IN THE UNITED STATES COURT OF APPEALS FOR VETERANS CLAIMS

ROBERT M. EUZEBIO,	)	
	)	
Appellant,	)	
	)	
v.	)	Vet. App. No. 17-2879
	)	
ROBERT L. WILKIE,	)	
Secretary of Veterans Affairs,	)	
	)	
Appellee.	)	

APPELLEE'S SUPPLEMENTAL CITATION OF AUTHORITIES UNDER RULE 30(b)

Pursuant to Vet.App. Rule 30(b), the Secretary submits the March 29, 2018, Memorandum from the Office of the Chairman of the Board of Veterans' Appeals in response to Appellant's March 5, 2018, submission of *The Purplebook* as a supplemental authority under Rule 30(b). The March 2018 Memorandum states that the Board adopts *The Purplebook*, effective March 23, 2018. This memorandum revoked the Decision Style Manual and the Policies and Responsibility Assignment manuals and implemented *The Purplebook* in their place. The date of the Board decision at issue is July 20, 2017.

Additionally, in response to Appellant's May 22, 2018, Notice of Intended Reliance On Information, the Secretary submits an extract from the National Academy of Science's (NAS) *Veterans and Agent Orange: Update 2014*. Appellant's May 2018 Notice presents selected passages from the Update. The Secretary has argued that the Update discusses limited or suggestive evidence of an association of exposure to Agent Orange and hypothyroidism, a different disease from Appellant's non-malignant thyroid nodules and that the Update was

neither actually, nor constructively before the Board. *See* Appellee's Brief (Br.) at 12-16. While the Court should not consider any of this material, (including the Purple Book and the Update) the Court should not consider Appellant's selections without being made aware of the other relevant parts of the Update . The extract from the NAS Update 2014 clarifies that there is inadequate or insufficient evidence to determine an association between exposure to chemicals of interest and disruption of the endocrine system (other than hypothyroidism).

WHEREFORE, the Secretary respectfully requests that the Court accept Appellee's submission of the March 29, 2018, Board Chairman's Memorandum and the extract from the Update 2014 under R. 30(b).

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EXHIBIT

Office of the Chairman
Board of Veterans' Appeals
Washington, D.C. 20420

Date: March 29, 2018

MEMORANDUM
NO. 01-18-04

SUBJ: THE PURPLEBOOK

1. BACKGROUND

a. The Board is adopting The Purplebook, a document containing the Board's internal policies and procedures. The Purplebook will serve as a repository of guidance for all Board employees on the internal operating processes of the Board. After implementation, The Purplebook will be hosted on an internal Sharepoint Site, and will be routinely updated by staff of the Office of Legislation, Regulations, and Policy (LRP).

b. Adoption of this document will ensure consistency and accountability in the handling of appeals throughout the Board. As The Purplebook will be routinely updated, this repository will also allow the Board to remain agile in implementing needed revisions to procedures in the future.

2. PURPOSE OF THIS MEMORANDUM

This memorandum revokes the BVA Directive 8430 "BVA Decision Preparation & Processing: Policies and Responsibility Assignment" and BVA Handbook 8430.2 "BVA Decision Preparation & Processing Procedures: Decision Style Manual" and implements The Purplebook in their place effective March 23, 2018.

3. ACCESS TO THE PURPLEBOOK

The Purplebook will be hosted on an internal Sharepoint which can be reached by following a link on the Board's internal homepage.

4. UPDATES TO THE PURPLEBOOK

The procedure for updating The Purplebook is detailed in section XIV. In brief, the document will be maintained by LRP. Any Board employee should notify LRP if they believe they discover an error in The Purplebook, and all other requests for changes should be submitted to LRP by the respective chief of any division, branch, or office. Updates will be published on a quarterly basis, and may be published more frequently if needed. LRP will maintain a revisions index and use a consistent version numbering to track all revisions.

MEMORANDUM NO. 01-18-04

5. RESCISSION

This memorandum is effective until expressly rescinded, modified, or superseded.

Cheryl L. Mason
Chairman

Attachments: The Purplebook v1.0.0 (VA Purplebook 01-18-v1.0.0)
The Purplebook Revisions Index

EXHIBIT

13

Other Chronic Health Outcomes

Chapter Overview

Based on new evidence and a review of prior studies, the committee for Update *2014 found:*

- *There is now limited or suggestive evidence of an association between hypothyroidism and exposure to the chemicals of interest (COIs) in this report.*

In previous updates that considered short-term adverse outcomes (see Appendix B), the committees found:

- *There is sufficient evidence of an association between the COIs and chloracne.*
- *There is limited or suggestive evidence of an association between the COIs and early onset peripheral neuropathy and porpohyria cutanea tarda.*

No additional scientifically relevant associations between the exposures of concern and adverse chronic health outcomes were noted. The current evidence supports the findings of earlier studies that:

- *No other adverse outcomes had sufficient evidence of an association with the COIs.*

- *No other adverse outcomes had limited or suggestive evidence of an association with the COIs.*
- *There is inadequate or insufficient evidence to determine whether there is an association between the COIs and respiratory disorders, gastrointestinal and digestive disease (including liver toxicity), kidney disease, adverse effects on endocrine function (other than hypothyroidism), eye problems, or bone conditions.*

This chapter discusses data on the possible association between exposure to the herbicides used in Vietnam—2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), picloram, and cacodylic acid—and several non-cancer health outcomes: respiratory disorders, gastrointestinal and digestive disease (including liver toxicity), adverse effects on thyroid homeostasis, kidney disease, eye problems, and bone conditions. The committee also considers the results of studies of exposure to polychlorinated biphenyls (PCBs) and other dioxin-like chemicals (DLCs) to be informative if they were reported in terms of TCDD toxic equivalents (TEQs) or concentrations of dioxin-like specific congeners. Although all studies reporting TEQs based on PCBs were reviewed, those studies that reported TEQs based only on mono-ortho PCBs (which are PCBs 105, 114, 118, 123, 156, 157, 167, and 189) were given very limited consideration because mono-ortho PCBs typically contribute less than 10 percent to total TEQs, based on the World Health Organization (WHO) revised toxicity equivalency factors (TEFs) of 2005 (La Rocca et al., 2008; van den Berg et al., 2006).

In previous updates, chloracne and porphyria cutanea tarda were considered with the chronic non-cancer conditions. They are accepted as being associated with dioxin exposure, but when they occur, it happens within a matter of months of the exposure. In *Update 2010*, the two health outcomes were moved to an appendix on short-term effects along with transient early-onset peripheral neuropathy, which had previously been discussed in the chapter on neurologic disorders.

For each type of health outcome, background information is followed by a brief summary of the findings described in earlier reports by the Institute of Medicine Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. In the discussion of the most recent scientific literature, the studies are grouped by exposure type (Vietnam veteran, occupational, or environmental). For articles that report on only a single health outcome and are not revisiting a previously studied population, the design information is summarized with the results; the design information on other studies can be found in Chapter 6. A synopsis of toxicologic and clinical information related to the biologic plausibility that the COIs can influence the occurrence of a health outcome is presented next and followed by a synthesis of all the material reviewed. Each health-outcome section ends with the present committee's conclusions regarding the strength of

the evidence that supports an association with the COIs. The categories of association and the committee's approach to categorizing the health outcomes are discussed in Chapters 1 and 2.

RESPIRATORY DISORDERS

For the purposes of this report, "non-cancerous respiratory disorders" are all acute and chronic lung diseases (other than cancers), a variety of conditions encompassed by the *International Classification of Diseases* (ICD), Ninth Revision (ICD-9 460–519) or Tenth Revision [ICD-10 J00–J99]. Acute non-cancerous respiratory disorders include pneumonia and other respiratory infections; they can increase in frequency and severity when the normal defense mechanisms of the lower respiratory tract are compromised. Chronic non-cancerous respiratory disorders generally take two forms: airways diseases and parenchymal diseases. Airway diseases are disorders—among them asthma and chronic obstructive pulmonary disease (COPD)—characterized by an obstruction of the flow of air out of the lungs. COPD, which is also known as chronic obstructive airways disease, includes such disorders as emphysema and chronic bronchitis. Parenchymal disease, or interstitial disease, generally includes disorders that cause inflammation and scarring of the deep lung tissue, including the air sacs and supporting structures. Parenchymal disease is less common than airways disease and is characterized by reductions in lung capacity, although it can include a component of airway obstruction. Some severe chronic lung disorders, such as cystic fibrosis, are hereditary. Because Vietnam veterans received health screenings before entering military service, few severe hereditary chronic lung disorders are expected in that population.

The most important risk factor for many non-cancerous respiratory disorders is inhalation of cigarette smoke. Although exposure to cigarette smoke is not associated with all diseases of the lungs, it is the major cause of many airways disorders, especially COPD; it contributes to some interstitial disease; and it compromises host defenses in such a way that people who smoke are generally more susceptible to some types of pneumonia. Cigarette smoking also makes almost every respiratory disorder more severe and symptomatic than it would otherwise be. The incidence rates of habitual cigarette smoking vary with occupation, socioeconomic status, and generation. For those reasons, cigarette smoking can be a major confounding factor in interpreting the literature on risk factors for respiratory disease. Vietnam veterans are reported to smoke more heavily than non-Vietnam veterans (Kang et al., 2006; McKinney et al., 1997).

It is well known that the causes of death from respiratory diseases, especially chronic diseases, are often misclassified on death certificates. Grouping various respiratory diseases for analysis, unless they all are associated with a given exposure, will lead to an attenuation of the estimates of relative risk (RR) and to a diminution of statistical power. Moreover, the diagnosis of the primary cause

Biologic Plausibility

Currently, there are no toxicologic studies relevant to exposure to any of the COIs and the occurrence of any form of nonmalignant kidney disease.

Synthesis

No statistical findings from epidemiology studies concerning kidney disease have been reported previously in the VAO series. The few findings on this health outcome reviewed by the current committee do not present any coherent pattern of an association between exposure to the COIs and kidney disorders.

Conclusion

The committee found that these first epidemiologic results addressing kidney disease in relation to exposure to the COIs constituted inadequate or insufficient evidence of an association between nonmalignant kidney diseases and exposure to the herbicides sprayed in Vietnam.

THYROID HOMEOSTASIS OR OTHER ENDOCRINE FUNCTIONS

This section discusses a variety of conditions related to endocrine function, excluding diabetes and other pancreatic disorders [ICD-9 250–251 or ICD-10 E08–E16], which were discussed in Chapter 12. Clinical disruptions of thyroid function in particular are grouped as ICD-9 240–246 or as ICD-10 E00–E07, E20–21, while the remaining endocrine disorders are grouped as ICD-9 252–259 or as ICD-10 E22–E35.

The thyroid secretes the hormones thyroxine (T_4) and triiodothyronine (T_3), which stimulate and help to regulate metabolism throughout the body. The thyroid also secretes calcitonin, a hormone that controls calcium concentration in the blood and the storage of calcium in bones. Secretion of T_4 and T_3 is under the control of thyroid-stimulating hormone (TSH), which is secreted by the anterior pituitary. Iodine operates in thyroid physiology both as a constituent of thyroid hormones and as a regulator of glandular function. Concentrations of those circulating hormones are regulated primarily by a negative-feedback pathway that involves three organs: the thyroid, the pituitary, and the hypothalamus. In the hypothalamus–pituitary–thyroid feedback scheme, the hypothalamus releases thyrotropin-releasing hormone (TRH), which stimulates the pituitary to produce TSH, which triggers the thyroid to produce T_4 and T_3. Cells in the hypothalamus and pituitary respond to concentrations of circulating T_4 and T_3. When T_4 and T_3 are low, the pituitary is stimulated to deliver more TSH to the thyroid, which increases T_4 and T_3 output. When circulating T_4 and T_3 are high, it triggers a

reduction in the output of TRH and TSH. The negative-feedback loop maintains hormone homeostasis.

A disruption of thyroid homeostasis can be stimulatory (hyperthyroidism) or suppressive (hypothyroidism). Both conditions are diagnosed on the basis of blood concentrations of thyroid hormones, TSH, and other proteins (antithyroid antibodies). The prevalence of thyroid dysfunction in adults in the general population ranges from 1 percent to 10 percent, depending on the group, the testing setting, sex, age, the method of assessment, and the presence of conditions that affect thyroid function. People who have subclinical (biochemical) conditions may or may not show other evidence (signs or symptoms) of thyroid dysfunction.

In *hypothyroidism*, the body lacks sufficient thyroid hormone. Overt hypothyroidism is seen as a high serum concentration of TSH and a low serum concentration of free T_4. Subclinical hypothyroidism is defined as a high serum concentration of TSH and a normal serum concentration of free T_4. People who have hypothyroidism typically have symptoms of low metabolism. Studies consistently show that subclinical hypothyroidism is common and occurs more frequently in women than in men (Canaris et al., 2000; Hollowell et al., 2002; Sawin et al., 1985). In the Framingham study, for example, among 2,139 people 60 years old or older, 14 percent of women and 6 percent of men had subclinical hypothyroidism (Sawin et al., 1985). Subclinical hypothyroidism is a risk factor for overt hypothyroidism. Studies have reported associations of hypothyroidism with a wide variety of other conditions. Chemically induced hypothyroidism can develop because of direct effects on the functional cell types in the thyroid gland or because of an induction of auto-antibodies that destroy thyroid tissue, such as in Hashimoto's disease, an auto-immune form of thyroiditis.

The term *hyperthyroidism* may involve any disease that results in overabundance of thyroid hormone. Clinical or overt hyperthyroidism is characterized as a low serum concentration of TSH and a high serum concentration of free T_4. Subclinical hyperthyroidism is defined as a low serum concentration of TSH and a normal serum concentration of free T_4. The prevalence of subclinical hyperthyroidism has been estimated at about 1 percent in men and 1.5 percent in women over 60 years old (Helfand and Redfern, 1998). Conditions associated with hyperthyroidism include diffuse toxic goiter and Graves disease, an autoimmune disease in which antibodies are produced that mimic the activity of TSH. Like hypothyroidism, hyperthyroidism is more common in women than in men, and, although it occurs at all ages, it is most likely to occur in people more than 15 years old. A form of hyperthyroidism called neonatal Graves disease occurs in infants born to mothers who have Graves disease. Occult hyperthyroidism may occur in patients more than 65 years old and is characterized by a distinct lack of typical symptoms.

It is important to distinguish between potential effects on adults and effects that may occur during development. In adults, the thyroid is able to compensate, within reasonable limits, for mild or moderate disruption (such as that caused by hyperplasia or goiter). In contrast, the fetus is highly sensitive to alterations in

thyroid hormones, and alterations in thyroid homeostasis can hamper the development of many organ systems, including the nervous and reproductive systems; such findings are discussed in Chapter 10, which addresses the potential effects of Vietnam veterans' exposure to herbicides on their offspring. Only observations on adults are considered here.

Summary of Previous Updates

Thyroid homeostasis in humans was first addressed with respect to the COIs by the VAO committee for *Update 2002*.

Extensive assessment of endocrine function in clinical examinations, including a series of thyroid-function tests, failed to show systematic differences in thyroid function when contrasting veterans who participated in Operation Ranch Hand and control veterans (AFHS, 1991a). In analyzing individual TCDD readings obtained for subjects in the AFHS, however, Pavuk et al. (2003) found statistically significantly increased TSH measures from the 1985 and 1987 examinations in the high-exposure category and a significantly increasing trend across the three TCDD categories in data gathered during the 1982, 1985, 1987, and 1992 examinations. Other studies of veterans of the Vietnam War have not documented an increased risk of thyroid disease.

Calvert et al. (1999) provided evidence of higher adjusted mean free-T_4 concentrations in TCDD-exposed workers in the NIOSH Cross-sectional Medical Study, but there was no dose–response relationship with serum TCDD. Bloom et al. (2006) found indications of an inverse relationship between the sum of DLCs and the concentration of free T_4 in anglers in New York State but no association between the sum of DLCs and TSH or T_3. Abdelouahab et al. (2008) described thyroid function in adult freshwater-fish consumers in Canada; dioxin-like congeners were associated with an increase in TSH and a decrease in T_4 but below the threshold at which clinical symptoms would be present. An analysis of 1999–2002 NHANES data (Turyk et al., 2007) found total T_4 to have a weak inverse relationship with serum TEQs; the effect was somewhat stronger in people over 60 years old and in women as compared with men. Clear effects of DLCs on thyroid function were not apparent in Inuit adults (Dallaire et al., 2009) or in a cross-sectional study of a Chinese community exposed to an electronic-waste recycling plant (Zhang J et al., 2010).

In a study focusing on pesticide use, Chevrier et al. (2008) did not find evidence of effects on thyroid function among women enrolled at the Center for the Health Assessment of Mothers and Children of Salinas in California. Goldner et al. (2010) also published negative results for an association between phenoxy-herbicide exposures and self-reported history of physician-diagnosed thyroid disease in women in the AHS. Schreinemachers (2010) did not find associations of recent exposure to 2,4-D with T_4 and TSH concentrations in subjects in NHANES III (1988–1994).

Table 13-3 summarizes findings of studies that have examined the association between dioxin-like congeners and markers of thyroid function. Shaded entries are new findings in this update.

As early as 1994, Koopman-Esseboom et al. noted an inverse association between dioxin-like congeners and markers of disrupted thyroid homeostasis in pregnant women. There has been considerable further study of maternal exposure and perinatal effects on thyroid function, which is not directly applicable to the adult exposure of the mostly male Vietnam veterans whose own health is the primary concern of these updates. A discussion of that material can be found in Chapter 10, on possible adverse effects on the offspring of Vietnam veterans.

Update of the Scientific Literature

Several new epidemiologic studies of occupational or environmental exposure to the COIs or of Vietnam veterans and effects on thyroid homeostasis have been published since *Update 2012*. Mass media coverage of conference presentations in 2010 created an expectation of results from a study of Graves disease, an autoimmune hyperthyroid condition. Two papers in preparation were mentioned in a descriptive article lacking actual data (Spaulding, 2011); however, because peer-reviewed publications derived from the preliminary findings still have not appeared, VAO committees have had to disregard this study.

Vietnam-Veteran Studies

In an effort to quantify herbicide exposures experienced during the Vietnam War, Yi et al. (2014a,b) generated EOIs for 111,726 men in the Korean Veterans Health Study by applying the Stellman model (Stellman et al., 2003b).

Yi et al. (2014a) gathered morbidity information for January 2000 through September 2005 on 111,726 of these veterans who had responded to a postal questionnaire in 2004. Claims data from the Health Insurance Review and Assessment of Korea and from the Veterans Health Service were searched for ICD-10 diagnoses corresponding to this set of subjects. With adjustment for age, military rank, smoking, drinking, physical activity, household income, herbicide exposure at home, and BMI, logistic regression on the logarithms of the individual EOI scores was performed. The EOI scores were also partitioned into groups with high or low potential for herbicide exposure. Adjusting for the same factors, the prevelances in the high and low groups were compared. Thyroid conditions overall [ICD-10 E00–E07] showed an indication of increased risk with herbicide exposure both in the internal comparison (OR = 1.06, 95% CI 1.00–1.12) and with analysis of individual scores (OR = 1.01, 95% CI 1.00–1.03). The pattern was very similar for both non-iodine-deficiency hypothyroidism [ICD-10 E03]: for high versus low (OR = 1.13, 95% CI 1.01–1.25) and for individual scores

TABLE 13-3 Selected Epidemiologic Studies—Thyroid Homeostasis (Shaded entries are new information for this update)

Study Population	Exposed Cases[a]	**Exposure of Interest**/Reported Results[a]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Incidence			
Cross-sectional analysis of Ranch Hand personnel (n = 1,009) and SEA veterans (n = 1,429); TSH, total T4, T3%			Pavuk et al., 2003
TSH uptake by TCDD category			
Comparisons (SEA veterans—no TCDD spraying)	1,247	Normal = 0–3 µIU/ml	
RH background (TCDD ≤ 10 ppt)	409	0.84 (p = 0.88)	
RH low (TCDD > 10 ppt, ≤ 94 ppt)	273	0.87 (p = 0.16)	
RH high (TCDD > 94 ppt)	275	0.90 (p = 0.04)	
T4 (thyroxine) means by TCDD category		Normal = 4.5–11.5 µg/dl	
Comparisons (SEA veterans—no TCDD spraying)	1,247	7.47	
RH background (TCDD ≤ 10 ppt)	409	7.56 (p = 0.19)	
RH low (TCDD > 10 ppt, ≤ 94 ppt)	273	7.54 (p = 0.38)	
RH high (TCDD > 94 ppt)	275	7.56 (p = 0.28)	
T3% (triiodothyronin) uptake by TCDD category		Normal 25%–35%	
Comparisons (SEA veterans—no TCDD spraying)	1,247	30.7	
RH background (TCDD ≤ 10 ppt)	409	30.7 (p = 0.19)	
RH low (TCDD > 10 ppt, ≤ 94 ppt)	273	30.7 (p = 0.98)	
RH high (TCDD > 94 ppt)	275	30.5 (p = 0.24)	
International Vietnam-Veteran Study			
Sample of 1,000 Male Australian Vietnam Veterans—prevalance		**All COIs**	
450 interviewed 2005–2006 vs respondents to 2004–2005 national survey (disorders of the thyroid gland)	450	1.4 (0.5–2.2)	O'Toole et al., 2009
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 42,421) vs low exposure (n = 69,305) (individual EOI scores) (HRs; ICD-10)		**All COIs**	

TABLE 13-3 Thyroid Homeostasis, continued

Study Population	Exposed Cases[a]	**Exposure of Interest**/Reported Results[a]	Reference
Prevalence (01/2000–09/2005)—log EOI scores			Yi et al., 2014a
Disorders of the thyroid gland [E00–E07]	5,408	1.0 (1.0–1.0)	
Non-iodine-deficiency hypothyroidism [E03]	1,444	1.0 (1.0–1.1)	
Other nontoxic goiter [E04]	953	1.0 (1.0–1.0)	
Thyrotoxicosis (hyperthyroidism) [E05]	2,476	1.0 (1.0–1.0)	
Thyroiditis [E06]	423	1.0 (1.0–1.1)	
Autoimmune thyroiditis [E06.3]	92	1.2 (1.1–1.3)	
Prevalence (01/2000–09/2005)—categorized high (n = 2,134) vs low (n = 3,274) (5.0% vs 4.7%)			
Disorders of the thyroid gland [E00–E07] (2,134 vs 3,274)		1.1 (1.0–1.1)	
Non-iodine-deficiency hypothyroidism [E03] (598 vs 846)		1.1 (1.0–1.3)	
Other nontoxic goiter [E04] (386 vs 567)		1.1 (1.0–1.3)	
Thyrotoxicosis (hyperthyroidism) [E05] (951 vs 1,525)		1.0 (0.9–1.1)	
Thyroiditis [E06] (175 vs 248)		1.2 (1.0–1.4)	
Autoimmune thyroiditis [E06.3] (48 vs 92)		1.9 (1.3–2.9)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort— Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
NIOSH Cohort—TCDD-exposed workers from 2,4,5-T plants in Newark, NJ, and Verona, MO, employed > 15 yrs earlier and matched controls (n = 260)			Calvert et al., 1999
TSH mU/l		Adjusted mean (SE)	
All workers	278	2.0 (0.1) p = 0.66	
TCDD < 20	75	2.2 (0.3) p = 0.28	
20 ≤ TCDD < 75	66	2.0 (0.3) p = 0.88	
75 ≤ TCDD < 238	66	1.9 (0.3) p = 0.94	
238 ≤ TCDD < 3,400	64	1.8 (0.3) p = 0.65	
Referents (< 20)	257	1.9 (0.1)	

continued

TABLE 13-3 Thyroid Homeostasis, continued

Study Population	Exposed Cases[a]	**Exposure of Interest**/Reported Results[a]	Reference
T4 nmol/l		Adjusted mean (SE)	
All workers	278	101.4 (1.0) p = 0.07	
TCDD < 20	75	102.7 (2.0) p = 0.08	
20 ≤ TCDD < 75	66	99.4 (2.1) p = 0.79	
75 ≤ TCDD < 238	66	102.7 (2.1) p = 0.09	
238 ≤ TCDD < 3,400	64	100.1 (2.2) p = 0.58	
Referents (< 20)	257	98.8 (1.1)	
Free T4 index nmol/l		Adjusted mean (SE)	
All workers	278	27.8 (0.3) p = 0.02	
TCDD < 20	75	27.7 (0.5) p = 0.15	
20 ≤ TCDD < 75	66	27.4 (0.6) p = 0.36	
75 ≤ TCDD < 238	66	28.2 (0.6) p = 0.03	
238 ≤ TCDD < 3,400	64	27.7 (0.6) p = 0.19	
Referents (< 20)	257	26.8 (0.3)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
AUSTRALIAN 2,4,5-T in Victoria, Australia (n = 37)		**2,4-D, 2,4,5-T**	Johnson et al., 2001
TSH vs estimated serum TCDD level	32	Normal = 0.3–5.0 µIU/ml	
Based on local levels		0.2	
Based on individual sampling LDs		–.03	
Based on back extrapolation		–1.4 (p < 0.05)	
T4 vs estimated serum TCDD level	32	Normal = 0.045–2.125 µg/ml	
Based on local levels		0.1	
Based on individual sampling LDs		–0.0	
Based on back extrapolation		–0.0	
T3 vs estimated serum TCDD level	32	Normal = 0.9–1.9 µg/ml	
Based on local levels		–0.1	
Based on individual sampling LDs		–0.4 (p < 0.05)	
Based on back extrapolation		–0.5 (p < 0.01)	
UNITED STATES			
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916 men), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; follow-ups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	

TABLE 13-3 Thyroid Homeostasis, continued

Study Population	Exposed Cases[a]	**Exposure of Interest**/Reported Results[a]	Reference
Incidence			
Thyroid disease among male pesticide sprayers (n = 22,327) in Iowa and North Carolina (1993–2010)			Goldner et al., 2013
Self-reported hypothyroid disease (n = 461)			
Self-reported 2,4-D exposure	392	1.4 (1.0–1.8)	
Self-reported 2,4,5-T exposure	153	1.4 (1.1–1.7)	
Self-reported 2,4,5-TP exposure	67	1.4 (1.1–1.8)	
Self-reported dicamba exposure	289	1.4 (1.1–1.7)	
Hypothyroid disease			
Self-reported 2,4-D use, higher than median	207	1.4 (1.1–1.9)	
Self-reported 2,4-D use, less than median	177	1.2 (1.0–1.8)	
Incidence			
Thyroid disease among female spouses (n = 19,529) in Iowa and North Carolina (1993–2003)			Goldner et al., 2010
Hyperthyroid			
Self-reported 2,4-D exposure	46	0.9 (0.7–1.3)	
Self-reported 2,4,5-T exposure	3	NA	
Self-reported dicamba exposure	17	0.8 (0.8–2.1)	
Hypothyroid			
Self-reported 2,4-D exposure	147	1.0 (0.8–1.1)	
Self-reported 2,4,5-T exposure	7	1.0 (0.5–2.2)	
Self-reported dicamba exposure	27	0.7 (0.5–1.0)	
Other thyroid conditions			
Self-reported 2,4-D exposure	87	1.2 (1.0–1.5)	
Self-reported 2,4,5-T exposure	4	NA	
Self-reported dicamba exposure	19	1.0 (0.6–1.5)	
ENVIRONMENTAL			
National Health and Nutrition Examination Survey		2,4-D	
NHANES III—analysis of data from subjects with detectable limits of urinary 2,4-D			Schreinemachers, 2010
TSH			
Detectable 2,4-D	102	1.6 mU/L	
Non-detectable 2,4-D	625	1.7 mU/L	

continued

TABLE 13-3 Thyroid Homeostasis, continued

Study Population	Exposed Cases[a]	**Exposure of Interest**/Reported Results[a]	Reference
T4			
Detectable 2,4-D	102	8.5 µg/dl	
Non-detectable 2,4-D	625	8.6 µg/dl	
NHANES (1999–2002, 2001–2002)—Associations with TEQs in individuals without thyroid disease			Turyk et al., 2007
Men (1999–2000)			
T4	402	–0.12 (–0.61 to 0.37)	
TSH	402	–0.09 (–0.38 to 0.20)	
Men (2000–2001)			
T4	497	–0.47 (–0.97 to 0.04)	
TSH	497	–0.02 (–0.20 to 0.16)	
Women (1999–2000)			
T4	310	–0.19 (–0.70 to 0.33)	
TSH	309	–0.15 (–0.14 to 0.44)	
Men (1999–2000)			
T4	386	–0.58 (–1.26 to 0.10)	
TSH	385	–0.06 (–0.15 to 0.35)	
Other Environmental Studies			
CANADA			
Cross-sectional study of Inuit residents (≥ 18 yrs of age) of Nunavik (Québec, Canada)	607	**dl PCBs**/correlation of dl-congeners (adjusted)	Dallaire et al., 2009
TSH		0.02	
fT4		–0.01	
fT3		–0.03 ($p < 0.05$)	
Cross-sectional study of freshwater fish consumers from two Canadian communities		**dl PCBs**/ dl-PCB congeners ß estimates	Abdelouahab et al., 2008
Men	124		
TSH		0.55 ($p < 0.001$)	
T4		–2.19 ($p < 0.05$)	
T3		–0.01	
Women	87		
TSH		0.04	
T4		0.04	
T3		–0.01	
Cross-sectional examination of serum from pregnant women attending Canadian prenatal diagnosis clinic	150	**dl compounds**	Foster et al., 2005
TSH correlation coefficient		ns (value nr)	
T4 correlation coefficient		ns (value nr)	

TABLE 13-3 Thyroid Homeostasis, continued

Study Population	Exposed Cases[a]	**Exposure of Interest**/Reported Results[a]	Reference
CHINA—cross-sectional study of a Chinese community in the vicinity of an electronic-waste recycling plant—maternal serum T4 levels at 16 weeks gestation (correlations with contaminant levels in cord blood)		**PCDDs, PCDFs, dl PCBs**	Zhang J et al., 2010
dl PCBs		r = –0.413 (p = 0.01)	
PCDD/Fs		r = –0.198 (p = 0.21)	
ITALY—Seveso Women's Health Study—Industrial accident July 10, 1976; 981 women between infancy and 40 yrs of age at time of accident, who resided in Zones A and B		**TCDD**	Chevrier et al., 2014
1996 thyroid hormone measurements (postmenarche at exposure):			
TSH	637	9.3 (–0.8–20.3)	
Total T4	629	–0.1 (–0.4–0.1)	
Free T4	634	0.0 (–0.1–0.1)	
Free T3	635	–0.0 (–0.0–0.0)	
JAPAN			
2,253 Japanese from general population not occupationally exposed to dioxins, aged 15–76 yrs in 2002–2008,		**Total Serum TEQ**	Nakamoto et al., 2013
Thyroid disease (10 cases in men; 63 cases in women)	73		
Quartile 1		1.0	
Quartile 2		1.0 (0.5–2.4)	
Quartile 3		1.2 (0.5–2.7)	
Quartile 4		0.7 (0.3–1.9)	
		p-trend = 0.32	
Yusho patients exposed in 1968 during Yusho incident; blood collection from participants 1996 and 1997	16	**PCDDs, PCDFs, dl PCBS**	Nagayama et al., 2001
TSH correlation coefficient		0.01 (p = 0.97)	
T4 correlation coefficient		0.03 (p = 0.90)	
T3 correlation coefficient		–0.09 (p = 0.74)	

continued

TABLE 13-3 Thyroid Homeostasis, continued

Study Population	Exposed Cases[a]	**Exposure of Interest**/Reported Results[a]	Reference
KOREA—105 pregnant Korean women provided blood samples the day before delivery		**dl mono-ortho PCB 118**	Kim et al., 2013
		β (95% CI)	
Free T_3		–0.020 (–0.091–0.005)	
Total T_3		–0.114 (–0.223–0.005)	
Free T_4		–0.049 (–0.136–0.038)	
Total T_4		–0.047 (–0.134–0.040)	
TSH		0.389 (–0.183–0.960)	
THE NETHERLANDS—Part of the prospective longitudinal Dutch PCB/Dioxin study; 105 health mother-infant pairs living in or around Rotterdam, recruited June 1990–February 1992		**Dioxins, PCBs**	Koopman-Esseboom et al., 1994
Maternal serum correlations with dioxin TEQs	78		
T4		–0.4 ($p \leq 0.001$)	
T3		–0.5 ($p \leq 0.001$)	
UNITED STATES			
CHAMACOS Study—334 pregnant women from Salinas Valley, CA, providing blood at 26 wks gestation		**dl PCBs** ß (95% CI)	Chevrier et al., 2008
Free T4 vs:			
PCB TEQs (pg/g)		–0.05 (–0.16 to 0.06)	
Mono-ortho PCBs (ng/g)		–0.09 (–0.19 to 0.01)	
PCB 118 (ng/g)		–0.05 (–0.15 to 0.06)	
PCB 156 (ng/g)		–0.06 (–0.13 to 0.01)	
Total T4 vs:			
PCB TEQs (pg/g)		0.26 (–0.45 to 0.96)	
Mono-ortho PCBs (ng/g)		–0.13 (–0.78 to 0.53)	
PCB 118 (ng/g)		–0.26 (–0.43 to 0.95)	
PCB 156 (ng/g)		–0.05 (–0.52 to 0.42)	
Adult men recruited from Massachusetts infertility clinic (2000–2003)	341	**dl PCBs** Estimated risk (95% CI)	Meeker et al., 2007
T3		0.02 (0.05–0.01)[a]	
fT4		0.01 (0.01–0.05)[a]	
fTSH		0.93 (0.84–1.03)[a]	

TABLE 13-3 Thyroid Homeostasis, continued

Study Population	Exposed Cases[a]	**Exposure of Interest**/Reported Results[a]	Reference
Sportfish anglers from New York exposed to dioxin-like compounds in diet	38	**PCDDs, PCDFs, dl PCBs** mean/median (range)	Bloom et al., 2006
TSH µUL/ml		2.0/1.4 (0.2–15.7)	
T4 µg/dL		6.3/6.4 (3.2–10.0)	
Free T4 ng/ml		1.1/1.1 (0.9–1.6)	
T3 ng/dL		92.6/87.5 (56.0–181.0)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenol; 2,4,5-TP, 2-(2,4,5-trichlorophenoxy) propionic acid; CATI, computer-assisted telephone interviewing; CI, confidence interval; COI, chemical of interest; dl, dioxin-like; dL, deciliter; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; LD, level of detection; ml, milliliter; NHANES, National Health and Nutrition Examination Survey; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; ns, nonsignificant; PCB, polychlorinated biphenyls; PCDD, polychlorinated dibenzo-*p*-dioxins; PCDD/Fs, chlorinated dioxins and furans combined; PCDF, polychlorinated dibenzofurans; ppt, parts per trillion; SE, standard error; SEA, Southeast Asia; RH, Ranch Hand; T3, triiodothyronine; T4, tetraiodothyronine; TCDD, tetrachlorodibenzo-*p*-dioxin; TEQ, (total) toxic equivalent; TSH, thyroid stimulating hormone.

[a]Adjusted coefficients for change in thyroid hormone level associated with an interquartile range increase in serum dioxin-like congeners.

(OR = 1.02, 95% CI 1.00–1.05), and for other nontoxic goiter [ICD-10 E04]: for high versus low (OR = 1.14, 95% CI 1.00–1.31) and for individual scores (OR = 1.01, 95% CI 0.98–1.04). The risk of thyroiditis [ICD-10 E06] overall was not found to be significantly associated with heribicide exposure. The strongest endocrine-related results, however, were for the specific subtype of thyroiditis, auto-immune thyroiditis [ICD-10 E06.3]: for high versus low (OR = 1.93, 95% CI 1.27–2.94) and for individual scores (OR = 1.16, 95% CI 1.05–1.28). The risk of hyperthyroidism [ICD-10 E05] was not significantly different from 1.00.

Yi et al. (2014b) screened the death records of the National Statistical Office for 1992–2005 to establish vital status for 180,639 of these Korean veterans of the Vietnam War. Results for deaths from endocrine diseases were presented only for the broad range of ICD-10 E00–E88, for which no significant association with herbicide exposure was noted for either the high versus low comparison or for the analysis based on individual scores. No information was provided on mortality for subtypes of endocrine conditions, so nothing was revealed about mortality from disorders specifically involving thyroid dysfunction.