16 to 2.03)¶	1.03 (0.92 to 1.16)	1.00 (0.89 to 1.13)
	>1117–10 339	9	4.76 (1.53 to 14.8)¶	21	1.33 (0.97 to 1.81)	0.87 (0.76 to 0.98)¶	0.88 (0.77 to 1.01)
	p_{trend}		<0.01¶		0.01¶	0.04¶	0.08
Chlordane§	0	92	1.00 (ref)	521	1.00 (ref)	1.00 (ref)	1.00 (ref)
	24–210	5	1.13 (0.39 to 3.27)	23	0.94 (0.72 to 1.23)	1.00 (0.89 to 1.11)	0.95 (0.85 to 1.06)
	>210–315	4	1.45 (0.43 to 4.91)	16	0.80 (0.58 to 1.10)	1.01 (0.89 to 1.15)	0.99 (0.87 to 1.14)
	>315–980	5	1.35 (0.45 to 4.11)	20	1.10 (0.82 to 1.47)	1.02 (0.91 to 1.15)	1.03 (0.91 to 1.16)
	>980–13 020	6	1.80 (0.57 to 5.73)	19	1.08 (0.78 to 1.48)	0.96 (0.84 to 1.09)	1.07 (0.93 to 1.22)
	p_{trend}		0.30		0.68	0.56	0.35
DDT§	0	92	1.00 (ref)	531	1.00 (ref)	1.00 (ref)	1.00 (ref)
	18–240	5	0.88 (0.27 to 2.83)	22	0.95 (0.71 to 1.28)	1.02 (0.90 to 1.15)	1.06 (0.94 to 1.20)
	>240–662	5	0.87 (0.28 to 2.76)	21	1.17 (0.87 to 1.56)	1.02 (0.91 to 1.15)	1.02 (0.90 to 1.16)
	>662–2625	5	0.69 (0.22 to 2.21)	22	0.91 (0.68 to 1.22)	1.10 (0.98 to 1.24)	1.05 (0.93 to 1.19)
	>2625–1 72 800	6	0.85 (0.26 to 2.81)	22	1.03 (0.75 to 1.41)	1.11 (0.98 to 1.26)	1.02 (0.89 to 1.16)
	p_{trend}		0.87		0.88	0.14	0.90
Heptachlor§	0	93	1.00 (ref)	550	1.00 (ref)	1.00 (ref)	1.00 (ref)
	26–182	5	1.65 (0.50 to 5.39)	19	1.33 (0.98 to 1.82)	0.86 (0.76 to 0.98)	0.89 (0.78 to 1.02)
	>182–474	6	2.15 (0.67 to 6.89)	18	1.21 (0.89 to 1.64)	1.06 (0.93 to 1.20)	0.93 (0.82 to 1.06)
	>474–980	6	1.27 (0.36 to 4.42)	18	1.14 (0.82 to 1.59)	0.93 (0.81 to 1.07)	0.99 (0.86 to 1.14)
	>980–30 680	4	0.63 (0.16 to 2.46)	18	1.00 (0.73 to 1.38)	1.06 (0.93 to 1.20)	1.06 (0.92 to 1.22)
	p_{trend}		0.75		0.68	0.73	0.57
Organophosphate							
Chlorpyrifos	0	60	1.00 (ref)	318	1.00 (ref)	1.00 (ref)	1.00 (ref)
	25–407	15	0.99 (0.52 to 1.87)	86	0.94 (0.81 to 1.09)	1.01 (0.95 to 1.07)	1.02 (0.96 to 1.09)
	>407–1005	18	1.22 (0.67 to 2.22)	85	0.99 (0.85 to 1.15)	1.03 (0.97 to 1.09)	1.02 (0.96 to 1.08)
	>1005–2807	20	1.35 (0.75 to 2.41)	85	1.03 (0.89 to 1.19)	1.07 (1.01 to 1.14)¶	1.02 (0.96 to 1.08)
	>2807–53 708	12	0.71 (0.36 to 1.41)	86	1.00 (0.86 to 1.16)	1.02 (0.96 to 1.09)	1.01 (0.95 to 1.07)
	p_{trend}		0.39		0.88	0.36	0.91
Diazinon§	0	86	1.00 (ref)	516	1.00 (ref)	1.00 (ref)	1.00 (ref)
	28–236	4	1.32 (0.42 to 4.11)	19	1.16 (0.87 to 1.54)	0.95 (0.84 to 1.06)	1.00 (0.88 to 1.13)
	>236–420	7	2.44 (0.95 to 6.30)	21	1.04 (0.79 to 1.36)	1.04 (0.93 to 1.16)	1.04 (0.93 to 1.17)
	>420–882	7	2.64 (1.00 to 6.98)¶	19	1.40 (1.06 to 1.86)¶	0.98 (0.87 to 1.10)	0.98 (0.87 to 1.11)
	>882–13 423	6	1.88 (0.68 to 5.17)	20	1.22 (0.92 to 1.62)	1.10 (0.98 to 1.23)	1.03 (0.92 to 1.17)
	p_{trend}		0.10		0.07	0.15	0.62
Fonofos	0	78	1.00 (ref)	433	1.00 (ref)	1.00 (ref)	1.00 (ref)
	28–368	11	1.23 (0.60 to 2.52)	55	0.95 (0.80 to 1.14)	0.98 (0.91 to 1.05)	0.98 (0.91 to 1.06)
	>368–982	11	1.16 (0.56 to 2.38)	54	0.94 (0.79 to 1.13)	1.06 (0.98 to 1.13)	1.03 (0.96 to 1.11)
	>982–2646	13	1.35 (0.68 to 2.69)	55	0.98 (0.82 to 1.17)	0.99 (0.92 to 1.06)	1.05 (0.97 to 1.13)
	>2646–21 948	10	1.09 (0.52 to 2.31)	54	1.16 (0.97 to 1.39)	1.03 (0.95 to 1.10)	0.96 (0.89 to 1.04)
	p_{trend}		0.73		0.11	0.53	0.51
Malathion§	0	29	1.00 (ref)	180	1.00 (ref)	1.00 (ref)	1.00 (ref)
	20–276	12	1.04 (0.47 to 2.28)	74	0.90 (0.76 to 1.07)	1.00 (0.93 to 1.08)	1.02 (0.95 to 1.10)
	>276–780	15	1.20 (0.55 to 2.60)	75	1.02 (0.86 to 1.22)	1.00 (0.93 to 1.08)	1.03 (0.95 to 1.11)
	>780–2250	14	0.95 (0.42 to 2.13)	77	0.90 (0.75 to 1.07)	1.03 (0.96 to 1.12)	1.02 (0.94 to 1.10)
	>2250–1 17 600	18	1.50 (0.69 to 3.27)	77	1.10 (0.91 to 1.33)	0.99 (0.91 to 1.07)	1.00 (0.92 to 1.09)
	p_{trend}		0.30		0.16	0.65	0.81
Phorate§	0	79	1.00 (ref)	429	1.00 (ref)	1.00 (ref)	1.00 (ref)
	28–236	6	0.81 (0.32 to 2.05)	36	0.95 (0.77 to 1.18)	1.01 (0.93 to 1.10)	1.00 (0.91 to 1.09)
	>236–588	6	0.76 (0.30 to 1.92)	38	1.03 (0.84 to 1.27)	1.02 (0.94 to 1.11)	1.04 (0.96 to 1.14)

continued

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Table 2 continued

				TSH and thyroid hormones			
	Intensity- weighted days	Subclinical hypothyroidism			TSH	T4	T3
		N†	OR (95% CI)	N‡	Expβ (95% CI)	Expβ (95% CI)	Expβ (95% CI)
	>588–1302	7	0.98 (0.41 to 2.35)	38	1.16 (0.94 to 1.43)	1.01 (0.93 to 1.10)	0.94 (0.87 to 1.03)
	>1302–37 758	8	1.10 (0.47 to 2.58)	37	1.03 (0.83 to 1.27)	1.03 (0.94 to 1.12)	0.98 (0.90 to 1.07)
	p_{trend}		0.80		0.54	0.55	0.43
Terbufos	0	62	1.00 (ref)	309	1.00 (ref)	1.00 (ref)	1.00 (ref)
	34–463	18	1.17 (0.63 to 2.16)	86	0.93 (0.80 to 1.08)	1.02 (0.96 to 1.08)	1.08 (1.01 to 1.15)¶
	>463–1259	15	0.87 (0.46 to 1.64)	86	0.97 (0.83 to 1.12)	1.01 (0.95 to 1.07)	1.03 (0.96 to 1.09)
	>1259–3368	12	0.65 (0.33 to 1.29)	86	0.91 (0.78 to 1.06)	1.00 (0.94 to 1.07)	1.07 (1.00 to 1.14)¶
	>3368–17 748	16	0.95 (0.51 to 1.78)	86	0.99 (0.85 to 1.15)	1.02 (0.96 to 1.08)	1.07 (1.00 to 1.13)¶
	p_{trend}		0.72		0.97	0.69	0.10
Carbamate							
Carbaryl§	0	71	1.00 (ref)	397	1.00 (ref)	1.00 (ref)	1.00 (ref)
	28–200	7	1.03 (0.42 to 2.55)	39	0.85 (0.69 to 1.05)	1.02 (0.93 to 1.11)	1.08 (0.99 to 1.19)
	>200–662	10	1.79 (0.78 to 4.11)	38	1.06 (0.86 to 1.32)	1.01 (0.92 to 1.10)	1.03 (0.94 to 1.13)
	>662–2315	9	1.42 (0.59 to 3.45)	40	1.18 (0.95 to 1.47)	1.06 (0.97 to 1.16)	1.03 (0.94 to 1.14)
	>2315–2 27 850	7	0.77 (0.27 to 2.23)	38	1.06 (0.83 to 1.36)	0.96 (0.87 to 1.07)	0.92 (0.83 to 1.03)
	p_{trend}		0.52		0.58	0.45	0.08
Carbofuran	0	67	1.00 (ref)	413	1.00 (ref)	1.00 (ref)	1.00 (ref)
	28–294	14	1.67 (0.86 to 3.24)	58	0.95 (0.81 to 1.13)	0.96 (0.90 to 1.03)	1.00 (0.94 to 1.08)
	>294–858	13	1.59 (0.80 to 3.13)	56	1.07 (0.90 to 1.28)	1.04 (0.97 to 1.12)	1.00 (0.93 to 1.08)
	>858–2016	12	1.32 (0.66 to 2.65)	56	1.05 (0.89 to 1.25)	0.97 (0.90 to 1.04)	1.01 (0.94 to 1.08)
	>2016–33 837	14	1.58 (0.81 to 3.07)	59	1.01 (0.85 to 1.19)	1.03 (0.96 to 1.10)	1.03 (0.96 to 1.11)
	p_{trend}		0.21		0.79	0.55	0.40
Pyrethroid							
Permethrin	0	89	1.00 (ref)	460	1.00 (ref)	1.00 (ref)	1.00 (ref)
	24–230	9	0.93 (0.43 to 2.01)	50	0.91 (0.76 to 1.09)	0.96 (0.90 to 1.04)	0.98 (0.90 to 1.05)
	>230–599	5	0.49 (0.19 to 1.28)	50	0.81 (0.68 to 0.98)¶	1.03 (0.96 to 1.11)	0.98 (0.91 to 1.06)
	>599–2021	10	1.09 (0.52 to 2.29)	50	1.05 (0.88 to 1.26)	1.03 (0.96 to 1.11)	1.03 (0.96 to 1.12)
	>2021–6 12 000	10	1.14 (0.54 to 2.39)	50	1.13 (0.94 to 1.35)	1.02 (0.95 to 1.10)	1.03 (0.95 to 1.11)
	p_{trend}		0.66		0.13	0.50	0.37

*Adjusted for age, state, body mass index, smoking, correlated pesticides
†Exposed cases
‡Total exposed
§Detailed information for these chemicals was collected on the take-home questionnaire at enrolment
¶p<0.05 compared with never users
DDT, dichlorodiphenyltrichloroethane; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone.

of subclinical hypothyroidism appeared to be higher among the BEEA Study participants compared with similarly aged thyroid disease-free adults in the general US population in the National Health and Nutrion Examination Survey (NHANES).[1] However, a direct comparison of our results with these published data from NHANES should be interpreted cautiously, as the NHANES prevalence estimates are based on measurements from 1988 to 1994 in a racially diverse population including men and women, using a different laboratory assay.

Insecticides

In our study, high use of the insecticide aldrin was positively associated with subclinical hypothyroidism and with levels of TSH, and inversely associated with T4. Aldrin is an organochlorine (OC) insecticide that was first produced in the USA in the 1950s and was primarily used on corn.[23] Most uses for aldrin were banned in the USA in 1974, and its use has similarly been banned or restricted in many other countries.[24] However, OCs have long half-lives and persist in the environment. Due to their lipophilic nature they biomagnify in the food chain and are detectable in human tissue and serum many years after exposure.[25] Our findings are consistent with a previous investigation among male applicators in the AHS in which higher prior use of aldrin was associated with self-reported hypothyroidism.[13] In contrast to our findings, a study of agricultural workers in Brazil reported no association between serum levels of aldrin or dieldrin, the major metabolite of aldrin, with TSH, T3 or T4 in men or women.[26] Another Brazilian study of agricultural workers found no association between serum levels of aldrin and dieldrin and TSH; however, dieldrin levels were associated with significantly lower free T4.[18] Evidence of a negative correlation between dieldrin and free T4 was also reported in a small study of women in India.[27] Rats exposed at low levels to a mixture of persistent pesticides and other contaminants, including aldrin and several other OCs, demonstrated alterations in thyroid gland morphology, serum thyroid hormone levels and hepatic thyroid hormone levels.[28] Additionally, studies suggest that aldrin is associated with follicular thyroid tumours in male and female rats, though these associations were only observed at low doses.[29]

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Table 3 Multivariate* regression models examining association between intensity-weighted days of specific herbicides and subclinical hypothyroidism (TSH >4.5 mIU/L) and natural log of TSH, T4 and T3

				TSH and thyroid hormones			
	Intensity-weighted days	Subclinical hypothyroidism			TSH	T4	T3
		N†	OR (95% CI)	N‡	Expβ (95% CI)	Expβ (95% CI)	Expβ (95% CI)
Dinitroaniline							
Pendimethalin§	0	68	1.00 (ref)	412	1.00 (ref)	1.00 (ref)	1.00 (ref)
	28–208	10	1.77 (0.81 to 3.87)	36	1.01 (0.82 to 1.24)	0.98 (0.90 to 1.07)	1.01 (0.92 to 1.11)
	>208–375	6	0.96 (0.38 to 2.45)	35	0.89 (0.72 to 1.11)	1.02 (0.94 to 1.12)	1.02 (0.93 to 1.12)
	>375–1920	5	0.78 (0.29 to 2.09)	36	1.05 (0.85 to 1.30)	1.04 (0.96 to 1.14)	1.03 (0.94 to 1.12)
	>1920–14 105	12	2.78 (1.30 to 5.95)¶	35	1.25 (1.01 to 1.55)¶	0.98 (0.90 to 1.07)	0.96 (0.87 to 1.05)
	p_{trend}		0.02¶		0.04¶	0.81	0.46
Trifluralin	0	55	1.00 (ref)	308	1.00 (ref)	1.00 (ref)	1.00 (ref)
	25–632	15	0.94 (0.47 to 1.87)	87	0.99 (0.84 to 1.15)	0.99 (0.92 to 1.05)	0.99 (0.93 to 1.06)
	>632–1411	13	0.74 (0.35 to 1.53)	87	0.90 (0.76 to 1.05)	1.05 (0.98 to 1.12)	1.01 (0.94 to 1.08)
	>1411–3906	23	1.42 (0.74 to 2.74)	87	1.05 (0.90 to 1.24)	0.98 (0.92 to 1.05)	0.98 (0.91 to 1.05)
	>3906–1 13 400	18	1.09 (0.55 to 2.17)	87	1.14 (0.97 to 1.34)	1.05 (0.99 to 1.13)	1.04 (0.97 to 1.11)
	p_{trend}		0.65		0.05	0.14	0.28
Thiocarbamate							
Butylate§	0	66	1.00 (ref)	390	1.00 (ref)	1.00 (ref)	1.00 (ref)
	43–319	7	1.19 (0.45 to 3.16)	40	0.94 (0.75 to 1.16)	1.00 (0.91 to 1.09)	0.98 (0.89 to 1.08)
	>319–882	8	1.30 (0.50 to 3.40)	39	1.10 (0.88 to 1.38)	0.99 (0.91 to 1.09)	1.00 (0.91 to 1.10)
	>882–2184	9	1.23 (0.50 to 3.02)	39	1.20 (0.96 to 1.49)	0.96 (0.88 to 1.05)	0.99 (0.90 to 1.09)
	>2184–22 925	12	1.78 (0.74 to 4.28)	42	1.11 (0.89 to 1.39)	0.99 (0.90 to 1.08)	0.97 (0.88 to 1.07)
	p_{trend}		0.21		0.24	0.72	0.53
EPTC	0	87	1.00 (ref)	510	1.00 (ref)	1.00 (ref)	1.00 (ref)
	33–225	8	1.65 (0.71 to 3.81)	34	1.01 (0.82 to 1.25)	1.00 (0.92 to 1.09)	1.02 (0.93 to 1.12)
	>225–588	6	1.12 (0.44 to 2.82)	32	0.93 (0.75 to 1.16)	0.99 (0.91 to 1.09)	1.00 (0.91 to 1.1)
	>588–1792	10	2.10 (0.96 to 4.58)	34	1.09 (0.88 to 1.35)	0.88 (0.81 to 0.96)¶	0.88 (0.80 to 0.96)¶
	>1792–16 461	9	2.05 (0.91 to 4.63)	33	1.24 (1.00 to 1.54)¶	1.03 (0.94 to 1.13)	1.03 (0.94 to 1.13)
	p_{trend}		0.05		0.04¶	0.97	0.93
Phenoxy							
2,4-D	0	25	1.00 (ref)	118	1.00 (ref)	1.00 (ref)	1.00 (ref)
	68–878	22	0.75 (0.39 to 1.44)	136	0.94 (0.81 to 1.10)	0.99 (0.93 to 1.05)	0.98 (0.92 to 1.05)
	>878–2604	26	0.81 (0.43 to 1.55)	138	1.01 (0.86 to 1.18)	0.99 (0.92 to 1.05)	0.99 (0.93 to 1.06)
	>2604–7229	24	0.70 (0.36 to 1.36)	134	1.04 (0.88 to 1.22)	0.97 (0.91 to 1.04)	0.97 (0.91 to 1.04)
	>7229–1 92 780	29	0.80 (0.40 to 1.58)	138	1.09 (0.92 to 1.29)	0.98 (0.91 to 1.05)	0.95 (0.88 to 1.02)
	p_{trend}		0.85		0.14	0.64	0.14
2,4,5-T§	0	88	1.00 (ref)	518	1.00 (ref)	1.00 (ref)	1.00 (ref)
	25–263	7	2.58 (0.94 to 7.06)	21	1.04 (0.78 to 1.38)	0.93 (0.83 to 1.04)	1.04 (0.93 to 1.17)
	>263–458	5	1.23 (0.41 to 3.70)	22	0.99 (0.74 to 1.31)	0.95 (0.85 to 1.06)	0.98 (0.87 to 1.10)
	>458–1392	6	1.72 (0.63 to 4.65)	22	1.28 (0.98 to 1.68)	1.03 (0.93 to 1.15)	1.00 (0.89 to 1.12)
	>1392–29 869	7	2.10 (0.78 to 5.71)	21	1.03 (0.78 to 1.37)	0.88 (0.78 to 0.98)¶	0.90 (0.80 to 1.02)
	p_{trend}		0.16		0.68	0.03¶	0.09
Triazine							
Atrazine	0	19	1.00 (ref)	101	1.00 (ref)	1.00 (ref)	1.00 (ref)
	25–980	23	0.76 (0.35 to 1.63)	142	0.86 (0.73 to 1.02)	1.02 (0.95 to 1.10)	1.06 (0.99 to 1.14)
	>980–2604	20	0.55 (0.25 to 1.23)	144	0.79 (0.66 to 0.94)¶	1.03 (0.96 to 1.11)	1.01 (0.94 to 1.09)
	>2604–6962	33	1.12 (0.50 to 2.48)	140	0.84 (0.70 to 1.02)	0.97 (0.90 to 1.05)	0.98 (0.91 to 1.06)
	>6962–1 13 400	32	1.16 (0.49 to 2.78)	145	0.88 (0.72 to 1.07)	0.99 (0.91 to 1.07)	1.00 (0.92 to 1.09)
	p_{trend}		0.28		0.97	0.45	0.50
Cyanazine	0	48	1.00 (ref)	294	1.00 (ref)	1.00 (ref)	1.00 (ref)
	25–455	16	0.89 (0.44 to 1.80)	90	0.97 (0.83 to 1.14)	0.98 (0.92 to 1.05)	0.97 (0.91 to 1.04)
	>455–1313	8	0.43 (0.18 to 1.01)	89	0.97 (0.83 to 1.13)	1.00 (0.94 to 1.06)	1.04 (0.98 to 1.11)
	>1313–3689	28	2.53 (1.34 to 4.78)¶	90	1.19 (1.02 to 1.39)¶	1.00 (0.94 to 1.07)	1.00 (0.94 to 1.07)
	>3689–1 13 400	20	1.26 (0.61 to 2.61)	89	1.13 (0.95 to 1.34)	1.04 (0.97 to 1.12)	1.04 (0.97 to 1.12)
	p_{trend}		0.25		0.11	0.23	0.30
Metribuzin§	0	61	1.00 (ref)	353	1.00 (ref)	1.00 (ref)	1.00 (ref)

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Table 3 continued

				TSH and thyroid hormones			
	Intensity-weighted days	Subclinical hypothyroidism			TSH	T4	T3
		N†	OR (95% CI)	N‡	Expβ (95% CI)	Expβ (95% CI)	Expβ (95% CI)
	33–221	5	0.48 (0.17 to 1.35)	48	0.89 (0.73 to 1.08)	1.06 (0.98 to 1.15)	1.06 (0.97 to 1.15)
	>221–385	9	0.94 (0.39 to 2.30)	50	0.88 (0.72 to 1.08)	0.97 (0.90 to 1.06)	0.93 (0.85 to 1.02)
	>385–1000	12	1.56 (0.67 to 3.67)	43	1.25 (1.01 to 1.55)¶	0.94 (0.86 to 1.03)	1.01 (0.92 to 1.11)
	>1000–14 850	9	0.73 (0.27 to 1.95)	49	0.89 (0.71 to 1.11)	0.96 (0.88 to 1.06)	0.98 (0.88 to 1.08)
	p_{trend}		0.75		0.62	0.28	0.64
Chloroacetanilide							
Alachlor	0	36	1.00 (ref)	218	1.00 (ref)	1.00 (ref)	1.00 (ref)
	25–502	29	2.34 (1.25 to 4.37)¶	107	1.03 (0.89 to 1.20)	1.00 (0.94 to 1.06)	0.98 (0.92 to 1.05)
	>502–1358	12	0.69 (0.33 to 1.44)	106	0.91 (0.78 to 1.05)	1.02 (0.96 to 1.09)	0.98 (0.92 to 1.04)
	>1358–4463	21	0.98 (0.50 to 1.92)	107	1.06 (0.91 to 1.24)	0.97 (0.91 to 1.03)	0.98 (0.92 to 1.05)
	>4463–68 162	21	0.99 (0.48 to 2.01)	106	0.99 (0.84 to 1.17)	1.04 (0.97 to 1.11)	0.99 (0.93 to 1.07)
	p_{trend}		0.66		0.98	0.28	0.95
Metolachlor	0	54	1.00 (ref)	317	1.00 (ref)	1.00 (ref)	1.00 (ref)
	25–455	19	1.47 (0.79 to 2.71)	84	1.02 (0.88 to 1.18)	0.98 (0.92 to 1.05)	0.97 (0.91 to 1.03)
	>455–1240	16	1.23 (0.64 to 2.37)	81	1.08 (0.93 to 1.26)	1.04 (0.98 to 1.11)	0.97 (0.91 to 1.03)
	>1240–4232	10	0.65 (0.30 to 1.39)	83	0.92 (0.79 to 1.08)	0.98 (0.92 to 1.04)	0.98 (0.92 to 1.05)
	>4232–68 162	21	1.44 (0.72 to 2.88)	83	1.18 (0.99 to 1.40)	0.97 (0.91 to 1.05)	0.98 (0.91 to 1.05)
	p_{trend}		0.41		0.07	0.43	0.74
Other herbicides							
Chlorimuron-ethyl§	0	74	1.00 (ref)	435	1.00 (ref)	1.00 (ref)	1.00 (ref)
	30–118	6	1.13 (0.44 to 2.89)	32	0.88 (0.70 to 1.10)	0.99 (0.90 to 1.08)	0.96 (0.87 to 1.06)
	>118–315	8	1.62 (0.69 to 3.84)	30	0.94 (0.75 to 1.18)	1.01 (0.92 to 1.11)	1.03 (0.93 to 1.13)
	>315–588	7	1.35 (0.56 to 3.26)	33	1.03 (0.83 to 1.28)	1.02 (0.93 to 1.12)	0.99 (0.90 to 1.09)
	>588–7560	7	1.45 (0.60 to 3.50)	32	1.05 (0.84 to 1.31)	1.04 (0.95 to 1.14)	0.99 (0.90 to 1.09)
	p_{trend}		0.3		0.66	0.35	0.81
Dicamba	0	42	1.00 (ref)	220	1.00 (ref)	1.00 (ref)	1.00 (ref)
	36–350	20	0.93 (0.50 to 1.73)	109	0.86 (0.75 to 1.00)¶	0.98 (0.92 to 1.04)	0.95 (0.90 to 1.02)
	>350–1046	15	0.68 (0.35 to 1.33)	103	0.94 (0.81 to 1.09)	0.96 (0.91 to 1.02)	0.99 (0.92 to 1.05)
	>1046–2699	19	0.91 (0.48 to 1.72)	106	0.97 (0.84 to 1.13)	1.00 (0.94 to 1.06)	1.01 (0.95 to 1.08)
	>2699–1 07 823	21	1.06 (0.57 to 1.98)	106	0.98 (0.84 to 1.14)	0.98 (0.92 to 1.04)	0.97 (0.91 to 1.03)
	p_{trend}		0.62		0.59	0.86	0.59
Glyphosate	0	32	1.00 (ref)	179	1.00 (ref)	1.00 (ref)	1.00 (ref)
	20–315	25	1.28 (0.71 to 2.32)	116	1.02 (0.88 to 1.17)	1.01 (0.95 to 1.07)	0.98 (0.92 to 1.04)
	>315–907	24	1.07 (0.60 to 1.93)	130	1.00 (0.87 to 1.15)	1.01 (0.95 to 1.07)	1.01 (0.95 to 1.07)
	>907–2622	21	0.95 (0.51 to 1.77)	123	1.01 (0.88 to 1.17)	1.01 (0.96 to 1.07)	0.99 (0.93 to 1.05)
	>2622–1 13 400	25	1.21 (0.66 to 2.24)	123	1.14 (0.99 to 1.33)	0.99 (0.94 to 1.05)	0.97 (0.91 to 1.03)
	p_{trend}		0.70		0.05	0.68	0.41
Imazethapyr	0	62		360			
	33–263	12	1.08 (0.53 to 2.17)	70	0.90 (0.77 to 1.06)	0.97 (0.91 to 1.04)	0.97 (0.91 to 1.04)
	>263–600	14	1.22 (0.63 to 2.37)	73	1.12 (0.96 to 1.31)	0.96 (0.90 to 1.02)	0.95 (0.89 to 1.02)
	>600–1176	14	1.20 (0.61 to 2.33)	73	0.97 (0.83 to 1.14)	0.94 (0.88 to 1.00)¶	0.96 (0.90 to 1.03)
	>1176–22 500	16	1.54 (0.81 to 2.95)	71	1.15 (0.98 to 1.35)	0.97 (0.91 to 1.03)	0.98 (0.92 to 1.05)
	p_{trend}		0.19		0.09	0.24	0.56
Petroleum distillates§	0	74	1.00 (ref)	413	1.00 (ref)	1.00 (ref)	1.00 (ref)
	25–372	6	1.27 (0.49 to 3.30)	27	0.93 (0.73 to 1.18)	0.98 (0.88 to 1.08)	0.99 (0.90 to 1.10)
	>372–1110	3	0.56 (0.16 to 1.92)	27	1.16 (0.91 to 1.47)	0.99 (0.89 to 1.09)	1.00 (0.90 to 1.11)
	>1110–3973	7	1.54 (0.62 to 3.84)	27	1.07 (0.84 to 1.36)	1.01 (0.92 to 1.12)	1.03 (0.93 to 1.14)
	>3973–2 53 333	5	0.97 (0.35 to 2.69)	27	1.22 (0.96 to 1.56)	1.00 (0.91 to 1.11)	0.89 (0.80 to 0.99)¶
	p_{trend}		0.95		0.09	0.93	0.045¶

*Adjusted for age, state, body mass index, smoking, correlated pesticides
†Exposed cases
‡Total exposed
§Detailed information for these chemicals was collected on the take-home questionnaire at enrolment
¶p<0.05 compared with never users
2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5 T, 2,4,5-trichlorophenoxyacetic acid; EPTC, S-Ethyl dipropylthiocarbamate; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone.

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Table 4 Multivariate regression models examining association between intensity-weighted days of specific fumigants/fungicides and subclinical hypothyroidism (TSH >4.5 mIU/L) and natural log of TSH, T4 and T3

				TSH and thyroid hormones			
	Intensity-weighted days	Subclinical hypothyroidism			TSH	T4	T3
		N†	OR (95% CI)	N‡	Expβ (95% CI)	Expβ (95% CI)	Expβ (95% CI)
Fumigant							
Carbon tetrachloride	0	113	1.00 (ref)	617	1.00 (ref)	1.00 (ref)	1.00 (ref)
Carbon disulfide§	6–170	4	1.70 (0.51 to 5.61)	14	1.06 (0.76 to 1.47)	0.97 (0.85 to 1.10)	0.95 (0.82 to 1.09)
	>170–18 563	3	1.08 (0.29 to 4.08)	14	1.01 (0.73 to 1.41)	0.94 (0.82 to 1.07)	0.89 (0.77 to 1.02)
	p_{trend}		0.87		0.93	0.33	0.09
Methyl bromide	0	117	1.00 (ref)	622	1.00 (ref)		1.00 (ref)
	12–1139	6	1.32 (0.44 to 4.02)	24	1.31 (0.98 to 1.74)	0.89 (0.80 to 1.00)	0.94 (0.83 to 1.06)
	>1139–1 02 000	3	0.45 (0.11 to 1.81)	26	0.75 (0.56 to 1.00)†	1.14 (1.01 to 1.28)†	1.11 (0.98 to 1.26)
	p_{trend}		0.23		0.02†	0.01†	0.06
Fungicide							
Captan	0	103	1.00 (ref)	566	1.00 (ref)	1.00 (ref)	1.00 (ref)
	2–12	3	0.40 (0.12 to 1.35)	36	0.87 (0.71 to 1.07)	1.07 (0.98 to 1.17)	1.07 (0.98 to 1.16)
	>12–46 500	10	1.89 (0.87 to 4.11)	34	1.23 (1.00 to 1.52)¶	0.99 (0.91 to 1.09)	0.99 (0.90 to 1.08)
	p_{trend}		0.09		0.05¶	0.87	0.73
Metalaxyl§	0	105	1.00 (ref)	560	1.00 (ref)	1.00 (ref)	1.00 (ref)
	3–141	6	1.06 (0.41 to 2.72)	28	1.06 (0.84 to 1.34)	1.02 (0.93 to 1.12)	1.03 (0.93 to 1.14)
	>141–30 341	4	0.60 (0.19 to 1.92)	28	0.87 (0.68 to 1.12)	1.02 (0.92 to 1.13)	0.98 (0.88 to 1.09)
	p_{trend}		0.39		0.27	0.72	0.67

*Adjusted for age, state, body mass index, smoking, correlated pesticides
†Exposed cases
‡Total exposed
§Detailed information for these chemicals was collected on the take-home questionnaire at enrolment
¶p<0.05 compared with never users
T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone.

Herbicides

We observed associations with subclinical hypothyroidism and TSH for pendimethalin, a selective dinitroaniline herbicide used for control of broadleaf and grassy weeds that is registered for both crop and residential uses.[30] Since 2003, pendimethalin has been among the top 10 most commonly applied pesticides in the USA for agricultural use, and among the top 5 for residential use.[31] In our study, higher pendimethalin use was also associated with anti-TPO positivity, suggesting that exposure may influence TSH through an autoimmune pathway. Pendimethalin has been shown in vivo to enhance the metabolism and excretion of T3 and T4, increase TSH, increase thyroid cell growth and cause thyroid follicular cell adenomas.[30 32] In previous analyses in the AHS cohort, pendimethalin was not associated with self-reported hypothyroidism in men or women.[13 14] Though the associations with subclinical hypothyroidism, TSH and anti-TPO at the highest levels of exposure are interesting, caution should be taken in interpreting these results. These findings are based on small numbers of exposed individuals and the exposure-response trends do not appear to be monotonic.

We noted significantly increased TSH levels among applicators with the highest EPTC use, with a significant exposure-response trend. Goldner *et al* found no significant associations with EPTC and self-reported hypothyroidism among AHS men or women;[13 14] however, there was evidence of non-significantly elevated risk among men with the highest exposure (above median intensity-weighted days of use). Recent studies evaluating EPTC and endocrine disruption found only modest effects on the hypothalamic-pituitary-thyroidal axis, noting decreases in serum T4 in rats at high doses and decreased thyroid weight in dogs.[33]

When individuals with anti-TPO positivity were removed from the analyses, the associations for pendimethalin and EPTC with subclinical hypothyroidism and TSH were attenuated, suggesting that the effect of these herbicides on TSH may be stronger among participants with anti-TPO positivity. It has been hypothesised that individuals with thyroid autoantibodies are more susceptible to chemical exposures known to interfere with thyroid production or metabolism due to inability to properly compensate by increasing hormone production.[34] Direct studies are needed to investigate this mechanism.

Use of 2,4,5-T was associated with significantly decreased T4 and a suggestive increase in subclinical hypothyroidism with no monotonic trend. First developed in the 1940s, US registrations of 2,4,5-T have been cancelled since 1985 due to serious health effects (eg, birth defects, cancer) caused by contamination with the dioxin 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) during the manufacturing process.[35 36] Goldner *et al* previously noted a significant positive association with self-reported hypothyroidism and ever use of 2,4,5-T among male pesticide applicators.[13] Additionally, US Air Force veterans who sprayed Agent Orange, an herbicide containing 2,4-D and TCDD-contaminated 2,4,5-T, had significantly increased TSH even 20+ years after exposure compared with unexposed veterans. Based on the exposure information in our study, it is not possible to disentangle the separate effects of TCDD and 2,4,5-T on TSH and thyroid hormones. However, there is extensive animal literature indicating that chronic exposure to TCDD is associated with lower T4 and higher TSH.[9 37] It is possible that the associations observed for 2,4,5-T are due to confounding by TCDD.

Fumigants and fungicides

Higher intensity-weighted days of methyl bromide use was associated with lower TSH, significantly higher T4 and non-significantly

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elevated T3. Methyl bromide was first registered for use in the USA as a soil fumigant in 1961, but has been banned since 2005 under the Clean Air Act and the Montreal Protocol on Substances that Deplete the Ozone Layer.[38] Methyl bromide has demonstrated neurotoxic effects,[38] though its potential for thyroid and other endocrine disruption has not been well-studied. In AHS, methyl bromide use was associated with non-significantly elevated odds of self-reported hypothyroidism among women;[14] hyperthyroidism among women and thyroid disease among men were not evaluated.[13 14] Despite relatively few individuals having been exposed to methyl bromide in our analysis, we noted consistent associations across TSH, T4 and T3.

We found that high use of the fungicide captan in our study was associated with higher TSH. These findings are consistent with those from an earlier AHS study,[13] where ever use of captan was associated with non-significantly elevated risk of self-reported hypothyroidism among male pesticide applicators. Fungicide exposure has been associated with increased TSH levels among pesticide applicators in Minnesota.[16 39] Thyroid cancer mortality was also significantly higher in the same agricultural areas of Minnesota with high fungicide use compared with non-agricultural areas.[40] While these studies did not investigate individual fungicides, captan was reportedly among the most commonly used fungicides during this time period in Minnesota.[40] Due to the small number of exposed applicators with subclinical hypothyroidism (n=1), we were not able to evaluate the fungicides maneb and mancozeb. These fungicides are applied in orchards and other settings where captan may be used, and were shown to be associated with both hypothyroidism and hyperthyroidism among AHS spouses.[14] However, in our study and in the cohort overall, use of captan and maneb/mancozeb are not correlated (Spearman's $\rho=0.02$ and $\rho=0.17$, respectively); it is unlikely that maneb/mancozeb use is confounding the relationship between captan and TSH in our study.

Strengths and limitations

The characterisation of altered thyroid function based on measured TSH and thyroid hormone levels was a strength of our investigation, as it allowed us to examine past pesticide exposure and subclinical changes in thyroid function. However, lack of laboratory measurement of free T4 was an important limitation and impacted our classification of subclinical hypothyroidism, which is often defined as TSH concentrations above the upper limit of the reference range (0.4–4.5 mIU/L) with normal free T4 levels. Individuals with TSH and free T4 outside the reference range may be considered to have overt hypothyroidism requiring medical attention;[8] we were not able to make this distinction in our study. We excluded participants with self-reported thyroid disease or thyroid medication. These individuals may have normal TSH and thyroid hormone levels due to treatment, potentially biasing results towards the null. Use of a single blood sample to characterise TSH and thyroid hormones is a potential limitation; however, TSH has been shown to be relatively stable over time (eg, up to 3 years).[41] To rule out confounding due to seasonality or diurnal variation we controlled for time of day and month of blood draw in our statistical models; neither was an important confounder. Measurement of multiple markers of thyroid function was a strength of our study, and we focused on results where we saw concordance between markers (eg, higher TSH and lower T4). However, for some analyses we had limited statistical power to detect associations, particularly for subclinical hypothyroidism and pesticides with low prevalence of use.

Another strength is the detailed pesticide exposure assessment for many pesticides reported at AHS enrolment.[20] Though exposure misclassification is a potential concern with self-reported pesticide use, the AHS intensity-weighting algorithm has been shown to correlate well with urinary pesticide measures.[22 42] Additionally, due to the prospective cohort design and objective nature of the outcome measures, any exposure misclassification would likely be non-differential with respect to health outcomes. We were also able to adjust for use of other pesticides, minimising potential confounding by use of correlated chemicals. For this study, we limited our analyses to self-reported lifetime days of use as reported at study enrolment. The evidence is unclear as to whether recent or chronic exposures have the greatest impact on thyroid function. Our strongest association was with cumulative exposure to aldrin where recent exposures would not be possible, as it has been banned in the USA since 1974. For chemicals with ongoing use (eg, pendimethalin), adjustment for use reported in follow-up questionnaires did not alter the reported main effects. For most pesticides, exposures reported at enrolment accounted for the majority of applicators' cumulative lifetime use. Future studies should examine windows of pesticide and other chemical exposures in relation to thyroid dysfunction and thyroid disease incidence.

CONCLUSIONS

Lifetime use of several pesticides was associated with increased TSH levels and subclinical hypothyroidism in our study population of male pesticide applicators. Our findings, taken together with limited epidemiologic studies and experimental evidence from animal models, suggest that certain pesticides may act as thyroid hormone disruptors. Furthermore, the agreement of our findings with previous results in the AHS for aldrin and self-reported hypothyroidism[13] suggest that subclinical hormone disruption may potentially lead to overt hypothyroid disease among those exposed to this chemical. Thyroid disease and thyroid hormone disruption can impact human health, and may increase risk of other diseases including thyroid cancer,[43–46] breast cancer,[47 48]non-Hodgkin's lymphoma[49] and cardiovascular disease.[50] Most studies of pesticides and endocrine disruption have been conducted only in animals; more epidemiologic studies are necessary to understand how chronic occupational exposures impact thyroid function in men and women. Additionally, future work should attempt to assess whether short-term exposure to pesticides impacts thyroid hormone function in a similar manner as long-term use.

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Occupational pesticide exposure and subclinical hypothyroidism among male pesticide applicators

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