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modify the immune response in gastrointestinal disorders. The available animal data do not support a plausible link between herbicide exposure and gastrointestinal toxicity in Vietnam veterans.

Conclusion

On the basis of the evidence reviewed here and in previous VAO reports, the committee concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure to the COIs and gastrointestinal and digestive diseases.

KIDNEY AND URINARY DISORDERS

Update 2014 was the first update for which the literature search identified studies reporting results concerning a possible association between exposure to the COIs and kidney diseases (ICD-9 580–589; ICD-10 N00–N29). The kidneys are located in the lower back region; their main function is to filter wastes and excess water out of the blood, which results in the production of urine. The kidneys are also responsible for helping maintain the body's chemical balance, helping control blood pressure, and synthesizing hormones. When problems arise with kidney function, it is often the result of damaged nephrons, which may leave the kidneys unable to filter blood and, thus, unable to remove wastes, which can then accumulate in the body. Chronic kidney disease is characterized by a gradual and usually permanent loss of kidney function that often results in renal failure. Diabetes, hypertension, and glomerulonephritis (acute inflammation) can all increase the risk of kidney disease.

Conclusions from *VAO* and Previous Updates

Publications from the Korean Veterans Health Study included findings for non-malignant kidney disease. Yi et al. (2013a) examined the prevalence of self-reported exposure based on six questions and self-reported kidney failure using a postal survey of 114,562 Korean veterans who had served in the Vietnam War. The incidence of kidney failure was compared by defining high and low categories of exposure based on the six exposure questions and also by exposure opportunity index (EOI) scores that were calculated. Self-reported kidney failure was statistically significantly increased when the analysis was based on perceived exposures, but it was not significant when the analysis was based on the EOI scores. In a study of cause-specific mortality through 2005 for 180,639 Korean veterans who were alive in 1992, Yi et al. (2014b) found that after adjustment for age in 1992 and rank, no differences in the hazard ratios were observed for acute renal failure or for chronic renal failure when the analyses were based on the EOI scores.

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Two environmental studies of non-U.S. populations were also considered. In a cross-sectional study of 2,264 Japanese men and women who had not been occupationally exposed to dioxins, self-reported kidney disease (not otherwise specified) was not associated with serum levels of dioxin-like PCDD/Fs or dioxin-like PCBs or with total TEQs after adjusting for possible confounders (Nakamoto et al., 2013). The second study sought to determine the factors contributing to a form of kidney disease not related to diabetes, hypertension, or any other recognized cause in adults in Sri Lanka (Jayatilake et al., 2013). Urine samples were taken from 57 cases and from 39 controls who were from non-endemic areas, and the samples were analyzed for 11 biomarkers of pesticides, including the COIs 2,4-D, 2,4,5-T, and 2,4,5-TCP. Of these, only 2,4-D was among the seven biomarkers found at concentrations above the limit of detection; 3.5% of the cases had 2,4-D concentrations above the reference limit of 0.3 µg/L. Since the urinary pesticide results were presented for only the cases, no inference can be made about the relative risk for this kidney condition in association with 2,4-D.

Based on these four studies, the committee for *Update 2014* concluded that there was inadequate or insufficient evidence of exposure to the COIs and non-malignant kidney diseases.

Update of the Epidemiologic Literature

One new study of Vietnam veterans and kidney and urinary disorders has been identified since *Update 2014*, as well as supporting occupational, environmental, and case-control studies of kidney and urinary disorders and exposure to the COIs.

Vietnam-Veteran Studies

Cox et al. (2015) used hospital discharge records from 1988 to 2009 to identify health conditions that affected 2,783 male New Zealand veterans who had served in Vietnam during 1964–1972. Age-specific hospitalization rates were calculated using the total number of annual hospitalizations published by the Ministry of Health and the average annual resident population. Standardized hospitalization rates and 99% CIs were calculated for the veteran cohort and the general population and the two rates were used to calculate an SHR for several conditions including kidney and urinary outcomes. An elevation in chronic renal failure risk was identified (SHR = 1.21, 95% CI 1.07–1.36), with an acceleration in the risk for later time periods. No significant associations were identified with urinary tract infections (OR = 1.06, 95% CI 0.66–1.46), benign prostatic hypertrophy (OR = 1.11, 95% CI 0.79–1.42), or urinary stones (OR = 1.06, 95% CI 0.81–1.31). The exposures were not validated through serum measurements and

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were assumed based on deployment to Vietnam, and the study did not control for smoking status, ethnicity, or other potentially important risk factors.

Occupational Studies

Two studies using data from the AHS were reviewed. Using a prospective cohort design with an average of 16 years of follow-up, Lebov et al. (2016) evaluated the association between use of 41 specific pesticides and end-stage renal disease in 55,580 male pesticide applicators. Significant associations were found with several non-COIs (p for trend < 0.05), but there were no statistically significant associations with the phenoxy herbicides (2,4-D p for trend = 0.32; 2,4,5,T p for trend = 0.55). An education level greater than high school and obesity at enrollment were also associated with end-stage renal disease, as were diabetes, high blood pressure, and kidney disease.

Lebov et al. (2015) evaluated the use of 50 pesticides and factors of use and exposure, including frequency and duration, duration of residence on a farm, specific farm tasks performed, household practices of pesticides, and end-stage renal disease in the wives of pesticide applicators (n = 31,142). End-stage renal disease was higher in women who were obese, who used nonsteroidal anti-inflammatory drugs, or who had diabetes and hypertension. There was a protective effect associated with the personal use of any pesticide (hazard ratio [HR] = 0.42, 95% CI 0.28–0.64), but among women who personally mixed or applied pesticides, positive associations were observed only for the highest category of lifetime exposure days (HR = 4.22, 95% CI 1.26–14.20), although the estimate was imprecise. Wives with end-stage renal disease who reported having direct exposure to phenoxy herbicides (n = 9; HR = 1.10, 95% CI 0.50–2.39) or 2,4-D (n = 9; HR = 1.11, 95% CI 0.51–2.41) were found not to be at an elevated risk of the disease. Among wives who reported no direct use of pesticides but whose husbands used phenoxy herbicides (n = 47; HR = 0.86, 95% CI 0.49–1.51), 2,4-D (n = 45; HR = 0.82, 95% CI 0.47–1.43), 2,4,5-T (n = 12; HR = 0.69, 95% CI 0.36–1.32), or 2,4,5-TP (n = 5; HR = 0.88, 95% CI 0.36–2.15), the risks of end-stage renal disease were all decreased.

A third occupational exposure study was identified. 't Mannetje et al. (2018) conducted a morbidity survey among a subset of workers who were employed at the New Plymouth, New Zealand, phenoxy herbicide production plant for at least 1 month between 1969 and 1984. The plant produced 2,4,5-T, and the workers were potentially exposed to 2,4,5-T, the intermediates of TCP and other chlorophenols, as well as to TCDD. Workers had previously been recruited and examined as part of the international cohort of producers of phenoxy herbicides led by IARC (Kogevinas et al., 1997); see Chapter 5 for more details on the IARC cohort and the New Zealand phenoxy producers. This study extends the follow-up period of these workers to approximately 30 years from their last 2,4,5-T production exposure. From the original cohort of 1,025 workers, 631

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were living, had a current address in New Zealand, and were below 80 years of age on January 1, 2006. For the current follow-up, 430 of the 631 workers were randomly selected and invited to participate in the morbidity survey, of whom 245 (57%) participated. The survey was administered in 2007–2008 by face-to-face interview, and information was collected on demographic factors and health information, including doctor-diagnosed conditions and the year of diagnosis. A blood sample was also collected at that time and was analyzed for TCDD, lipids, thyroid hormones, and other substances. For 111 participants, a neurological examination was conducted. Associations between exposure and health outcomes were assessed using logistic regression models that controlled for age, gender, smoking, BMI, and ethnicity using two different methods of exposure: having worked in a TCDD-exposed job (based on occupational records) and having serum TCDD concentration ≥10 pg/g lipid (18%). Mean TCDD concentrations were 19 pg/g lipid in the 60 men directly involved in phenoxy/TCP production and 6 pg/g lipid in the 141 men and 43 women who worked in other parts of the plant. Compared with the people in the non-highly exposed jobs, the people who had ever worked in a highly exposed job at the plant were no more likely to have a doctor-diagnosed kidney function problem (n = 13; OR = 0.82, 95% CI 0.34–1.99). When compared by serum TCDD concentration, no difference in the risk of kidney function problems was found for workers in the high- versus low-exposure groups (n = 5; OR = 1.03, 95% CI 0.32–3.33).

Environmental Studies

Using data from the 1999–2004 cycles of NHANES, Everett and Thompson (2016) evaluated the association of blood levels of three chlorinated dibenzo-*p*-dioxins, one chlorinated dibenzofuran, and four dioxin-like PCBs with nephropathy (microalbuminuria or macroalbuminuria) among 1,505 adolescents and young adults (12–30 years of age) with normal glycohemoglobin (A1c < 5.7%). In logistic regression models 1,2,3,6,7,8-hexachlorodibenzo-*p*-dioxin (OR = 51.1, 95% CI 4.1–641.6), PCB 126 (OR = 8.9, 95% CI 2.0–39.7), PCB 169 (OR = 9.4, 95% CI 1.02–87.6), and PCB 156 (OR = 17.9, 95% CI 2.1–152.6) were associated with nephropathy (OR = 7.1, 95% CI 1.8–28.1) when one or more of these four dioxin-like chemicals was elevated; however, the effect estimates are quite imprecise. The effect was driven by females (OR = 17.4, 95% CI 3.4–88.6), as among males there were no cases of nephropathy when one or more of the four dioxin-like chemicals were elevated. These results were verified by TEQs; TEQ8 ≥ 50.12 fg/g was associated with nephropathy among females (OR = 11.9, 95% CI 1.6–87.2) but not males. Thus, in a cross-sectional study, dioxin-like chemicals were associated with nephropathy among young females, but not males, though reverse causality cannot be excluded, and the effect estimates were very imprecise.

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Two analyses using data from the cross-sectional, community-based study in the Annan District of Tainan City, Taiwan, where a former PCP factory had operated, and had released PCDD/Fs into the surrounding area, were identified that examined outcomes related to kidney disease (J. W. Chang et al., 2013; C. Y. Huang et al., 2016). As described in Chapter 5, people who were 18 years of age and older and who were residents of the exposure area were asked to participate in the study. Health examinations were performed on each participating individual, and serum samples had been previously collected and measured for levels of dioxins by the Tainan City Bureau of Health. A self-administered questionnaire, which was administered at the same time as the examination, was used to collect demographic information and medical history. C. Y. Huang et al. (2016) examined chronic kidney disease, defined as having an estimated glomerular filtration rate ≤ 60 mL/min/1.73m^2 or having been diagnosed by a physician. People diagnosed with congenital kidney disease, IgA nephropathy, post-infectious kidney disease, or medicine-induced kidney disease were excluded from the study. Of the 2,828 participating individuals, 1,427 had high dioxin levels (defined as > 20 pg WHO98-TEQ_{DF}/g lipid in the serum), and 156 had chronic kidney disease. High dioxin levels were associated with an increased prevalence of chronic kidney disease compared with low dioxin levels (10.9% versus 1.6%, respectively, $p < 0.001$). After adjustment for PCDD/Fs, gender, mercury, metabolic syndrome, age, fasting glucose, insulin, and uric acid, a high dioxin level was found to be significantly associated with chronic kidney disease (OR = 1.74, 95% CI 1.02–2.97). The strengths of this study include a large population, adjustments for age, fasting glucose, insulin, and uric acid, as well as serum measurements of exposure and a clear definition of chronic kidney disease. However, this study is limited by having had no follow-up of renal function measurements, the fact that the serum PCDD/Fs levels were collected over an extended period of time that ended about 3 years before the interview and health examination, unknown age at first exposure to PCDD/Fs, unknown duration of exposure, unknown cumulative exposure dose, the cross-sectional design, and a lack of additional data collection. Data on other potential confounders, such as waist circumference, dietary intake, and socioeconomic status, were not available.

Case-Control Studies

Raines et al. (2014) examined agricultural behaviors and health outcomes via questionnaire in a Nicaraguan community. Of the 424 total participants, 151 reported an occupational history of agriculture. The pesticides that were reported by participants as commonly used included 2,4-D. Decreased glomerular filtration rate was found in 9.8% of the women and 41.9% of the men. Glomerular filtration rate was associated with cutting sugarcane during dry season (OR = 5.86, 95% CI 2.45–14.01) and sugarcane chewing (OR = 3.24, 95% CI 1.39–7.58). Glomerular filtration rate was also associated with non-deliberate pesticide inhalation

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(OR = 3.31, 95% CI 1.32–8.31). This study is limited by its lack of exposure validation through serum or other measures.

Other Identified Studies

Two other studies of kidney and urinary disorders were identified, but both were limited by a lack of exposure specificity (Orantes et al., 2015; Ruder et al., 2014). In a study of women in agricultural communities in El Salvador (Orantes et al., 2015), the authors examined exposures to various agrochemicals, which may have included organophosphate insecticides as well as phenoxy herbicides (2,4,-D, hedonal), but the results were not stratified by chemical exposures, and thus the study was not considered further.

A third study was also identified, but instead of being limited by exposure specificity, it was limited by the fact that the outcomes examined were not diagnosed health outcomes but rather indicators of biologic effects. In a separate analysis of people residing near the former PCP factory in Taiwan, J. W. Chang et al. (2013) evaluated associations between PCDD/Fs and the risk of hyperuricemia (too much uric acid in the blood) in a subset of healthy subjects from the community health study (n = 1,531). Serum levels of 17 2,3,7,8-substituted PCDD/Fs were measured, and associations were tested between the serum TEQ_{DF}-2005 (total PCDD/Fs 2005 WHO TEQ) and various factors, including uric acid, glomerular filtration rates, and hyperuricemia risk. Hyperuricemia is a measure of disturbed metabolism, not a health outcome, and therefore this study was not considered relevant to the committee's task.

Biologic Plausibility

Studies of mice, rats, goldfish, and zebrafish have documented kidney toxicity from TCDD exposure. Studies of 2,4-D in goldfish and TCDD in rats report oxidative stress in kidneys (Matviishyn et al., 2014; Palaniswamy et al., 2014). Q. Liu et al. (2014) investigated the effects of developmental exposure to TCDD in zebrafish and found kidney lesions and the dysregulation of the genes involved in renal necrosis and cell death as well as decreased hematopoietic cells in the kidney marrow. Aida-Yasuoka et al. (2014) reported a chance finding that C57BL/6J mouse pups are more susceptible to TCDD-induced hydronephrosis than BALB/cA mice; in pups exposed to TCDD on postnatal days 1–7, the prevalence of hydronephrosis was 64% in the C57BL/6J pups and 0% in BALB/cA pups. In both strains of mice, the Ahr receptors are highly responsive to TCDD; however, genetic differences were found in expression of renal m-Prostaglandin E synthase-1 and early growth response 1 (Egr-1). In a study of mice, Bu et al. (2017) found that Ahr activation up-regulates glucose transporter 9 (Glut9), which plays a role in maintaining uric acid homeostasis.

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Synthesis

Since *Update 2014*, seven studies have been reviewed for kidney disease and urinary disorder outcomes related to exposure to the COIs. A hospitalization study of New Zealand Vietnam veterans found that chronic renal failure risk was statistically significantly increased among the veterans compared with the standardized general population of New Zealand, but there was no difference in the prevalence of other kidney or urinary outcomes (Cox et al., 2015); however, there was no exposure validation, some of the conditions (such as urinary tract infections) do not typically require hospitalization, and potentially important risk factors were not adjusted for in the analysis. In a 30-year follow-up study of New Zealand workers in a plant that produced 2,4,5-T, having a doctor-diagnosed kidney function problem was not different for workers in high- versus low-exposure groups, based on reported job and duties in the plant or on serum TCDD levels. Two analyses of end-stage renal disease in the AHS (Lebov et al., 2015, 2016) found no statistically significant associations with the phenoxy herbicides 2,4-D or 2,4,5-T among the male pesticide applicators or their wives. In an analysis of NHANES, Everett and Thompson (2016) evaluated the association of the blood levels of three chlorinated dibenzo-*p*-dioxins, one chlorinated dibenzofuran, and four dioxin-like PCBs with nephropathy among 1,505 adolescents and young adults and found that dioxin-like chemicals were associated with nephropathy among young females, but not males, although the effect estimates were very imprecise. An environmental exposure study of Taiwanese residents living in close proximity to a former PCP-producing factory found that those who had high serum dioxin levels had a statistically significantly elevated risk of chronic kidney disease (Huang et al., 2016). A second analysis of this population was identified (Chang et al., 2013), but because it examined hyperuricemia, which is a measure of disturbed metabolism and not a recognized health outcome, it was not considered as part of the evidence base of chronic kidney conditions related to exposure to the COIs. A cross-sectional study of agricultural behaviors, including the use of 2,4-D, and health outcomes in a Nicaraguan community (Raines et al., 2014) found a decreased glomerular filtration rate to be associated with cutting sugarcane, sugarcane chewing, and non-deliberate pesticide inhalation, but no serum or other objective measure of exposure were collected. Studies of mice, rats, goldfish, and zebrafish document kidney toxicity from TCDD exposure, but such outcomes do not present a consistent mechanism for the kidney dysfunction diseases in humans. Epidemiology studies concerning exposure to the COIs and kidney diseases were not reported prior to *Update 2014*. However, the new epidemiologic findings reviewed do not present a coherent pattern of an association between exposure to the COIs and kidney or urinary disorders.

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Conclusion

After reviewing the new evidence of exposure to the COIs and non-malignant kidney and urinary outcomes, the committee concludes that there remains inadequate or insufficient evidence of an association between exposure to the COIs and non-malignant kidney or urinary disorders.

THYROID HOMEOSTASIS AND OTHER ENDOCRINE FUNCTIONS

This section discusses a variety of conditions related to endocrine function, excluding diabetes and other pancreatic disorders, which were discussed in Chapter 10: Cardiovascular and Metabolic Outcomes. In particular, clinical disruptions of thyroid function 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. Thyroid homeostasis in humans was first addressed with respect to the COIs by the committee for *Update 2002*.

The thyroid secretes the hormones thyroxine (T4) and triiodothyronine (T3), 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 T4 and T3 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 in turn triggers the thyroid to produce T4 and T3. Cells in the hypothalamus and pituitary respond to concentrations of circulating T4 and T3. When T4 and T3 are low, the pituitary is stimulated to deliver more TSH to the thyroid, which increases T4 and T3 output. When circulating T4 and T3 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% to 10%, 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 signs or symptoms of thyroid dysfunction.

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