Supplement: Compendium Tables of Health Outcomes

Since *Update 2010*, the reported findings on a given condition from a particular study population described in any of the Veterans and Agent Orange (VAO) reports are gathered and presented in reverse chronologic order in order to provide the full history of the study of each endpoint in each group studied. The current update has attempted to shift the focus further to the total picture presented by a study population by clustering related findings and shifting the citations that were the source of particular results to the far right of the results tables. For instance, all incidence findings on the Seveso cohort over the successive follow-up periods are grouped first, and they are followed by all the analogous mortality findings, even when that means separating various sorts of results from the same publication.

Within the three general types of exposure that cohorts or cross-sectional study populations may have experienced, the order of the study populations (Vietnam veterans, occupationally exposed workers, and environmentally exposed people) roughly reflects the degree of importance attributed to the information generated. Because of substantial differences in the nature and intensity of their exposures, the occupational-study populations have been partitioned into those involved in the production of herbicides and other industrial products contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and those involved in occupational use of the herbicides of interest. In *Update 2012* this entailed splitting the findings on cohorts of sprayers from those on cohorts of production workers in the large International Agency for Research on Cancer (IARC) cohort of phenoxy herbicide workers.

The studies of subgroups are presented after those on an overarching cohort. For example, when first reported (Saracci et al., 1991), the original IARC Cohort of Phenoxy Herbicide Workers was composed of 20 cohorts in 10 countries that had been studied separately. When the mortality in those workers was followed up (Kogevinas et al., 1997), they were augmented with 16 additional cohorts—4 German study populations and 12 groups of workers studied separately in US manufacturing facilities—which together make up the independently studied National Institute for Occupational Safety and Health (NIOSH) cohort. To simplify the location of underlying information on study populations, the discussion of the study populations presented in these tables follows the order in which the findings on each population are discussed in Chapter 5 and follow the same order of outcomes as the report presents.

Given the current technology that allows for hundreds of pages to be simultaneously searched for key words and the hundreds of studies reviewed over the course of the VAO series, reprinting individual summaries of each study would not be useful. Instead, should a reader require more background and context concerning a particular

study in the tables, they are encouraged to search the applicable full report for the primary author's last name that corresponds to the volume in which the study was first reviewed.

For example, studies published in 1993 and before would be included in the original volume *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* [https://www.nap.edu/catalog/2141] (IOM, 1994).

Veterans and Agent Orange: Update 1996 (IOM, 1996) [https://ww.nap.edu/catalog/5203], 1993–1995
Update 1998 (IOM, 1999) [https://www.nap.edu/catalog/6415], 1995–1997
Update 2000 (IOM, 2001) [https://www.nap.edu/catalog/10098], 1997–2000
Update 2002 (IOM, 2003) [https://www.nap.edu/catalog/10603], 2000–2002
Update 2004 (IOM, 2005) [https://www.nap.edu/catalog/11242], 2002–2004
Update 2006 (IOM, 2007) [https://www.nap.edu/catalog/11906], 2004–2006
Update 2008 (IOM, 2009) [https://www.nap.edu/catalog/12662], 2006–2008
Update 2010 (IOM, 2011a) [https://www.nap.edu/catalog/13166], 2008–2010
Update 2012 (IOM, 2014) [https://www.nap.edu/catalog/18395], 2010–2012
Update 2014 (NASEM, 2016a) [https://www.nap.edu/catalog/21845], 2012–2014

TABLE 1 Selected Epidemiologic Studies—Immune Effects in Adult Humans (shaded entries are new information for Update 11 [2018])

Study Population	Exposure/Results	Reference
VIETNAM VETERANS		
US Air Force Health Study—Ranch Hand veterans vs SEA veterans	**All COIs**	
Participants in 1997 examination cycle, Ranch Hands vs comparisons (incidence)	No change in surface markers for B and T cells, no change in serum Ig, no change in autoantibodies (antinuclear antibody, smooth muscle autoantibody, parietal cell autoantibody, rheumatoid factor, and monoclonal immunoglobulins) and no dose-related change in DTH response	Michalek et al., 1999b
Participants in 1987 examination cycle, Ranch Hands vs comparisons (morbidity)	No change in surface markers for B and T cells	Wolfe et al., 1990
Participants in 1985 examination cycle, Ranch Hands vs comparisons (morbidity and mortality)	No change in surface markers for B and T cells	Wolfe et al., 1985
US CDC Vietnam Experience Study— Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed	**All COIs**	
Morbidity—Deployed vs nondeployed	No differences in infections, no changes in B and T cell-surface markers, WBC counts, or circulating serum Ig	CDC, 1988b
Mortality (1965–2000)	No suggestion of excess deaths due to immune-system disorders (ICD-9 240–279, which covers endocrine, nutritional, metabolic, and immunity disorders)	Boehmer et al., 2004
US VA Cohort of Monozygotic Twins	**All COIs**	
Physical health—morbidity	Increase in skin conditions of unknown etiology, no increase in blood disorders	Eisen et al., 1991
US American Legion Cohort	**All COIs**	
Physical health and reproductive outcomes	Increase in skin conditions and arthritis	Stellman SD et al., 1988b
State Studies of US Vietnam Veterans	**All COIs**	
Michigan Vietnam Veterans (deployed vs nondeployed)	Increased mortality from infectious (including parasitic) diseases	Visintainer et al., 1995
New Jersey Agent Orange Commission	Depressed response to tetanus in DTH tests, decrease in CD4 and SmIg+ B cells	Kahn et al., 1992b
Texas Agent Orange Advisory Committee	Increase in percentage of active T rosette-forming cells	Newell, 1984
New Zealand Vietnam Veterans served between 1962 and 1971	**All COIs**	
New Zealand Vietnam Veterans—2,783 men from NZVA database of veterans who served and had complete information	A statistically significant increased risk was observed for rheumatoid arthritis (n = 25; SHR = 1.70, 99% CI 1.03–2.36) and osteoarthrosis (n = 179; SHR = 1.32, 99% CI 1.12–1.51) but not infective arthritis (n = 26; SHR = 1.39, 99% CI 0.85–1.92) or systemic lupus erythematosus (SHR = 1.82, 95% CI 0.22–3.41)	Cox et al., 2015
Sample of 1,000 Male Australian Vietnam Veterans–prevalence	**All COIs**	
Australian Vietnam Veterans—longitudinal cohort study of 67 conditions in randomly selected Vietnam veterans vs general population	Increase in hay fever, increases in infectious and parasitic diseases, increase in arthritis	O'Toole et al., 2009

continued

TABLE 1 Continued

Study Population	Exposure/Results	Reference
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)	**All COIs**	
1983–1985—Australian Vietnam Veterans—longitudinal cohort study of 67 conditions in randomly selected Vietnam veterans vs general population	Increase in hay fever, increases in infectious and parasitic diseases, increase in arthritis	CDVA, 1997b
Korean Vietnam Veterans	**All COIs**	
Immunotoxicologic study	Increase in IgE and IL-4, decrease in IgG1 and IFN-gamma, no change in lymphocyte counts	Kim et al., 2003
Vietnamese Vietnam Veterans	**All COIs**	
Antinuclear and sperm autoantibodies	No change in autoantibodies to sperm, antinuclear bodies	Chinh et al., 1996
OCCUPATIONAL STUDIES		
IARC Phenoxy Herbicide Cohort—Dutch workers from 2 plants that produced and formulated chlorophenoxy herbicides (Plant A, n = 1,167; Plant B, n = 1,143)	**Chlorophenoxy herbicides:** Negative correlation between TCDD exposure and markers of humoral immunity, except perhaps for C4	Saberi Hosnijeh et al., 2011
IARC Phenoxy Herbicide Cohort— Subset of **Dutch workers** (n = 85) from 2 plants that produced and formulated chlorophenoxy herbicides (high exposure = 47, low exposure = 38); serum collected 30 years after exposure	**Chlorophenoxy herbicides:** General reduction in most analyte levels with the strongest effects for fractalkine, fibroblast growth factor (FGF_2), and transforming growth factor alpha (TGF-α)	Saberi Hosnijeh et al., 2012a
	High vs low: CD4/CD8 ratio increased ($p = 0.05$); no difference for other cell counts and lymphocyte subsets Decrease in B cells with increasing serum TCDD	Saberi Hosnijeh et al., 2012b
	Soluble CD27 and CD30 levels not related to TCDD levels; With exclusion of chronically ill subjects, IL1RA decreased with increasing TCDD levels	Saberi Hosnijeh et al., 2013a
IARC Phenoxy Herbicide Cohort—German production workers (2,479 workers at 4 plants, in IARC as of 1997)	**Dioxins, phenoxy herbicides**	
Cross-sectional study of 153 male workers in six chemical plants in Germany	**TCDD (**during production of TCP): DTH responses not correlated with dioxin concentration; slight decrease in IgM was reported with increasing dioxin exposure; overall lymphoid counts not different	Benner et al., 1994
German production workers at BASF Ludwigshafen Plant—BASF Cleanup workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)	**Focus on TCDD**	
138 surviving workers from a larger cohort of 254 exposed workers after an accident in a BASF TCP production facility	**TCDD:** Among 14 immune measures; regression analysis of TCDD concentration suggested marginal positive associations with IgG, IgA, C3, and C4; marginal reductions in some lymphocyte population were also reported	Ott et al., 1994

TABLE 1 Continued

Study Population	Exposure/Results	Reference
IARC Phenoxy Herbicide Cohort—German production workers at Boehringer-Ingelheim Plant in Hamburg (1,144 men working > 1 month in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954)	**Dioxins, 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Updated and expanded evaluation of 158 workers in a German chemical plant with differing exposure studied in two trials	**TCDD** (or "TCDD toxic equivalents" from PCDD/PCDF): No differences in serum Ig or cytokine (IL-1, IL-6, TNF-α)	Neubert et al., 2000
19 highly exposed chemical workers vs 28 unexposed controls in two chemical plants in Hamburg, Germany	**TCDD** (in chemical plant): In subset of leukocytes, increase in CD8+ memory T cells and decrease in naïve T cells (CD45RA+) after TCDD exposure, as was stimulated IFN-gamma production from whole blood cultures associated with TCDD exposure	Ernst et al., 1998
192 workers in a German pesticide plant, including 29 highly exposed and 28 controls compared for immune functional tests	**TCDD** (or TEQs from PCDD/PCDF exposure): No significant changes in TCDD and lymphocyte subsets, antibody responses to vaccination, lymphocyte proliferation, or autoantibody production; decrease in chromate resistance of PHA-stimulated lymphocytes in highest exposure group	Jung et al., 1998
Comparison of 11 2,4,5-trichlorophenol production workers 20 years after exposure vs 10 unexposed age-matched workers in the same company	**TCDD:** No differences in any lymphoid subset or in mitogen-induced proliferation; TCDD exposure was associated with decreases in MLR response and in stimulation with IL-2 in vitro	Tonn et al., 1996
Examination of eight trichlorophenol production workers who developed chloracne and were re-examined 15–25 years after initial exposure	**TCDD:** Reduced gamma globulins in the most-exposed workers; no significant effects on T4, T8 ratios.	Jansing and Korff, 1994
89 volunteers involved in decontamination work at a chemical plant in Hamburg, Germany; no control population	**TCDD** (or equivalents via PCDD/PCDF exposure): Potentially complicated by age differences among the compared groups; only subtle, clinically nonsignificant changes were seen among immune-cell surface markers in a comparison of higher exposed vs low-exposed to moderately exposed workers	Neubert et al., 1993, 1994
NIOSH Cohort (current and former workers from chemical plants in New Jersey and Missouri, 2 of the 12 plants included in the NIOSH Mortality Study)	**Dioxins, phenoxy herbicides**	
Cross-sectional study of 259 TCDD-exposed 2,4,5-trichlorophenate (and its derivatives) workers (mean serum TCDD, 223 ppt) and 243 unexposed residential controls (mean serum TCDD, 6 ppt)	**TCDD** (exposure in a chemical plant): No significant changes in serum Ig or major leukocyte categories; TCDD associated with decreased circulating CD26 cells (activated T cells)	Halperin et al., 1998
1987 cross-sectional study of 281 chemical-plant workers in NJ and MO at least 15 years after exposure vs 260 unexposed controls	**TCDD** (as a contaminant in chemical production): Increase in TCDD associated with a decrease in CD3/Ta1 (helper lymphocytes) cells	Sweeney et al., 1997/1998

continued

TABLE 1 Continued

Study Population	Exposure/Results	Reference
Other Studies of Industrial Workers (not related to IARC or NIOSH phenoxy cohorts)		
Cohort study of electric arc furnace workers (331 exposed workers for 6731 person-years), rates of health fee exemptions were compared between workers and the general population of Trento, Italy	**Dioxin and PCBs:** Rates of exemption for rheumatoid arthritis were more common among workers (3 cases among workers, age adjusted RR = 6.18 95% CI: 2.00–19.02)	Cappelletti et al., 2016
A cross-sectional morbidity survey (n = 245) former employees of a pesticide production plant exposed to TCDD in New Zealand	IgG was negatively associated with **TCDD** (linear regression p = 0.05), those in highly exposed TCDD jobs were not more likely to have doctor diagnosed nasal allergies including hay fever (n = 21; OR = 1.00; 95% CI 0.48–2.08), when compared by serum TCDD concentration ≥ 10 pg/g lipid, no difference in nasal allergies was found (n = 7; OR = 0.80; 95% CI 0.27–2.37)	't Mannetje et al., 2018
EUROPIT Study—Prospective multicenter cohort study (Bulgaria, Finland, Italy, The Netherlands) of 238 pesticide-exposed workers vs 198 unexposed workers	**Pesticide factories** (not specifically TCDD): Reduced antibody responses to hepatitis B vaccination among exposed workers carrying a specific IL-1 allele	Baranska et al., 2008
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)		
Agricultural Health Study (AHS)— 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; followups with CATIs 1999–2003 and 2005–2010	**Pesticides/herbicides**	
Nested case (n = 275 total, 132 incident) control (n = 24,018 non-cases) of spouses of licensed pesticide applicators	Women with rheumatoid arthritis were more likely to have reported lifetime use of any specific pesticides vs no pesticides, after adjustment for age, state of residence, and smoking history (OR = 1.4, 95% CI 1.0–1.8), though incident cases of rheumatoid arthritis did not have a statistically significant association (OR = 1.4; 95% CI 0.93–2.1). Non-significant protective effects were observed for COIs, 2,4-D (OR = 0.75, 95% CI 0.51–1.1), dicamba (OR = 0.68, 95% CI 0.32–1.5)	Parks et al., 2016
Comparison from the AHS of 534 cases of self-reported physician-diagnosed depression vs 17,051 controls	Both high-level acute pesticide exposure (OR = 2.6, 95% CI 1.7–3.8) and cumulative pesticide exposure (OR = 1.5, 95% CI 1.2–2.0) were positively associated with increase in depression	Beseler et al., 2008
29,074 female spouses of pesticide applicators in the AHS	Depression was significantly associated with pesticide poisoning (OR = 3.3, 95% CI 1.7–6.2) but not with lower cumulative exposure	Beseler et al., 2006
Nested case-control study of rheumatoid arthritis in agricultural families (57,000 pesticide applicators and their spouses)	No strong risk factors were identified for pesticide mixing or application or for any specific class of pesticides in the AHS of rheumatoid arthritis	De Roos et al., 2005b

TABLE 1 Continued

Study Population	Exposure/Results	Reference
Other Studies of Herbicide-Using Workers		
Longitudinal study of 10 farmers during 1994 within 7 days before and 1–12 days and 50–70 days after exposure	**2,4-D and MCPA formulations:** Decreases in percentages of CD4, CD8, CTL, CD8-DR, and NK cells and in NK activity and mitogen-stimulated lymphoproliferation; CD4:CD8 ratio was unaltered; CD3 and CD8 percentages had recovered by the second assessment period; no significant correlations between immune changes and amount of pesticides applied	Faustini et al., 1996
ENVIRONMENTAL STUDIES		
Seveso Cleanup Workers	**TCDD**	
Prospective study using analysis of samples from 36 cleanup workers (divided into three groups based on time spent in the contamination area); pre-employment samples and samples after 9 months were analyzed for comparison with samples from 31 nonexposed workers	No differences in WBC counts and platelet counts	Ghezzi et al., 1982
Seveso, Italy Residential Cohort— Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group)	**TCDD**	
Study of 101 chloracne cases vs 211 controls 20 years after the accident; relatively low statistical power was available because the study examined the occurrence of individual diseases	Persistent increase in TCDD in chloracne cases; younger people seemed to be more susceptible; no major trends in disease occurrence	Baccarelli et al., 2005a
Study of 62 people from a highly exposed zone and 53 from noncontaminated areas 20 years after the accident	Plasma concentration of TCDD was determined; multivariate regression analysis showed significant decrease in plasma IgG with increasing TCDD concentration and no changes in IgM, IgA, or C3	Baccarelli et al., 2002
45 children (3–7 years of age) living in exposed areas vs 45 nonexposed children as controls	No differences in serum IG, mitogen responses of lymphocytes (PHA and pokeweed), or percentage of rosette-forming lymphocytes	Pocchiari et al., 1979
Times Beach (MO) Cohort	**TCDD**	
Regression analysis used for comparisons among 41 exposed people for adipose-tissue, TCDD vs immune measures; three exposed groups defined by tissue dioxin	No TCDD–DTH response relationships were reported; no change in mitogen responsiveness; some serum markers (A/G ratio and serum IgG) were affected	Webb et al., 1989
82 people in more highly contaminated areas vs 40 in low-risk exposure areas as controls	No differences in DTH response or T-cell subsets (T4/T8)	Webb et al., 1987
80 people in highly contaminated areas vs 40 controls in lower-risk areas	No differences in DTH induration or T-cell subset analysis (T4/T8)	Stehr et al., 1986
Pilot study of small numbers of people; for comparisons, people were assigned to two environmental-exposure groups: those in high-risk areas (27 men, 23 women, and 15 children) and those in low-risk areas (12 men, 10 women, and 8 children)	Multitest DTH evaluation to seven recall antigens was performed, no statistical differences were reported, and only trends were noted; no statistical differences were reported for T-cell markers (T3, T4, and T8) or mitogen-induced lymphocyte proliferation (PHA, Con A, and pokeweed mitogen), and only trends were noted	Knutsen, 1984

continued

TABLE 1 Continued

Study Population	Exposure/Results	Reference
Quail Run Mobile Home Park (MO) Cohort	**TCDD**	
A subset of the previously anergic persons in the Stehr-Green et al. (1987) study were re-evaluated in the DTH test with a higher DTH test dose and highly trained, blinded readers	Retesting of DTH failed to produce the differences observed initially	Evans et al., 1988
Small (ill-defined) samples were used; comparisons of residents of the Quail Run Mobile Home Park with residents of St. Louis–area trailer parks as controls	DTH suppression in the exposed group was reported, but data from two of four readers were discarded; no differences in T-cell mitogen stimulation; decreases in percentages of T3, T4, and T11 cells in the exposed group	Knutsen et al., 1987
154 people in highly contaminated area vs 155 in three low–environmental-contamination areas as controls	Increase in anergy and decrease in induration for DTH in exposed group; data from some readers were excluded; decrease in percentages of T3, T4, and T11 cells, but no difference in cell number of T4/T8 ratio	Stehr-Green et al., 1987
80 people in a high-exposure risk group vs 40 controls	Decreases in DTH indurations, number of positive reactors, and percentages of T3, T4, and T11 cells in the exposed group	Andrews et al., 1986
154 people in the exposed area vs 155 non-exposed people in an uncontaminated area	Recall antigen multitest for DTH, increase in percentage of anergy and decrease in induration in exposed group; data from two of four readers were excluded	Hoffman et al., 1986
Other Environmental Studies		
Belgium (Flanders)—200 people 17–18 years of age in three areas of Flanders (Belgium); TEQ values were calculated from serum dioxin-like PCB concentrations and relationships with immune measures were examined	**Dioxins and PCBs:** Decreases in eosinophil and NK-cell counts with increasing TEQ; IgE concentrations; history of upper airway allergy, and odds of a positive RAST test correlated negatively with serum TEQ; IgA concentrations correlated positively with TEQ	Van den Heuvel et al., 2002
Finland—123 men and 132 women from high fish-consumption group	**TEQ for dioxins, furans, and PCBs:** CRP was not associated with overall TEQ for men ($p = 0.29$) or women ($p = 0.94$)	Tururen et al., 2012
Germany—Cross-sectional study of 221 teachers who worked in German day-care centers treated with wood preservatives vs 189 teachers who worked in untreated facilities	**Dioxin in wood preservatives,** exposure primarily via inhalation: No effects of inhaled dioxin were seen on T4 or T8 cell numbers or on the ratio; some evidence of a dose–response relationship was seen for risk of anergy (or hypoergy) in the DTH assay	Wolf and Karmaus, 1995
Japan—1,063 men and 1,201 women without occupational dioxin exposure from 125 areas	**All WHO 2005 DLCs:** Self-reported asthma not associated with DLCs; marginal association of atopic dermatitis and allergic rhinitis with DLCs	Nakamoto et al., 2013
US (Seattle)—109 postmenopausal women tested for immune function at start and after one year exercise program	**Mono-ortho PCBs 105, 118, 156:** PHA-induced T-lymphocyte proliferation decreased with PCB levels after one year, but not at start; NK cytotoxicity not associated with PCBs at either time	Spector et al., 2014
US (NHANES)	**Dioxin-like PCBs**	
1,721 adults assessed for serum dioxin-like PCBs and self-reported arthritis	Association between serum dioxin-like PCBs and prevalence of arthritis particularly among women	Lee et al., 2007a
632 women and 670 men assessed for dioxin-like PCBs and serum antinuclear antibodies	In women only, TEQ for PCBs associated with positivity for antinuclear antibodies ($p < 0.001$)	Gallagher et al., 2013

TABLE 1 Continued

Study Population	Exposure/Results	Reference
CASE-CONTROL STUDIES		
Norway—blood samples from 24 Norwegian hobby fishermen were compared with those of 10 male referents as controls	**PCDD,** exposure from food: The study generally lacks experimental details; no differences in an NK cell marker or in NK activity were seen; apparently, some effects on lymphoid markers were observed but specific details are lacking	Lovik et al., 1996
Sweden—23 high consumers of fatty fish from the Baltic Sea (containing low concentrations of PCDD) vs 20 low consumers or nonconsumers of fish as controls	**PCDD,** exposure from food: Blood PCDDs were significantly different between the groups; mercury concentrations also differed; NK cells correlated negatively with blood concentrations of persistent organic chemicals; no other	Svensson et al., 1994
South Korea (Ansan)—comparison of immune measures in 31 waste-incineration workers vs 84 controls	**TCDD** (via waste incineration): Lymphoid subsets, IFN-gamma, and Ig not statistically different; decrease in IL-4 and increase in T-cell activation (measured as combined CD3 and CD69 markers) associated with TCDD exposure	Oh et al., 2005
United Kingdom (Derbyshire)—18 chemical workers in a 2,4,5-T in the Coalite Oils and Chemical, Ltd. factory exposed as a result of an industrial accident 17 years before study vs 15 matched controls	**TCDD:** No changes in serum Ig classes, increases in antinuclear antibodies and immune complexes, and increase in circulating NK cells (Leu7+) in exposed workers	Jennings et al., 1988
United States (California)—telephone interviews concerning environmental and occupational chemical exposures were conducted with 50 AIDS patients (with Kaposi sarcoma) and 50 homosexual men as controls	**Chemical exposures, including pesticides, and Agent Orange:** No significant differences were reported in a small study that generally lacked focus	Hardell et al., 1987
Vietnam—Case control study of individuals living near Da Nang Air base (n = 36 women and 24 men) for more than 10 years and healthy age, BMI, and sex matched controls who were recruited from non-sprayed areas	Serum dioxin was measured and expressed as bioanalytic equivalents (BEQ)/g fat, blood samples were also tested for AhR, IL-1β, TNFα, IL-6, IL-22, and β-actin expression. No differences in AhR expression levels between the exposed subjects with rheumatoid arthritis and those without rheumatoid arthritis. Expression of IL-1 β, TNFα, and IL-6 were increased with dioxin exposure, median fold increase and (1.5 interquartile range) IL-1 β = 11.18-fold (6.76–20.72), $p < 0.05$; TNF = 6.64-fold (3.43–13.67), $p < 0.05$; IL-6 = 2.93-fold (1.80–5.18), $p < 0.05$. IL-22 was decreased 0.05-fold (0.01–0.11), $p < 0.01$. No association was observed between cytokine levels and dioxin levels.	Nguyen et al., 2017

ABBREVIATIONS: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; AHS, Agricultural Health Study; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; Con A, concanavalin A; CRP, C-reactive protein; DTH, delayed-type hypersensitivity; ICD, *International Classification of Diseases*; IFN-gamma, interferon-gamma; Ig, immunoglobulin; IL, interleukin; IL1RA, interleukin one receptor agonist; MCPA, methyl-4-chlorophenoxyacetic acid; MLR, mixed lymphocyte response; MO, Missouri; NHANES, National Health and Nutrition Examination Survey; NIOSH, National Institute for Occupational Safety and Health; NK, natural killer; OR, odds ratio; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCDF, polychlorinated dibenzofurans; PHA, phytohemagglutinin; RAST, radioallergosorbent; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; TEQ, total toxic equivalent; TNF, tumor necrosis factor; VA, US Department of Veterans Affairs; WBC, white blood cell.

TABLE 2 Selected Epidemiologic Studies—Oral, Nasal, and Pharyngeal Cancers (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	Akhtar et al., 2004
Incidence			
Ranch Hand veterans (n = 1,189)	6	0.9 (0.4–1.9)	
With tours between 1966–1970	6	1.1 (0.5–2.3)	
SEA comparison veterans (n = 1,776)	5	0.6 (0.2–1.2)	
With tours between 1966–1970	4	0.6 (0.2–1.4)	
Mortality			
Through 1999—White subjects vs national rates			
Ranch Hand veterans (n = 1,189)	0	0.0 (nr)	
SEA comparison veterans (n = 1,776)	1	0.5 (nr)	
US VA Cohort of Army Chemical Corps—Expanded as of 1997 to include all Army men with chemical MOS (2,872 deployed vs 2,737 nondeployed) serving during Vietnam era (July 1, 1965–March 28, 1973)		**All COIs**	
Mortality—Oral cavity and pharyngeal cancer			
Through 2005			Cypel and Kang, 2010
Deployed veterans (2,872) vs nondeployed (2,737)	6 vs 2	1.7 (0.3–8.7)	
Army Chemical Corps vs US men			
Vietnam cohort	6	1.5 (0.6–3.3)	
Non-Vietnam cohort	2	0.8 (0.1–2.8)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Mortality			
1965–2000 (ICD-140–149)	6	nr	Boehmer et al., 2004
US CDC Selected Cancers Study—Case-control study of incidence (Dec 1, 1984–Nov 30, 1989) among US males born 1929–1953		**All COIs**	CDC, 1990a
89 nasopharyngeal carcinomas			
Vietnam service	3	0.5 (0.2–1.8)	
62 nasal carcinomas			
Vietnam service	2	0.7 (0.2–2.9)	
State Studies of US Vietnam Veterans			
Michigan Vietnam-era veterans, proportionate mortality study (1974–1989)—deployed vs nondeployed (lip, oral cavity, pharynx)	12	1.0 (0.5–1.8)	Visintainer et al., 1995
International Vietnam-Veterans Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000 (head and neck)	247	1.5 (1.3–1.6)	ADVA, 2005b
Navy	56	1.6 (1.1–2.0)	
Army	174	1.6 (1.3–1.8)	
Air Force	17	0.9 (0.5–1.5)	

TABLE 2 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Mortality			
All branches, return–2001			ADVA, 2005a
Head and neck	101	1.4 (1.2–1.7)	
Navy	22	1.5 (0.9–2.1)	
Army	69	1.5 (1.1–1.8)	
Air Force	9	1.1 (0.5–2.0)	
Nasal	3	0.8 (0.2–2.2)	
1980–1994			CDVA, 1997a
Lip (ICD-9 140)	0	nr	
Nasopharyngeal cancer (ICD-9 147)	2	0.5 (0.1–1.7)	
Nasal cavities (ICD-9 160)	2	1.2 (0.1–4.1)	
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Incidence			
1982–2000			ADVA, 2005c
Head and Neck	44	2.0 (1.2–3.4)	
Mortality			
1966–2001			ADVA, 2005c
Head and neck	16	1.8 (0.8–4.3)	
Nasal	0	0.0 (0.0–48.2)	
1982–1994			CDVA, 1997b
Nasopharyngeal cancer (ICD-9 147)	1	1.3 (0.0– > 10)	
Nasal cavities (ICD-9 160)	0	0.0 (0.0– > 10)	
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008)			
Head and neck	19	1.3 (0.8–2.1)	
Oral cavity, pharynx and larynx	18	1.3 (0.8–2.1)	
Mortality (1988–2008)			
Head and neck	11	2.2 (1.1–3.9)	
Oral cavity, pharynx and larynx	11	2.1 (1.1–3.8)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs)		**All COIs**	
Incidence (1992–2003)			Yi and Ohrr, 2014
Lip (C00)	1 vs 2	1.4 (0.1–26.2)	
Tongue (C01–C02)	17 vs 14	1.0 (0.5–2.2)	
Mouth (C03–C06)	23 vs 9	2.5 (1.1–5.7)	
Salivary gland (C07–C08)	13 vs 2	7.0 (1.5–32.3)	
Tonsil (C09)	10 vs 12	0.9 (0.4–2.2)	
Other oropharynx (C10)	6 vs 3	2.0 (0.5–8.2)	
Nasopharynx (C11)	21vs 29	0.7 (0.4–1.2)	
Hypopharynx (C12–C13)	18 vs 12	1.0 (0.5–2.2)	
Nose, sinuses, etc. (C30–C31)	11 vs 8	1.8 (0.7–4.7)	
Mortality (1992–2005)			Yi et al., 2014b
Oral cavity cancer (C00–C14)			
Categorized high vs low	45 vs 37	1.1 (0.7–1.7)	
HR per unit of log EOI (n = 180,639)	82	1.1 (0.9–1.2)	

continued

TABLE 2 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992			Kogevinas et al., 1997
Oral cavity, pharynx cancer (ICD-9 140–149)	26	1.1 (0.7–1.6)	
13,831 exposed to highly chlorinated PCDDs	22	1.3 (0.8–2.0)	
7,553 not exposed to highly chlorinated PCDDs	3	0.5 (0.1–1.3)	
Nasal, nasal sinus cancer (ICD-9 160)	3	1.6 (0.3–4.7)	
13,831 exposed to highly chlorinated PCDDs	0	0.0 (0.0–3.5)	
7,553 not exposed to highly chlorinated PCDDs	3	3.8 (0.8–11.1)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort			Saracci et al., 1991
Bucal cavity, pharynx (ICD-8 140–149)	11	1.2 (0.6–2.1)	
Nose, nasal cavities (ICD-8 160)	3	2.9 (0.6–8.5)	
British MCPA Plant—All manual employees employed January 1947–December 1975 (n = 1,146), ever potentially exposed to phenoxy herbicides (n = 1,544), potentially exposed to phenoxy herbicides ≥ 1 year (n = 848) (not included in IARC cohort)		**MCPA**	
Mortality through 2012, all workers			Coggon et al., 2015
Lip (ICD-10 C00)	0	0.00 (0.00–11.53)	
Tongue (ICD-10 C01–02)	8	1.93 (0.83–3.80)	
Mouth (ICD-10 C03–06)	2	0.53 (0.06–1.90)	
Pharynx (ICD-10 C09–C14.2)	4	0.49 (0.13–1.25)	
Nose (ICD-10 C30–C31)	3	1.80 (0.37–5.26)	
Mortality through 2012, workers ever exposed to phenoxy herbicides			
Lip (ICD-10 C00)	0	0.00 (0.00–17.45)	
Tongue (ICD-10 C01–02)	5	1.63 (0.53–3.80)	
Mouth (ICD-10 C03–06)	1	0.36 (0.01–1.99)	
Pharynx (ICD-10 C09–C14.2)	4	0.66 (0.18–1.68)	
Nose (ICD-10 C30–C31)	3	2.50 (0.52–7.31)	
Mortality through 2012, workers ever exposed to phenoxy herbicides ≥ 1 year			
Lip (ICD-10 C00)	0	0.00 (0.00–35.84)	
Tongue (ICD-10 C01–02)	3	2.16 (0.45–6.32)	
Mouth (ICD-10 C03–06)	0	0.00 (0.00–2.89)	
Pharynx (ICD-10 C09–C14.2)	0	0.00 (0.00–1.34)	
Nose (ICD-10 C30–C31)	0	0.00 (0.00–6.66)	
Mortality through 1983			Coggon et al., 1986
Lip (ICD-9 140)	0	nr	
Tongue (ICD-9 141)	1	1.1 (0.0–6.2)	
Pharynx (ICD-9 146–149)	1	0.5 (0.0–3.0)	
Nose (ICD-9 160)	3	4.9 (1.0–14.4)	

TABLE 2 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–1991 (lip, oral cavity, pharynx)			Hooiveld et al., 1998
All working anytime in 1955–1985	1	2.3 (0.1–12.4)	
Cleaned up 1963 explosion	1	7.1 (0.2–39.6)	
German Production Workers—2,479 workers at 4 plants (in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
All for plants—Buccal cavity, pharynx (ICD-9 140–149)	9	3.0 (1.4–5.6)	Becher et al., 1996
Tongue	3	nr	
Floor of mouth	2	nr	
Tonsil	2	nr	
Pharynx	2	nr	
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 month in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4, 5-TCP**	
Mortality 1951–1992	0	—	Becher et al., 1996
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 month in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1965–1989	0	—	Becher et al., 1996
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 month in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1956–1989	6	8.2 (3.0–17.9)	Becher et al., 1996
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Mortality			
Through 1987		90% CI	Zober et al., 1990
Buccal cavity, pharynx	1	4.8 (0.3–22.9)	
Squamous-cell carcinoma of tonsil	1	nr	
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 month in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–2007 (ICD-9 140–149)	11	2.2 (1.1–3.9)	Manuwald et al., 2012
Men	9	2.0 (0.9–3.8)	
Women	2	3.4 (0.4–12.5)	
Mortalilty 1952–1989	3	1.8 (0.4–5.2)	Becher et al., 1996
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004 (buccal cavity and pharynx)			McBride et al., 2009a
Ever-exposed workers	3	2.6 (0.5–7.6)	
Never-exposed workers	0	0.0 (0.0–11.5)	

continued

TABLE 2 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Production Workers—Mortality 1969–2000			
713 men and 100 women worked > 1 month in 1969–1984	2	2.8 (0.3–9.9)	't Mannetje et al., 2005
Lip (ICD-9 140)	0	nr	
Mouth (ICD-9 141–145)	2	5.4 (0.7–20.0)	
Oropharynx (ICD-9 146)	0	nr	
Nasopharynx (ICD-9 147)	0	0.0 (0.0–41.8)	
Hypopharynx, other (ICD-9 148–149)	0	nr	
Phenoxy herbicide sprayers (> 99% men)	1	1.0 (0.0–5.7)	't Mannetje et al., 2005
Lip (ICD-9 140)	0	nr	
Mouth (ICD-9 141–145)	0	0.0 (0.0–7.5)	
Oropharynx (ICD-9 146)	0	nr	
Nasopharynx (ICD-9 147)	1	8.3 (0.2–46.3)	
Hypopharynx, other (ICD-9 148–149)	0	nr	
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, Washington, and Wichita, Kansas) and workers who made PCP and TCP at two additional plants (in Midland, Michigan, and Sauget, Illinois)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122) (buccal, pharynx; ICD-9 140–149)	5	0.8 (0.3–1.8)	
PCP and TCP (n = 720)	1	0.5 (0.0–2.7)	
PCP (no TCP) (n = 1,402)	4	0.9 (0.2–2.3)	
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)	7	1.1 (0.4–2.2)	Burns CJ et al., 2011
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM (oral cavity, pharynx)			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	33	0.9 (0.6–1.3)	
Ever	15	0.5 (0.3–0.9)	
Danish male, female paper workers			Rix et al., 1998
Buccal cavity (ICD-7 140–144)			
Men	24	1.0 (0.7–1.5)	
Women	4	1.5 (0.4–3.8)	
Pharynx (ICD-7 145–149)			
Men	15	2.0 (1.1–3.3)	
Women	2	2.1 (0.2–7.6)	
Tonsil cancers among pharyngeal cancers	11	nr	
Northwestern US paper and pulp workers—5 mills in Washington, Oregon, and California, 3,523 worked ≥ 1 year 1945–1955, mortality through March 1977		90% CI	Robinson et al., 1986
Buccal cavity, pharynx (ICD-7 140–148)	1	0.1 (0.0–0.7)	
Nasal (ICD-7 160)	0	nr	

TABLE 2 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Danish self-employed farmers			
Lip	182	1.8 ($p < 0.05$)	
Tongue	9	0.6 (nr)	
Salivary glands	13	0.9 (nr)	
Mouth	14	0.5 ($p < 0.05$)	
Pharynx	13	0.3 ($p < 0.05$)	
Nasal cavities, sinuses	11	0.6 (nr)	
Danish farming employees			
Lip	43	2.1 ($p < 0.05$)	
Tongue	2	0.6 (nr)	
Salivary glands	0	0.0 (nr)	
Mouth	0	0.0 ($p < 0.05$)	
Pharynx	9	1.1 (nr)	
Nasal cavities, sinuses	5	1.3 (nr)	
Danish gardeners—incidence from 3,156 male and 859 female gardeners (buccal cavity, pharynx, ICD-7 140–148)		**Herbicides**	Hansen et al., 2007
10-year followup (1975–1984) reported in Hansen et al. (1992)	6	1.1 (0.4–2.5)	
25-year followup (1975–2001)			
Born before 1915 (high exposure)	3	0.7 (0.2–2.3)	
Born 1915–1934 (medium exposure)	6	0.7 (0.3–1.4)	
Born after 1934 (low exposure)	0	0.0 (0.0–1.0)	
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 weeks) not IARC		**Phenoxy herbicides**	Asp et al., 1994
Buccal, pharynx (ICD-8 140–149)			
Incidence	5	1.0 (0.3–2.3)	
Mortality 1972–1989	0	0.0 (0.0–3.0)	
"Other Respiratory" (ICD-8 160, 161, 163)—nose, larynx, pleura			
Incidence	4	1.1 (0.3–2.7)	
Mortality 1972–1989	1	0.5 (0.0–2.9)	
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401) (buccal cavity, pharynx)	18	0.3 (0.2–0.5)	Torchio et al., 1994
Italian Farmers—mortality odds ratios from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Self-employed	13	0.9 (nr)	
Employee	4	0.5 (nr)	

continued

TABLE 2 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of 649 incident buccal cavity cancer cases and 49 incident nasopharynx cancer cases vs 19,904 men with any incident cancer			Reif et al., 1989
Forestry workers (n = 134)		**Herbicides**	
Buccal cavity	3	0.7 (0.2–2.2)	
Nasopharynx	2	5.6 (1.6–19.5)	
Aged 20–59	1	3.5 (0.6–22.6)	
Aged ≥ 60	1	13.4 (2.7–65.1)	
Sawmill workers (n = 139)		**Herbicides, chlorophenols**	
Nasopharynx	0	—	
NORWEGIAN farmers born 1925–1971—incidence, lip cancer		**Pesticides**	Nordby et al., 2004
Reported pesticide use	nr	0.7 (0.4–1.0)	
SWEDEN			
Swedish pesticide applicators—incidence			Wiklund et al., 1989a
Lip cancer	14	1.8 (1.0–2.9)	
Incident cancer cases 1961–1973 with agriculture as economic activity in 1960 census (male, female)		99% CI	Wiklund, 1983
Lip	508	1.8 (1.6–2.2)	
Tongue	32	0.4 (0.2–0.6)	
Salivary Gland	68	1.0 (0.7–1.4)	
Mouth	70	0.6 (0.5–0.8)	
Throat	84	0.5 (0.4–0.7)	
Nose, nasal sinuses	64	0.8 (0.6–1.2)	
THE NETHERLANDS			
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000			Swaen et al., 2004
Nose	0	—	
Pharynx	0	—	
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	21	2.3 (1.4–3.5)	
Nonwhites (n = 11,446)	0	—	
Women			
Whites (n = 2,400)	1	12.2 (0.2–68.0)	
Nonwhites (n = 2,066)	0	0.0 (0.0–103.6)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	

TABLE 2 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	93	0.6 (0.5–0.7)	
Commercial applicators	5	0.5 (0.2–1.3)	
Spouses	22	0.6 (0.4–1.0)	
Enrollment through 2002—buccal cavity			Alavanja et al., 2005
Private applicators (men and women)	66	0.7 (0.5–0.8)	
Lip	25	1.4 (0.9–2.1)	
Spouses of private applicators (> 99% women)	14	0.7 (0.4–1.2)	
Lip	2	1.4 (0.2–5.1)	
Commercial applicators	5	0.9 (0.3–2.2)	
Lip	3	2.7 (0.6–8.0)	
Mortality			
Enrollment through 2007, vs state rates (buccal cavity, pharynx)	16	0.3 (0.2–0.6)	Waggoner et al., 2011
Enrollment through 2000, vs state rates (buccal cavity, pharynx)			Blair et al., 2005a
Private applicators (men and women)	5	0.3 (0.1–0.7)	
Spouses of private applicators (> 99% women)	0	0.0 (0.0–25.4)	
White Male Residents of Iowa—Lip cancer on death certificate, usual occupation: farmers vs not		**Herbicides**	
> 20 years old when died 1971–1978—PMR	20	2.1 ($p < 0.01$)	Burmeister, 1981
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Incidence			
10-year followup to 1991—men			Bertazzi et al., 1993
Buccal cavity (ICD-9 140–149)			
Zone B	6	1.7 (0.8–3.9)	
Zone R	28	1.2 (0.8–1.7)	
Nose, nasal cavities (ICD-9 160)			
Zone R	0	nr	
10-year followup to 1991—women			Bertazzi et al., 1993
Buccal cavity (ICD-9 140–149)			
Zone B	0	nr	
Zone R	0	nr	
Nose, nasal cavities (ICD-9 160)			
Zone R	2	2.6 (0.5–13.3)	

continued

TABLE 2 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
CASE-CONTROL STUDIES			
US Case-Control Studies			
US males born 1929–1953, all 70 nasal cancers (carcinomas, 11 lymphomas, 5 sarcomas) in CDC (1990a) study population		**Herbicides, pesticides**	Caplan et al., 2000
Selected landscaping, forestry occupation	26	1.8 (1.1–3.1)	
Living, working on farm	23	0.5 (0.3–0.8)	
Herbicides, pesticides	19	0.7 (0.4–1.3)	
Phenoxy herbicides	5	1.2 (0.4–3.3)	
International Case-Control Studies			
Residents of northern **Sweden** (44 nasal, 27 nasopharyngeal cancers		**Phenoxy acids, chlorophenols**	Hardell et al., 1982
Phenoxy herbicide exposed	8	2.1 (0.9–4.7)	
Chlorophenol exposure	9	6.7 (2.8–16.2)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DCP, 2,4-dichlorophenol; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job-exposure matrix; MCPA, 2 methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MOS, military occupational specialty; n, number; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCP, pentachlorophenol; PM, proportionate mortality; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; SIR, standardized incidence ratio; TCP, trichlorophenol; UK, United Kingdom.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

TABLE 3 Selected Epidemiologic Studies—Esophageal Cancer (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Mortality			
1965–2000	6	1.2 (0.4–4.0)	Boehmer et al., 2004
State Studies of US Vietnam Veterans			
Michigan Vietnam-era veterans, PM study of deaths (1974–1989)—deployed vs nondeployed	9	0.9 (0.4–1.6)	Vistainer et al., 1995
International Studies of Vietnam Veterans			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	70	1.2 (0.9–1.5)	ADVA, 2005b
Navy	19	1.6 (0.9–2.4)	
Army	40	1.1 (0.7–1.4)	
Air Force	11	1.5 (0.8–2.8)	
Mortality			
All branches, return–2001	67	1.1 (0.8–1.3)	ADVA, 2005a
Navy	13	1.0 (0.5–1.7)	
Army	42	1.0 (0.7–1.3)	
Air Force	12	1.5 (0.8–2.6)	
1980–1994	23	1.2 (0.7–1.7)	CDVA, 1997a
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Incidence			
1982–2000	9	1.9 (0.6–6.6)	ADVA, 2005c
Mortality			
1966–2001	10	1.3 (0.5–3.6)	ADVA, 2005c
1982–1994	1	1.3 (0.0– >10)	CDVA, 1997b
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs)		**All COIs**	
Incidence (1992–2003)—esophagus (C15) categorized high (n = 113) vs low (n = 71)	113	1.4 (1.0–1.9)	Yi and Ohrr, 2014
Mortality (1992–2005)—esophagus categorized high (n = 98) vs low (n = 64)		1.3 (0.9–1.8)	Yi et al., 2014b
HR per unit of log EOI (n = 180,639)	162	1.0 (0.9–1.1)	

continued

TABLE 3 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	28	1.0 (0.7–1.4)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	20	1.3 (0.8–1.9)	
7,553 not exposed to highly chlorinated PCDDs	6	0.5 (0.2–1.1)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	8	0.6 (0.3–1.2)	Saracci et al., 1991
British MCPA Plant—All manual employees employed January 1947–December 1975 (n = 1,146), ever potentially exposed to phenoxy herbicides (n = 1,544), potentially exposed to phenoxy herbicides ≥ 1 year (n = 848) (not included in IARC cohort)		**MCPA**	
Mortality through 2012, all workers			Coggon et al., 2015
Esophagus (ICD-10 C15)	55	0.99 (0.74–1.28)	
Mortality through 2012, workers ever exposed to phenoxy herbicides			
Esophagus (ICD-10 C15)	46	1.11 (0.81–1.48)	
Mortality through 2012, workers ever exposed to phenoxy herbicides ≥ 1 year			
Esophagus (ICD-10 C15)	17	0.89 (0.52–1.43)	
Mortality through 1983	8	0.9 (0.4–1.9)	Coggon et al., 1986
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 month in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–2007 (ICD-9 150)			Manuwald et al., 2012
Men	11	2.6 (1.3–4.6)	
Women	0	nr	
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	4	2.5 (0.7–6.4)	
Never-exposed workers	1	2.1 (0.1–12.2)	
Production Workers (713 men and 100 women worked > 1 month in 1969–1984)			
Mortality 1969–2000	2	2.0 (0.2–7.0)	't Mannetje et al., 2005
Phenoxy herbicide sprayers (> 99% men)	1	0.7 (0.0–4.0)	

TABLE 3 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, Michigan) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1937–2011 Potential dioxin exposure (n = 2,192), TCP production (n = 1,419), PCP production (n = 577), Both TCP and PCP (n = 196)			Collins et al., 2016
TCP or PCP, Esophageal Cancer (ICD-10 C15)	13	1.32 (0.71–2.26)	
TCP, Esophageal Cancer (ICD-10 C15)	8	1.09 (0.47–2.14)	
PCP, Esophageal Cancer (ICD-10 C15)	5	1.52 (0.49–3.54)	
1942–2003 (n = 1,615)			Collins et al., 2009b
Trichlorophenol workers	5	1.0 (0.3–2.2)	
Pentachlorophenol workers	2	0.8 (0.1–2.9)	
All Dow PCP-Exposed Workers—all workers from two plants that only made PCP (in Tacoma, Washington, and Wichita, Kansas) and workers who made PCP and TCP at two additional plants (in Midland, Michigan, and Sauget, Illinois)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122)	8	1.0 (0.4–2.0)	
PCP and TCP (n = 720)	2	0.8 (0.1–3.0)	
PCP (no TCP) (n = 1,402)	6	1.1 (0.4–2.3)	
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	27	0.7 (0.4–1.0)	
Ever	26	0.8 (0.5–1.2)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	32	0.4 ($p < 0.05$)	
Employee	13	0.9 (nr)	
Women			
Self-employed	1	1.4 (nr)	
Employee	2	0.4 (nr)	
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 weeks) not IARC		**Phenoxy herbicides**	
Incidence	3	1.6 (0.3–4.6)	Asp et al., 1994
Mortality 1972–1989	2	1.3 (0.2–4.7)	

continued

TABLE 3 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of 385 incident esophageal cancer cases vs remainder of 19,904 men with any incident cancer			Reif et al., 1989
Forestry workers (n = 134)		**Herbicides**	
	4	1.8 (0.7–4.8)	
Aged 20–59	1	1.6 (0.2–11.3)	
Aged ≥ 60	3	1.9 (0.6–5.8)	
Sawmill workers (n = 139)		**Herbicides, Chlorophenols**	
	2	0.7 (0.2–2.9)	
SWEDEN			
Incidence cancer cases 1961–1973 with agriculture as economic activity in 1960 census (male, female)	169	99% CI 0.6 (0.5–0.7)	Wiklund, 1983
UNITED STATES			
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	52	0.6 (0.5–0.9)	
Commercial applicators	2	nr	
Spouses	2	nr	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	48	0.5 (0.4–0.7)	
Spouses (n = 676)	3	nr	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	16	0.5 (0.3–0.9)	
Spouses of private applicators (> 99% women)	1	0.3 (0.1–1.9)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group)		**TCDD**	
Incidence			
20-year followup to 1996—men and women			
Zone A	0		Pesatori et al., 2009
Zone B	1	0.3 (0.0–1.9)	
Zone R	35	1.3 (0.9–1.9)	

TABLE 3 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
CASE-CONTROL STUDIES			
US Case-Control Studies			
Nebraska—agricultural pesticide use and adenocarcinoma of the esophagus	137	**Phenoxy herbicides, 2,4-D**	Lee et al., 2004b
Insecticides		0.7 (0.4–1.1)	
Herbicides		0.7 (0.4–1.2)	
International Case-Control Studies			
UK men, 18–35 years of age from counties with particular chemical manufacturing—mortality		**Herbicides, Chlorophenols**	Magnani et al., 1987
Herbicides	nr	1.6 (0.7–3.6)	
Chlorophenols	nr	1.2 (0.7–2.2)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DCP, 2,4-dichlorophenol; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job-exposure matrix; MCPA, 2 methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; n, number; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCP, pentachlorophenol; PM, proportionate mortality; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

TABLE 4 Selected Epidemiologic Studies—Stomach Cancer (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Incidence			
1982–2003—White SEA comparison veterans only (n = 1,482). Serum TCDD (pg/g) based on model with exposure variable $\log_e$(TCDD)			Pavuk et al., 2005
Per unit increase of –$\log_e$(TCDD) (pg/g) Quartiles (pg/g):	24	1.8 (0.8–3.9)	
0.4–2.6	4	nr	
2.6–3.8	3	1.0 (0.2–4.8)	
3.8–5.2	7	2.0 (0.5–8.2)	
> 5.2	10	3.3 (0.9–12.5)	
Number of years served in SEA (per year of service)			
Quartiles (years in SEA):	24	1.2 (1.0–1.4)	
0.8–1.3	4	nr	
1.3–2.1	4	1.0 (0.2–3.8)	
2.1–3.7	5	1.1 (0.3–4.2)	
3.7–16.4	11	2.1 (0.6–7.3)	
Through 1999—White subjects vs national rates			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	16	0.6 (0.4–1.0)	
With tours between 1966–1970	14	0.6 (0.4–1.1)	
SEA comparison veterans (n = 1,776)	31	0.9 (0.6–1.2)	
With tours between 1966–1970	24	0.9 (0.6–1.3)	
Mortality			
Through 1999—White subjects vs national rates			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	6	0.4 (0.2–0.9)	
SEA comparison veterans (n = 1,776)	14	0.7 (0.4–1.1)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Mortality			
1965–2000	5	nr	Boehmer et al., 2004
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1982			Breslin et al., 1988
Army, deployed (n = 19,708) vs nondeployed (n = 22,904)	88	1.1 (0.9–1.5)	
Marine Corps, deployed (n = 4,527) vs nondeployed (n = 3,781)	17	0.8 (0.4–1.6)	
State Studies of US Vietnam Veterans			
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans	1	nr	Anderson et al., 1986a,b

TABLE 4 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	104	0.9 (0.7–1.1)	ADVA, 2005b
Navy	28	1.1 (0.7–1.6)	
Army	66	0.9 (0.7–1.1)	
Air Force	10	0.7 (0.3–1.3)	
Mortality			
All branches, return–2001	76	0.9 (0.7–1.2)	ADVA, 2005a
Navy	22	1.3 (0.8–1.8)	
Army	50	0.9 (0.7–1.2)	
Air Force	4	0.4 (0.1–1.0)	
1980–1994	32	1.1 (0.7–1.4)	CDVA, 1997a
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Incidence			
1982–2000	11	0.6 (0.2–1.2)	ADVA, 2005c
Mortality			
1966–2001	7	0.7 (0.2–2.0)	ADVA, 2005c
1982–1994	4	1.7 (0.3– > 10)	CDVA, 1997b
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008)	9	0.8 (0.4–1.6)	
Mortality (1988–2008)	9	1.3 (0.6–2.4)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs)		**All COIs**	
Incidence (1992–2003)—Stomach (C16) categorized high (n = 1,154) vs low (n = 973)		1.1 (1.0–1.2)	Yi and Ohrr, 2014
Mortality (1992–2005)—Stomach (C16) categorized high (n = 613) vs low (n = 464)		1.2 (1.0–1.3)	Yi et al., 2014b
HR per unit of log EOI (n =180,639)	1,077	1.1 (1.0–1.1)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates		**Phenoxy herbicides, chlorophenols**	
Mortality 1939–1992	72	0.9 (0.7–1.1)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	42	0.9 (0.7–1.2)	
7,553 not exposed to highly chlorinated PCDDs	30	0.9 (0.6–1.3)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort			Saracci et al., 1991
Nested case-control study	40	0.9 (0.6–1.2)	
Mortality, incidence of women in production (n = 699) and spraying (n = 2) compared to national death rates and cancer incidence rates	1	**TCDD** 1.4 (nr)	Kogevinas et al., 1993

continued

TABLE 4 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
British MCPA Plant—All manual employees employed January 1947–December 1975 (n = 1,146), ever potentially exposed to phenoxy herbicides (n = 1,544), potentially exposed to phenoxy herbicides ≥ 1 year (n = 848) (not included in IARC cohort)		**MCPA**	
Mortality through 2012, all workers			Coggon et al., 2015
Stomach (ICD-10 C16)	66	0.78 (0.61–1.00)	
Mortality through 2012, workers ever exposed to phenoxy herbicides			
Stomach (ICD-10 C16)	43	0.73 (0.53–0.99)	
Mortality through 2012, workers ever exposed to phenoxy herbicides ≥ 1 year			
Stomach (ICD-10 C16)	21	0.75 (0.46–1.15)	
Mortality through 1983	26	0.9 (0.6–1.3)	Coggon et al., 1986
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence 1943–1982			Lynge, 1985
Men	12	1.3 (nr)	
Women	1	0.7 (nr)	
Mortality 1955–2006	14	1.1 (0.8–1.5)	Boers et al., 2012
TCDD plasma level (hazard ratios, by tertile)			
Background (≤ 0.4)	8	—	
Low (0.4–1.9)	1	0.1 (0.0–1.0)	
Medium (1.9–9.9)	2	0.5 (0.1–2.6)	
High (≥ 9.9)	3	2.5 (0.7–9.2)	
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–2006 (HRs for lagged TCDD plasma levels)	6	1.5 (1.1–2.2)	Boers et al., 2012
Mortality 1955–2006	5	2.2 (0.4–13.2)	Boers et al., 2010
Mortality 1955–1991	3	1.0 (0.2–2.9)	Hooiveld et al., 1998
Mortality 1955–1985	2	0.9 (0.1–3.4)	Bueno de Mesquita et al., 1993
Dutch production workers in Plant B (414 men exposed during production 1965–1986; 723 unexposed) (in IARC cohort)		**2,4-D; MCPA; MCPP; highly chlorinated dioxins unlikely**	
Mortality 1965–2006	4	1.2 (0.3–4.7)	Boers et al., 2010
Mortality 1965–1986	0	0.0 (0.0–6.5)	Bueno de Mesquita et al., 1993
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 month in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992	0	nr	Becher et al., 1996
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 month in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1965–1989	0	nr	Becher et al., 1996

TABLE 4 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 month in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1956–1989	2	0.6 (0.1–2.3)	Becher et al., 1996
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Incidence			
1960–1992	3	1.0 (0.2–2.9)	Ott and Zober, 1996a
TCDD < 0.1 μg/kg of body weight	0	0.0 (0.0–3.4)	
TCDD 0.1–0.99 μg/kg of body weight	1	1.3 (0.0–7.0)	
TCDD > 1 μg/kg of body weight	2	1.7 (0.2–6.2)	
Mortality			Zober et al., 1990
Through 1987		90% CI	
	3	3.0 (0.8–7.7)	
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 month in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–2007 (ICD-9 140–149)	17	1.0 (0.6–1.6)	Manuwald et al., 2012
Men	17	1.3 (0.7–2.0)	
Women	0	nr	
Mortalilty 1952–1989	12	1.3 (0.7–2.2)	Becher et al., 1996
Mortality 1952–1989—stats on men only, 1,184 (tables all for 1,148 men, not necessarily German nationals) vs national rates (also vs gas workers); same observation period as Becher et al., 1996	12	1.2 (0.6–2.1)	Manz et al., 1991
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	4	1.4 (0.4–3.6)	
Never-exposed workers	2	2.3 (0.3–8.4)	
Production Workers (713 men and 100 women worked > 1 month in 1969–1984)			
Mortality 1969–2000	2	1.1 (0.1–4.0)	't Mannetje et al., 2005
Phenoxy herbicide sprayers (> 99% men)	3	1.4 (0.3–4.0)	
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993	13	1.0 (0.6–1.8)	Steenland et al., 1999
Through 1987	10	1.0 (0.5–1.9)	Fingerhut et al., 1991
≥ 1-year exposure, ≥ 20-year latency	4	1.4 (0.4–3.5)	
Mortality—754 Monsanto workers, among most highly exposed workers from Fingerhut et al. (1991)	0	0.0 (0.0–1.1)	Collins et al., 1993

continued

TABLE 4 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, Michigan) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1937–2011 Potential dioxin exposure (n = 2,192), TCP production (n = 1,419), PCP production (n = 577), Both TCP and PCP (n = 196)			Collins et al., 2016
TCP or PCP, Stomach Cancer (ICD-10 C16)	14	1.40 (0.77–2.35)	
TCP, Stomach Cancer (ICD-10 C16)	11	1.58 (0.79–2.83)	
PCP, Stomach Cancer (ICD-10 C16)	5	1.30 (0.42–3.04)	
1942–2003 (n = 1,615)	8	1.4 (0.6–2.7)	Collins et al., 2009b
1940–1994 (n = 2,187 men)	nr	1.5 (0.7–2.7)	Bodner et al., 2003
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, Washington, and Wichita, Kansas) and workers who made PCP and TCP at two additional plants (in Midland, Michigan, and Sauget, Illinois)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122)	9	0.9 (0.4–1.7)	
PCP and TCP (n = 720)	3	1.0 (0.2–2.9)	
PCP (no TCP) (n = 1,402)	6	0.8 (0.3–1.8)	
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)	3	0.8 (0.2–2.3)	Burns CJ et al., 2011
Through 1994 (n = 1,517) (digestive organs, peritoneum)	16	0.7 (0.4–1.2)	Burns et al., 2001
Through 1982 (n = 878)	0	nr (0.0–3.7)	Bond et al., 1988
Dow PCP Production Workers (1937–1989 in Midland, Michigan) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	4	1.2 (0.3–3.1)	Collins et al., 2009c
Mortality 1940–1989 (n = 770)			Ramlow et al., 1996
0-year latency	4	1.7 (0.5–4.3)	
15-year latency	3	1.8 (0.4–5.2)	
Other Studies of Industrial Workers (not related to IARC or NIOSH phenoxy cohorts)		**Dioxins, phenoxy herbicides**	
1,412 white male US Flavor and fragrance chemical plant workers (1945–1965)		**Dioxin, 2,4,5-T** <u>*Expected exposed cases*</u>	Thomas, 1987
	6	4.2	
Automobile workers from Hubei province in China (worked 1 year during 1980–1985)		**PCDD/F**	Wang et al., 2013
Mortality (1980–2005) (n = 3,529)	15	1.3 (0.6–2.7)	

TABLE 4 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	146	0.9 (0.8–1.1)	
Ever	98	0.9 (0.7–1.1)	
14,362 **Danish paper workers** employed 1943–1990, followed through 1993			Rix et al., 1998
Men	48	1.1 (0.8–1.4)	
Women	7	1.0 (0.4–2.1)	
New Hampshire pulp and paper workers, 883 white men working ≥ 1 year, mortality through July 1985	5	1.2 (0.4–2.8)	Henneberger et al., 1989
Pulp and Paper cohorts independent of IARC cohort			
United Paperworkers International, 201 white men employed ≥ 10 year and dying 1970–1984	1	0.5 (0.1–3.0)	Solet et al., 1989
Northwestern US paper and pulp workers—5 mills in Washington, Oregon, and California, 3,523 worked ≥ 1 year 1945–1955, mortality through March 1977	17	90% CI 1.2 (0.8–1.9)	Robinson et al., 1986
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Canadian Farm Operator Study—156,242 men farming in Manitoba, Saskatchewan, and Alberta in 1971; mortality from stomach cancer June 1971–December 1987			
Linkage of records for ~70,000 male Saskatchewan farmers (1971–1985)	246	0.9 (0.8–1.0)	Wigle et al., 1990
DENMARK			
Danish farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	286	0.9 (nr)	
Employee	71	1.2 (nr)	
Women			
Self-employed	5	1.0 (nr)	
Employee	5	1.7 (nr)	
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	126	0.7 (0.6–0.9)	Torchio et al., 1994
Italian rice growers with documented phenoxy use (n = 1,487)	39	**Phenoxy herbicides** 1.0 (0.7–1.3)	Gambini et al., 1997
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of incident stomach cancer cases vs remainder of 19,904 men with any incident cancer		**Herbicides**	Reif et al., 1989
Forestry workers (n = 134)	13	2.2 (1.3–3.9)	
Aged 20–59	3	0.7 (0.2–2.2)	
Aged ≥ 60	10	2.4 (1.2–4.5)	
		Herbicides, Chlorophenols	
Sawmill workers (n = 139)	7	1.0 (0.4–2.1)	

continued

TABLE 4 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
SWEDEN			
348 Swedish railroad workers (1957–October 1978)—total exposure to herbicides	3	**Phenoxy acids** 2.2 (nr)	Axelson et al., 1980
Incident stomach cancer cases 1961–1973 with agriculture as economic activity in 1960 census	2,599	99% CI 1.1 (1.0–1.2)	Wiklund, 1983
THE NETHERLANDS			
Dutch licensed herbicide sprayers—1,341 certified before 1980			
Through 2000 (stomach, small intestine)	3	0.4 (0.1–1.3)	Swaen et al., 2004
Through 1987 (stomach, small intestine)	1	0.5 (0.0–2.7)	Swaen et al., 1992
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	657	1.0 (1.0–1.1)	
Nonwhites (n = 11,446)	115	1.1 (0.9–1.3)	
Women			
Whites (n = 2,400)	12	1.2 (0.6–2.0)	
Nonwhites (n = 2,066)	23	1.9 (1.2–2.8)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	61	0.9 (0.7–1.1)	
Commercial applicators	2	nr	
Spouses	15	0.9 (0.5–1.5)	
Enrollment through 2002			Alavanja et al., 2005
Private applicators	462	0.8 (0.8–0.9)	
Spouses of private applicators (> 99% women)	161	0.9 (0.7–1.0)	
Commercial applicators	24	1.0 (0.6–1.4)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	26	0.5 (0.3–0.8)	
Spouses (n = 676)	5	0.4 (0.1–1.0)	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	10	0.5 (0.2–1.0)	
Spouses of private applicators (> 99% women)	4	1.1 (0.3–2.8)	
California United Farm Workers of America		**2,4-D**	
Nested case-control study of agricultural exposure and gastric cancer in UFW cohort			Mills and Yang, 2007
Ever worked in area where 2,4-D used	42	1.9 (1.1–3.3)	
Quartile of lifetime exposure to 2,4-D (lb)			
0	58	1.0	
1–14	17	2.2 (1.0–4.6)	
15–85	14	1.6 (0.7–3.5)	
85–1,950	11	2.1 (0.9–5.1)	

TABLE 4 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
US Department of Agriculture Workers—nested case-control study of white men dying 1970–1979 of stomach cancer		**Herbicides**	
Agricultural extension agents	10	0.7 (0.4–1.4)	Alavanja et al., 1988
Forest conservationists		p-trend < over years worked	Alavanja et al., 1989
Soil conservationists	9	0.7 (0.3–1.3)	
Florida pesticide applicators licensed 1965–1966 (n = 3,827)—mortality through 1976		**Herbicides**	Blair et al., 1983
Any pesticide (dose-response by length of licensure)	4	*Expected exposed cases* 3.3	
White Male Residents of Iowa—stomach cancer on death certificate, usual occupation: farmers vs not		**Herbicides**	
> 30 years old when died 1964–1978—case-control			Burmeister et al., 1983
H_0: only for "modern methods" → born after 1900	1,812	1.3 ($p < 0.05$)	
Born before 1880	458	1.3 ($p < 0.05$)	
Born 1980–1900	639	1.3 ($p < 0.05$)	
Born after 1900	715	1.3 ($p < 0.05$)	
> 20 years old when died 1971–1978—PMR	338	1.1 ($p < 0.01$)	Burmeister, 1981
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Incidence			
20-year followup to 1996—men and women			
Zone A	3	0.9 (0.3–2.7)	Pesatori et al., 2009
Zone B	19	0.9 (0.6–1.4)	
Zone R	131	0.8 (0.7–1.0)	
10-year followup to 1991—men			Bertazzi et al., 1993
Zone B	7	1.0 (0.5–2.1)	
Zone R	45	0.9 (0.7–1.2)	
10-year followup to 1991—women			Bertazzi et al., 1993
Zone B	2	0.6 (0.2–2.5)	
Zone R	25	1.0 (0.6–1.5)	
Mortality			
25-year followup to 2001—men and women			Consonni et al., 2008
Zone A	3	0.7 (0.2–2.0)	
Zone B	24	0.8 (0.5–1.2)	
Zone R	212	1.0 (0.8–1.1)	
20-year followup to 1996			Bertazzi et al., 2001
Zones A and B—men	16	0.9 (0.5–1.5)	
Zones A and B—women	11	1.0 (0.6–1.9)	
15-year followup to 1991—men			Bertazzi et al., 1997, 1998
Zone B	10	0.8 (0.4–1.5)	
Zone R	76	0.9 (0.7–1.1)	

continued

TABLE 4 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
15-year followup to 1991—women			Bertazzi et al., 1997, 1998
Zone A	1	0.9 (0.0–5.3)	
Zone B	7	1.0 (0.4–2.1)	
Zone R	58	1.0 (0.8–1.3)	
10-year followup to 1986—men			Bertazzi et al., 1989a
Zone A, B, R	40	0.8 (0.6–1.2)	
10-year followup to 1986—women			Bertazzi et al., 1989a
Zone A, B, R	22	1.0 (0.6–1.5)	
10-year followup to 1986—men			Bertazzi et al., 1989b
Zone B	7	1.2 (0.6–2.6)	
Ecological Study of Residents of Chapaevsk, Russia		**Dioxin**	Revich et al., 2001
Incidence—crude incidence rate in 1998 vs			
Men			
Regional (Samara)	nr	44.0 (nr)	
National (Russia)	nr	48.1 (nr)	
Women			
Regional (Samara)	nr	17.6 (nr)	
National (Russia)	nr	20.7 (nr)	
Mortality—1995–1998 (SMR vs regional rates)			
Men	59	1.7 (1.3–2.2)	
Women	45	0.7 (0.5–0.9)	
FINLAND			
Finnish fishermen (n = 6,410) and spouses (n = 4,260) registered between 1980 and 2002 compared to national statistics		**Serum dioxin**	Turunen et al., 2008
Fisherman	16	0.8 (0.5–1.3)	
Spouses	2	0.3 (0.0–1.1)	
JAPAN			
Residents of municipalities with and without waste incineration plants (cross-sectional)		**Dioxin emissions** age-adjusted mortality (per 100,000)	Fukuda et al., 2003
Men			
With		38.2 ± 7.8 vs	
Without		39.0 ± 8.8 (p = 0.29)	
Women			
With		20.7 ± 5.0 vs	
Without		20.7 ± 5.8 (p = 0.92)	
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995a
Incidence			
East coast	24	1.6 (1.0–2.4)	
West coast	71	0.9 (0.7–1.2)	
Mortality			
East coast	17	1.4 (0.8–2.2)	
West coast	63	0.9 (0.7–1.2)	

TABLE 4 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
CASE-CONTROL STUDIES			
US Case-Control Studies			
Eastern **Nebraska**—population-based case-control, agricultural pesticide use and adenocarcinoma of stomach	170	**Herbicides, pesticides**	Lee et al., 2004b
Insecticides		0.9 (0.6–1.4)	
Herbicides		0.9 (0.5–1.4)	
International Case-Control Studies			
Swedish—population-based case-control study of residents (40–79 years of age) with gastric adenocarcinoma (February 1989–January 1995)		**Phenoxy herbicides**	Ekström et al., 1999
All occupational herbicide exposures	75	1.6 (1.1–2.2)	
Phenoxyacetic acid exposure	62	1.8 (1.3–2.6)	
Hormoslyr (2,4-D, 2,4,5-T)	48	1.7 (1.2–2.6)	
2,4-D only	3	nr (vs 0 controls)	
MCPA	11	1.8 (0.8–4.1)	
Duration of Exposure			
Non-exposed to all herbicides	490	1.0	
< 1 month	11	1.6 (0.7–3.5)	
1–6 months	30	1.9 (1.1–3.2)	
7–12 months	7	1.7 (0.6–4.7)	
> 1 year	13	1.4 (0.6–3.0)	
Other herbicide exposure	13	1.0 (0.5–1.9)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,5-DCP, 2,5-dichlorophenol; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job-exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; n, number; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; PMR, proportionate mortality ratio; SEA, Southeast Asia; SIR, standardized incidence ratio; SMR, standardized mortality ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; UFW, United Farm Workers of America; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

TABLE 5 Selected Epidemiologic Studies—Colon and Rectal Cancers (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Mortality			
1965–2000	9	1.0 (0.4–2.6)	Boehmer et al., 2004
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1982 (colon, other gastrointestinal, ICD-8 152–154, 158, 159)			Breslin et al., 1988
Army, deployed (n = 19,708) vs nondeployed (n = 22,904)	209	1.0 (0.7–1.3)	
Marine Corps, deployed (n = 4,527) vs nondeployed (n = 3,781)	33	1.3 (0.7–2.2)	
US VA Cohort of Female Vietnam Veterans		**All COIs**	
Mortality			
Through 2004			Cypel and Kang, 2008
US Vietnam veterans	11	0.5 (0.2–1.0)	
Vietnam-veteran nurses—colon	9	0.6 (0.2–1.4)	
Through 1991			Dalager et al., 1995a
US Vietnam veterans	4	0.4 (0.1–1.2)	
Vietnam-veteran nurses—colon	4	0.5 (0.2–1.7)	
State Studies of US Vietnam Veterans			
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans			Anderson et al., 1986a,b
Colon	6	1.0 (0.4–2.2)	
Rectum	1	nr	
International Studies of Vietnam Veterans			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
Colon—All branches, 1982–2000	376	1.1 (1.0–1.2)	ADVA, 2005b
Navy	91	1.3 (1.0–1.5)	
Army	239	1.1 (0.9–1.2)	
Air Force	47	1.1 (0.8–1.5)	
Rectum—All branches, 1982–2000			ADVA, 2005a
Navy	54	1.1 (0.8–1.4)	
Army	152	1.0 (0.8–1.1)	
Air Force	28	1.0 (0.6–1.4)	
Validation Study		*Expected number of exposed cases*	
Men—colorectal cancer	188	221 (191–251)	AIHW, 1999
Men—self-reported colon cancer	405	117 (96–138)	CDVA, 1998a
Women—self-reported colon cancer	1	1 (0–5)	CDVA, 1998b

TABLE 5 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Mortality			
Colon—All branches, return–2001	176	1.0 (0.8–1.1)	ADVA, 2005a
Navy	49	1.3 (0.9–1.6)	
Army	107	0.9 (0.7–1.0)	
Air Force	21	0.9 (0.5–1.3)	
Rectum—All branches, return–2001			ADVA, 2005a
Navy	13	0.8 (0.4–1.4)	
Army	44	0.9 (0.6–1.1)	
Air Force	12	1.3 (0.6–2.2)	
1980–1994			CDVA, 1997a
Colon	78	1.2 (0.9–1.5)	
Rectum	16	0.6 (0.4–1.0)	
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Incidence			
1982–2000			ADVA, 2005c
Colon	54	0.9 (0.7–1.4)	
Rectum	46	1.4 (0.9–2.2)	
Mortality			
1966–2001			ADVA, 2005c
Colon	29	0.8 (0.5–1.3)	
Rectum	10	1.8 (0.6–5.6)	
1982–1994			CDVA, 1997b
Colon	6	0.6 (0.2–1.5)	
Rectum	3	0.7 (0.2–9.5)	
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008) (colorectal)	63	1.0 (0.7–1.2)	
Mortality (1988–2008) (colorectal)	20	1.0 (0.6–1.6)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores)		**All COIs**	
Incidence (1992–2003)		**HRs**	Yi and Ohrr, 2014
Small intestine (C17) (19 vs 11)		2.3 (1.0–5.2)	
Colon cancer (C18) (210 vs 228)		0.9 (0.7–1.1)	
Rectal cancer (C19–C20) (265 vs 231)		1.1 (1.0–1.4)	
Anus (C21) (7 vs 2)		3.3 (0.6–17.1)	
Mortality (1992–2005)			Yi et al., 2014b
HR per unit of log EOI (n = 180,639)			
Small intestine (C17)	19	1.1 (0.9–1.4)	
Colorectal (C18–C21)	366	1.0 (1.0–1.1)	
High exposure vs low exposure			
Small intestine (C17) (14 vs 5)		2.9 (1.0–8.3)	
Colorectal (C18–C21) (187 vs 179)		1.0 (0.8–1.2)	

continued

TABLE 5 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Non-cancer mortality			Vena et al., 1998
Mortality 1939–1992			Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs			
Colon	86	1.1 (0.9–1.3)	
Rectum	44	1.1 (0.8–1.4)	
7,553 not exposed to highly chlorinated PCDDs			
Colon	52	1.0 (0.8–1.3)	
Rectum	29	1.3 (0.9–1.9)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort			Saracci et al., 1991
Nested case-control study			
Colon (except rectum)	41	1.1 (0.8–1.5)	
Rectum	24	1.1 (0.7–1.6)	
British MCPA Plant—All manual employees employed January 1947–December 1975 (n = 1,146), ever potentially exposed to phenoxy herbicides (n = 1,544), potentially exposed to phenoxy herbicides ≥ 1 year (n = 848) (not included in IARC cohort)			
Mortality through 2012, all workers			Coggon et al., 2015
Large Intestine (ICD-10 C18)	77	0.97 (0.77–1.22)	
Rectum (ICD-10 C19–21)	39	0.76 (0.54–1.04)	
Mortality through 2012, workers ever exposed to phenoxy herbicides			
Large Intestine (ICD-10 C18)	50	0.87 (0.65–1.15)	
Rectum (ICD-10 C19–21)	31	0.84 (0.57–1.19)	
Mortality through 2012, workers ever exposed to phenoxy herbicides ≥ 1 year			
Large Intestine (ICD-10 C18)	23	0.86 (0.54–1.29)	
Rectum (ICD-10 C19–21)	14	0.81 (0.44–1.36)	
Mortality through 1983			Coggon
Colon	19	1.0 (0.6–1.6)	
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence 1943–1982			Lynge, 1985
Men			
Colon	10	1.0 (nr)	
Rectum	14	1.4 (nr)	
Women			
Colon	1	0.3 (nr)	
Rectum	2	1.0 (nr)	

TABLE 5 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–1991			Hooiveld et al., 1998
Colon	3	1.4 (0.3–4.0)	
Rectum	1	1.0 (0.0–5.6)	
Mortality 1955–1985			Bueno de Mesquita et al., 1993
Large intestine, except colon	3	2.4 (0.5–7.0)	
Rectum	0	0.0 (0.0–5.6)	
Dutch production workers in Plant B (414 men exposed during production 1965–1986; 723 unexposed) (in IARC cohort)		**2,4-D; MCPA; MCPP; highly chlorinated dioxins unlikely**	
Mortality 1965–1986	3	1.8 (0.4–5.4)	Bueno de Mesquita et al., 1993
Large intestine, except rectum	0	0.0 (0.0–9.5)	
Rectum	0	0.0 (0.0–19.4)	
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 month in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992			Becher et al., 1996
Colon	0	nr	
Rectum	0	nr	
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 month in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1965–1989			Becher et al., 1996
Colon	1	2.2 (0.1–2.2)	
Rectum	0	nr	
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 month in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1956–1989			Becher et al., 1996
Colon	0	nr	
Rectum	1	0.9 (0.0–4.9)	
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Incidence			
1960–1992—colorectal	5	1.0 (0.3–2.3)	Ott and Zober, 1996a
TCDD < 0.1 μg/kg of body weight	2	1.1 (0.1–3.9)	
TCDD 0.1–0.99 μg/kg of body weight	2	1.4 (0.2–5.1)	
TCDD > 1 μg/kg of body weight	1	0.5 (0.0–3.0)	
Mortality		90% CI	
Through 1987—colon, rectum	2	2.5 (0.4–7.8)	Zober et al., 1990
Through 1970—(n = 74; 70 initially exposed, 4 involved with cleaning and testing procedures)	1	0.4 (nr)	Theiss et al., 1982

continued

TABLE 5 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 month in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–2007 (ICD-9 140–149)			Manuwald et al., 2012
Colon (ICD-9 153)	12	0.7 (0.4–1.3)	
Men	7	0.6 (0.3–1.3)	
Women	5	0.9 (0.3–2.1)	
Rectum, rectosigmoid junction, anus (ICD-9 154)	13	1.7 (0.9–2.9)	
Men	11	2.0 (0.98–3.5)	
Women	2	1.0 (0.1–3.7)	
Mortalilty 1952–1989			Becher et al., 1996
Colon	2	0.4 (0.1–1.4)	
Rectum	6	1.9 (0.7–4.0)	
Mortality 1952–1989—stats on men only, 1,184 (tables for 1,148 men, not necessarily German nationals) vs national rates (also vs gas workers); same observation period as Becher et al., 1966			Manz et al., 1991
Colon	8	0.9 (0.4–1.8)	
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Large intestine			
Ever-exposed workers	3	0.6 (0.1–1.7)	
Never-exposed workers	0	0.0 (0.0–2.0)	
Rectum			
Ever-exposed workers	6	2.0 (0.7–4.4)	
Never-exposed workers	2	2.1 (0.3–7.7)	
Production Workers (713 men and 100 women worked > 1 month in 1969–1984)			
Mortality 1969–2000			't Mannetje et al., 2005
Phenoxy herbicide producers (men and women)			
Colon	2	0.6 (0.0–2.3)	
Rectum, rectosigmoid junction, anus	5	2.5 (0.8–5.7)	
Phenoxy herbicide sprayers (> 99% men)			
Colon	8	1.9 (0.8–3.8)	
Rectum, rectosigmoid junction, anus	4	1.5 (0.4–3.8)	
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993			Steenland et al., 1999
Small intestine, colon	34	1.2 (0.8–1.6)	
Rectum	6	0.9 (0.3–1.9)	

TABLE 5 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Through 1987			Fingerhut et al., 1991
Entire NIOSH cohort			
Small intestine, colon	25	1.2 (0.8–1.8)	
Rectum	5	0.9 (0.3–2.1)	
≥ 1-year exposure, ≥ 20-year latency			
Small intestine, colon	13	1.8 (1.0–3.0)	
Rectum	2	1.2 (0.1–4.2)	
Mortality, colon cancer—754 Monsanto workers, among most highly exposed workers from Fingerhut et al. (1991)	3	0.5 (0.1–1.3)	Collins et al., 1993
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, Michigan) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1937–2011 Potential dioxin exposure (n = 2,192), TCP production (n = 1,419), PCP production (n = 577), Both TCP and PCP (n = 196)			Collins et al., 2016
TCP or PCP, Large Intestinal Cancer (ICD-10 C18)	31	1.13 (0.77–1.61)	
TCP, Large Intestinal Cancer (ICD-10 C18)	22	1.11 (0.69–1.67)	
PCP, Large Intestinal Cancer (ICD-10 C18)	12	1.23 (0.64–2.15)	
TCP or PCP, Rectal Cancer (ICD-10 C15)	4	0.68 (0.18–1.73)	
TCP, Rectal Cancer (ICD-10 C15)	3	0.72 (0.15–2.11)	
PCP, Rectal Cancer (ICD-10 C15)	1	0.44 (0.01–2.48)	
1942–2003 (n = 1,615)			Collins et al., 2009b
Large intestine	18	1.2 (0.7–1.8)	
Rectum	2	0.6 (0.1–2.1)	
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, Washington, and Wichita, Kansas) and workers who made PCP and TCP at two additional plants (in Midland, Michigan, and Sauget, Illinois)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
Intestine (ICD-9 152–153)			
1940–2005 (n = 2,122)	26	1.1 (0.7–1.6)	
PCP and TCP (n = 720)	11	1.4 (0.7–2.6)	
PCP (no TCP) (n = 1,402)	15	0.9 (0.5–1.5)	
Rectum (ICD-9 154)			
1940–2005 (n = 2,122)	2	0.4 (0.0–1.3)	
PCP and TCP (n = 720)	1	0.5 (0.0–3.0)	
PCP (no TCP) (n = 1,402)	1	0.3 (0.0–1.5)	
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)			Burns CJ et al., 2011
Colon	16	1.0 (0.6–1.6)	
Rectum	6	0.8 (0.3–1.7)	
Through 1982 (n = 878)			Bond et al., 1988
Colon	4	2.1 (0.6–5.4)	
Rectum	1	1.7 (0.0–9.3)	

continued

TABLE 5 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Dow PCP Production Workers (1937–1989 in Midland, Michigan) (**not** in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)			Collins et al., 2009c
Large intestine	10	1.2 (0.6–2.3)	
Rectum	1	0.5 (0.0–2.9)	
Mortality 1940–1989 (n = 770)			Ramlow et al., 1996
0-year latency			
Colon	4	0.8 (0.2–2.1)	
Rectum	0	nr	
15-year latency			
Colon	4	1.0 (0.3–2.6)	
Rectum	0	nr	
Other Studies of Industrial Workers (not related to IARC or NIOSH phenoxy cohorts)			
1,412 white male US Flavor and fragrance chemical plant workers (1945–1965)		**Dioxin, 2,4,5-T**	Thomas, 1987
Colon	4	0.6 (nr)	
Rectum	6	2.5 (nr)	
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Colon	62	0.7 (0.6–1.0)	
Rectum	60	0.9 (0.7–1.1)	
Danish paper workers			Rix et al., 1998
Men			
Colon	58	1.0 (0.7–1.2)	
Rectum	43	0.9 (0.6–1.2)	
Women			
Colon	23	1.1 (0.7–1.7)	
Rectum	15	1.5 (0.8–2.4)	
New Hampshire pulp and paper workers, 883 white men working ≥ 1 year, mortality through July 1985			Henneberger et al., 1989
Colon	9	1.0 (0.5–2.0)	
Rectum	1	0.4 (0.0–2.1)	
Pulp and Paper cohorts independent of IARC cohort			
United Paperworkers International, 201 white men employed ≥ 10 year and dying 1970–1984			Solet et al., 1989
Colon	7	1.5 (0.6–3.0)	
Northwestern US paper and pulp workers—5 mills in Washington, Oregon, and California, 3,523 worked ≥ 1 year 1945–1955, mortality through March 1977			Robinson et al., 1986
Intestines (ICD-7 152, 153)	7	0.4 (0.2–0.7)	

TABLE 5 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed			
Colon	277	0.7 ($p < 0.05$)	
Rectum	309	0.8 ($p < 0.05$)	
Employee			
Colon	45	0.6 ($p < 0.05$)	
Rectum	55	0.8 (nr)	
Women			
Self-employed			
Colon	14	0.9 (nr)	
Rectum	5	0.6 (nr)	
Employee			
Colon	112	0.9 (nr)	
Rectum	55	0.8 (nr)	
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000			Swaen et al., 2004
Colon	7	1.0 (0.4–2.1)	
Rectum	5	2.1 (0.7–4.8)	
Through 1987			Swaen et al., 1992
Colon	4	2.6 (0.7–6.5)	
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)			Torchio et al., 1994
Colon	84	0.6 (0.5–0.7)	
Rectum	nr	nr	
Italian rice growers with documented phenoxy use (n = 1,487)		**Phenoxy herbicides**	Gambini et al., 1997
Intestines	27	1.1 (0.7–1.6)	
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of incident cancer cases (colon, rectum, or small intestine) vs remainder of 19,904 men with any incident cancer			Reif et al., 1989
Forestry workers (n = 134)		**Herbicides**	
Colon	7	0.5 (0.2–1.1)	
Rectum	10	1.2 (0.6–2.3)	
Small intestine	2	5.2 (1.4–18.9)	
Aged 20–59	2	11.2 (3.4–36.4)	
Aged ≥ 60	0	—	
Sawmill workers (n = 139)		**Herbicides, chlorophenols**	
Small intestine	0	—	

continued

TABLE 5 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
SWEDEN			
Incident cancer cases 1961–1973 with agriculture as economic activity in 1960 census			Wiklund, 1983
Colon	1,332		
Rectum		99% CI	
	1,083	0.8 (0.7–0.8)	
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Colon			
Men			
Whites (n = 119,648)	2,291	1.0 (0.9–1.0)	
Nonwhites (n = 11,446)	148	0.8 (0.7–0.9)	
Women			
Whites (n = 2,400)	59	1.0 (0.8–1.3)	
Nonwhites (n = 2,066)	40	1.0 (0.7–1.3)	
Rectum			
Men			
Whites (n = 119,648)	367	1.0 (0.9–1.1)	
Nonwhites (n = 11,446)	22	0.7 (0.5–1.1)	
Women			
Whites (n = 2,400)	4	0.5 (0.1–1.3)	
Nonwhites (n = 2,066)	5	1.1 (0.3–2.5)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Colon			
Private applicators	339	0.9 (0.8–1.0)	
Commercial applicators	17	1.0 (0.6–1.6)	
Spouses	144	0.8 (0.7–1.0)	
Rectum			
Private applicators	117	0.9 (0.7–1.1)	
Commercial applicators	8	1.2 (0.5–2.3)	
Spouses	30	0.7 (0.5–1.0)	
Enrollment through 2005—Interactions between dicamba and body mass index			Andreotti et al., 2010
Trend (with dicamba use reported)	96	1.1 (1.0–1.1)	
Trend (with no dicamba use reported)	102	1.0 (1.0–1.1)	
Enrollment through 2005—colorectal cancer			Lee WJ et al., 2007
2,4-D	204	0.7 (0.5–0.9)	
2,4,5-T	65	0.9 (0.7–1.2)	
2,4,5-TP	24	0.8 (0.5–1.2)	
Dicamba	110	0.9 (0.7–1.2)	

TABLE 5 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Enrollment through 2002—colon cancer			Samanic et al., 2006
Dicamba—lifetime days exposure			
None	76	1.0	
1– < 20	9	0.4 (0.2–0.9)	
20– < 56	20	0.9 (0.5–1.5)	
56– < 116	13	0.8 (0.4–1.5)	
≥ 116	17	1.4 (0.8–2.9)	
		p-trend = 0.10	
Dicamba—intensity-weighted quartiles			
None	76	1.0	
Lowest	16	0.6 (0.4–1.1)	
Second	17	0.7 (0.4–1.2)	
Third	6	0.5 (0.2–1.2)	
Highest	20	1.8 (1.0–3.1)	
		p-trend = 0.02	
Enrollment through 2002			Alavanja et al., 2005
Colon			
Private applicators (men, women)	208	0.9 (0.8–1.0)	
Spouses of private applicators (> 99% women)	87	0.9 (0.7–1.1)	
Commercial applicators (men, women)	12	0.2 (0.6–2.1)	
Rectum			
Private applicators (men, women)	94	0.8 (0.7–1.0)	
Spouses of private applicators (> 99% women)	23	0.6 (0.4–0.9)	
Commercial applicators (men, women)	7	1.3 (0.5–2.6)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Intestine			
Applicators (n = 1,641)	158	0.8 (0.6–0.9)	
Spouses (n = 676)	68	0.9 (0.7–1.1)	
Rectum			
Applicators (n = 1,641)	32	0.7 (0.5–1.0)	
Spouses (n = 676)	4	nr	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Colon			
Private applicators (men, women)	56	0.7 (0.6–1.0)	
Spouses of private applicators (> 99% women)	31	1.2 (0.8–1.6)	
Rectum			
Private applicators (men, women)	nr	nr	
Spouses of private applicators (> 99% women)	nr	nr	
US Department of Agriculture Workers—nested case-control study of white men dying 1970–1979 of cancer		**Herbicides**	
Agricultural extension agents			Alavanja et al., 1988
Colon	41	1.0 (0.7–1.5)	
Rectum	5	nr	
Forest conservationists			Alavanja et al., 1989
Colon	44	1.5 (1.1–2.0)	
Rectum	9	1.0 (0.5–1.9)	

continued

TABLE 5 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Florida Licensed Pesticide Applicators [common phenoxy use assumed but not documented; had been listed by Blair et al., 1983]		**Herbicides**	
Pesticide applicators in Florida licensed 1965–1966 (n = 3,827)—mortality through 1976		**Herbicides**	Blair et al., 1983
Any pesticide (dose-response by length of licensure)			
Colon	5	0.8 (nr)	
Rectum	2	nr	
White Male Residents of Iowa—colon cancer on death certificate, usual occupation: farmers vs not		**Herbicides**	
> 20 years old when died 1971–1978—PMR			Burmeister, 1981
Colon	1,064	0.9 (0.9–1.0)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Incidence			
20-year followup to 1996—men and women			
Zone A			Pesatori et al., 2009
Colon	2	0.7 (0.2–2.7)	
Rectum	0		
Zone B			
Colon	19	1.0 (0.7–1.6)	
Rectum	17	1.8 (1.1–2.9)	
Zone R			
Colon	137	1.0 (0.9–1.3)	
Rectum	71	1.1 (0.8–1.4)	
10-year followup to 1991—men			Bertazzi et al., 1993
Zone B			
Colon	2	0.5 (0.1–2.0)	
Rectum	3	1.4 (0.4–4.4)	
Zone R			
Colon	32	1.1 (0.8–1.6)	
Rectum	17	1.1 (0.7–1.9)	
10-year followup to 1991—women			Bertazzi et al., 1993
Zone B			
Colon	2	0.6 (0.1–2.3)	
Rectum	2	1.3 (0.3–5.4)	
Zone R			
Colon	23	0.8 (0.5–1.3)	
Rectum	7	0.6 (0.3–1.3)	

TABLE 5 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Mortality			
25-year followup to 2001—men and women			Consonni et al., 2008
Zone A			
Colon	3	1.0 (0.3–3.0)	
Rectum	1	0.9 (0.1–6.4)	
Zone B			
Colon	12	0.6 (0.3–1.1)	
Rectum	11	1.5 (0.8–2.8)	
Zone R			
Colon	137	0.9 (0.7–1.3)	
Rectum	50	0.9 (0.7–1.3)	
20-year followup to 1996			Bertazzi et al., 2001
Zones A and B—men			
Colon	10	1.0 (0.5–1.9)	
Rectum	9	2.4 (1.2–4.6)	
Zones A and B—women			
Colon	5	0.6 (0.2–1.4)	
Rectum	3	1.1 (0.4–3.5)	
15-year followup to 1991—men			Bertazzi et al., 1997
Zone B			
Colon	5	0.8 (0.3–2.0)	
Rectum	7	2.9 (1.2–5.9)	
Zone R			
Colon	34	0.8 (0.6–1.1)	
Rectum	19	1.1 (0.7–1.8)	
15-year followup to 1991—women			Bertazzi et al., 1997
Zone A			
Colon	2	2.6 (0.3–9.4)	
Zone B			
Colon	3	0.6 (0.1–1.8)	
Rectum	2	1.3 (0.1–4.5)	
Zone R			
Colon	33	0.8 (0.6–1.1)	
Rectum	12	0.9 (0.5–1.6)	
10-year followup to 1986—men			Bertazzi et al., 1989a,b
Zone A, B, R—colon	20	1.0 (0.6–1.5)	
Zone A, B, R—rectum	10	1.0 (0.5–2.7)	
Zone B—rectum	2	1.7 (0.4–7.0)	
10-year followup to 1986—women			Bertazzi et al., 1989a
Zone A, B, R—colon	12	0.7 (0.4–1.2)	
Zone A, B, R—rectum	7	1.2 (0.5–2.7)	

continued

TABLE 5 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Ecological Study of Residents of Chapaevsk, Russia		**Dioxin**	Revich et al., 2001
Incidence— Crude incidence rate in 1998 vs			
Men			
Regional (Samara)			
Colon	nr	21.7 (nr)	
Rectum	nr	17.1 (nr)	
National (Russia)			
Colon	nr	17.9 (nr)	
Rectum	nr	16.6 (nr)	
Women			
Regional (Samara)			
Colon	nr	15.4 (nr)	
Rectum	nr	11.2 (nr)	
National (Russia)			
Colon	nr	14.1 (nr)	
Rectum	nr	10.3 (nr)	
Mortality—1995–1998		SMR vs regional rates	
Men			
Colon	17	1.3 (0.8–2.2)	
Rectum	21	1.5 (1.0–2.4)	
Women			
Colon	24	1.0 (0.7–1.5)	
Rectum	24	0.9 (0.6–1.4)	
FINLAND			
Finnish community exposed to chlorophenol contamination (men and women)		**Chlorophenol**	Lampi et al., 1992
Colon—men, women	9	1.1 (0.7–1.8)	
Finnish fishermen (n = 6,410) and spouses (n = 4,260) registered between 1980 and 2002 compared to national statistics		**Serum dioxin**	Turunen et al., 2008
Fisherman		SMRs	
Colon	8	0.5 (0.2–1.0)	
Rectum	8	0.8 (0.4–1.6)	
Spouses			
Colon	10	1.3 (0.6–2.4)	
Rectum	8	2.1 (0.9–4.2)	
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995a
Incidence			
East coast			
Colon	5	0.4 (0.1–0.9)	
Rectum	9	0.9 (0.4–1.6)	
West coast			
Colon	82	1.0 (0.8–1.2)	
Rectum	59	1.1 (0.8–1.4)	

TABLE 5 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Mortality			
East coast			
Colon	1	0.1 (0.0–0.7)	
Rectum	4	0.7 (0.2–1.9)	
West coast			
Colon	58	1.0 (0.8–1.3)	
Rectum	31	1.0 (0.7–1.5)	
CASE-CONTROL STUDIES			
International Case-Control Studies			
421 **Egyptian** colorectal cancer cases and 439 hospital controls	nr	**Herbicides** 5.5 (2.4–12.3)	Lo et al., 2010
Swedish patients (1970–1977)		**Phenoxy acids, chlorophenols**	Hardell, 1981
Colon			
Exposed to phenoxy herbicides	11	1.3 (0.6–2.8)	
Exposed to chlorophenols	6	1.8 (0.6–5.3)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,4,5-TP, 2-(2,4,5-trichlorophenoxy) propionic acid; 2,5-DCP, 2,5-dichlorophenol; AFHS, Air Force Health Study; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job-exposure matrix; MCPA, methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; n, number; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; PMR, proportionate mortality ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

TABLE 6 Selected Epidemiologic Studies—Hepatobiliary Cancers (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Mortality			
1965–2000—liver, intrahepatic bile ducts (ICD-9 155)	5	nr	Boehmer et al., 2004
US CDC Selected Cancers Study—case-control study of incidence (Dec 1, 1984–Nov 30, 1989) among US males born 1929–1953	8	**All COIs** 1.2 (0.5–2.7)	CDC, 1990a
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1982—liver, bile duct			Breslin et al., 1988
Army, deployed (n = 19,708) vs nondeployed (n = 22,904)	34	1.0 (0.8–1.4)	
Marine Corps, deployed (n = 4,527) vs nondeployed (n = 3,781)	6	1.2 (0.5–2.8)	
State Studies of US Vietnam Veterans			
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans	0	nr	Anderson et al., 1986a,b
Retrospective review of 390 patients within the Dayton, Ohio VAMC with chronic hepatitis C related cirrhosis and hepatocellular cancer.	79	1.76 (0.85–3.64)	Krishnamurthy et al., 2016
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/ 23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	27	0.7 (0.4–1.9)	ADVA, 2005b
Navy	8	1.0 (0.4–1.9)	
Army	18	0.7 (0.4–1.1)	
Air Force	1	0.2 (0.0–1.2)	
Mortality			
All branches, return–2001	48	0.9 (0.6–1.1)	ADVA, 2005a
Navy	11	1.0 (0.5–1.7)	
Army	33	0.9 (0.6–1.2)	
Air Force	4	0.6 (0.2–1.5)	
1980–1994			CDVA, 1997a
Liver (ICD-9 155)	8	0.6 (0.2–1.1)	
Gallbladder (ICD-9 156)	5	1.3 (0.4–2.8)	
Australian Conscripted Army National Service 18,940 deployed vs 24,642 nondeployed		**All COIs**	
Incidence			
1982–2000	2	2.5 (0.1–147.2)	ADVA, 2005c
Mortality			
1966–2001 (liver, gallbladder)	4	2.5 (0.4–27.1)	ADVA, 2005c
1982–1994	1	nr	CDVA, 1997b

TABLE 6 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual exposure opportunity scores)		**All COIs**	
		HRs	
Incidence (1992–2003)—categorized high (n = 85,809) vs low (n = 94,442)			Yi and Ohrr, 2014
Liver (C22)	1,023	1.1 (1.0–1.2)	
Gall bladder, etc. (C23–C24)	125	1.2 (0.9–1.6)	
Mortality (1992–2005)—categorized high (n = 85,809) vs low (n = 94,442)			Yi et al., 2014b
HR per unit of log EOI (n = 2,053)			
Liver (C22)	2,053	1.0 (1.0–1.1)	
Gallbladder (C23–C24)	215	1.1 (1.0–1.1)	
High exposure vs low exposure			
Liver (C22) (1,107 vs 946)		1.1 (1.0–1.2)	
Gallbladder (C23–C24) (120 vs 95)		1.2 (0.9–1.6)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	15	0.7 (0.4–1.2)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	12	0.9 (0.5–1.5)	
7,553 not exposed to highly chlorinated PCDDs	3	0.4 (0.1–1.2)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort			Saracci et al., 1991
Liver, gallbladder, bile duct (ICD-8 155–156)	4	0.4 (0.1–1.1)	
British MCPA Plant—All manual employees employed January 1947–December 1975 (n = 1,146), ever potentially exposed to phenoxy herbicides (n = 1,544), potentially exposed to phenoxy herbicides ≥ 1 year (n = 848) (not included in IARC cohort)			
Mortality through 2012, all workers			Coggon et al., 2015
Liver cancer (ICD-10 C22)	20	1.24 (0.76–1.91)	
Mortality through 2012, workers ever exposed to phenoxy herbicides			
Liver cancer (ICD-10 C22)	14	1.14 (0.62–1.91)	
Mortality through 2012, workers ever exposed to phenoxy herbicides ≥ 1 year			
Liver cancer (ICD-10 C22)	4	0.72 (0.20–1.85)	
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence 1943–1982			Lynge, 1985
Men	3	1.0 (nr)	
Women	0	nr	
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 month in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992	0	—	Becher et al., 1996

continued

TABLE 6 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 month in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1965–1989	0	—	Becher et al., 1996
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 month in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1956–1989	1	1.2 (0.0–6.9)	Becher et al., 1996
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Incidence			
1960–1992—liver, gallbladder, bile duct	2	2.1 (0.3–7.5)	Ott and Zober, 1996a
TCDD < 0.1 μg/kg of body weight	1	2.8 (0.1–15.5)	
TCDD 0.1–0.99 μg/kg of body weight	0	0.0 (0.0–15.4)	
TCDD > 1 μg/kg of body weight	1	2.8 (0.1–15.5)	
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 month in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortalilty 1952–1989	0	—	Becher et al., 1996
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	2	1.4 (0.2–5.1)	
Never-exposed workers	0	0.0 (0.0–8.2)	
Production Workers (713 men and 100 women worked > 1 month in 1969–1984)			
Mortality 1969–2000—ICD-9 155			't Mannetje et al., 2005
Phenoxy herbicide producers (men and women)	1	1.6 (0.0–8.8)	
Phenoxy herbicide sprayers (> 99% men)	0	0.0 (0.0–4.2)	
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993			Steenland et al., 1999
Liver, biliary tract (ICD-9 155–156)	7	0.9 (0.4–1.6)	
Through 1987 (liver, biliary tract)	6	1.2 (0.4–2.5)	Fingerhut et al., 1991
≥ 1-year exposure, ≥ 20-year latency	1	0.6 (0.0–3.3)	
Mortality—754 Monsanto workers, among most highly exposed workers from Fingerhut et al. (1991); liver, biliary tract	2	1.4 (0.2–5.2)	Collins et al., 1993
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, Michigan) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)	2	0.5 (0.1–1.6)	Collins et al., 2009b
March 1949–1978 (n = 121); 121 TCP workers with chloracne	0	nr	Zack and Suskind, 1980
Through 1982 (n = 878); liver, biliary tract (ICDA-8 155–156)	0	1.2 (nr)	Bond et al., 1988

TABLE 6 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, Washington, and Wichita, Kansas) and workers who made PCP and TCP at two additional plants (in Midland, Michigan, and Sauget, Illinois)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122) (liver and biliary; ICD–9 155–156)	9	1.2 (0.6–2.3)	
PCP and TCP (n = 720)	0	– (0.0–1.6)	
PCP (no TCP) (n = 1,402)	9	1.8 (0.8–3.4)	
Dow PCP Production Workers (1937–1989 in Midland, Michigan) (**not** in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
1937–2011 Potential dioxin exposure (n = 2,192), TCP production (n = 1,419), PCP production (n = 577), Both TCP and PCP (n = 196)			Collins et al., 2016
TCP or PCP, Biliary passages and liver (ICD-10 C18)	4	0.46 (0.13–1.18)	
TCP, Biliary passages and liver (ICD-10 C18)	4	0.62 (0.17–1.58)	
PCP, Biliary passages and liver (ICD-10 C18)	0	0.00 (0.0–1.25)	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	0	0.0 (0.0–1.7)	Collins et al., 2009c
Mortality 1940–1989 (n = 770); liver, primary (ICDA-8 155–156)			Ramlow et al., 1996
0-year latency	0	nr	
15-year latency	0	nr	
Other Studies of Industrial Workers (*not* related to IARC or NIOSH phenoxy cohort)			
Automobile workers from Hubei province in China (worked 1 year during 1980–1985)		**PCDD/F**	Wang et al., 2013
Mortality (1980–2005) (n = 3,529)	32	1.7 (1.2–2.4)	
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	27	0.9 (0.6–1.3)	
Ever	16	0.7 (0.4–1.1)	
Danish paper workers			Rix et al., 1998
Men			
Liver	10	1.1 (0.5–2.0)	
Gallbladder	9	1.6 (0.7–3.0)	
Women			
Liver	1	0.6 (0.0–3.2)	
Gallbladder	4	1.4 (0.4–3.7)	
Pulp and Paper cohorts independent of IARC cohort			
United Paperworkers International, 201 white men employed ≥ 10 year and dying 1970–1984	2	2.0 (0.2–7.3)	Solet et al., 1989

continued

TABLE 6 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Liver			
Self-employed	23	0.4 ($p < 0.05$)	
Employee	9	0.8 (nr)	
Gallbladder			
Self-employed	35	0.8 (nr)	
Employee	7	0.8 (nr)	
Women			
Liver			
Family workers	5	0.5 (nr)	
Gallbladder			
Self-employed	7	2.7 ($p < 0.05$)	
Employee	1	0.7 (nr)	
Family workers	17	1.0 (nr)	
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	0	nr	Swaen et al., 2004
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 weeks) not IARC (liver, biliary tract)		**Phenoxy herbicides**	
Incidence	3	0.9 (0.2–2.6)	Asp et al., 1994
Mortality 1972–1989	2	0.6 (0.1–2.2)	
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	15	0.6 (0.3–0.9)	Torchio et al., 1994
Italian rice growers with documented phenoxy use (n = 1,487)	7	**Phenoxy herbicides** 1.3 (0.5–2.6)	Gambini et al., 1997
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of incident hepatobiliary cancer cases vs remainder of 19,904 men with any incident cancer			Reif et al., 1989
Forestry workers (n = 134)		**Herbicides**	
Liver	1	0.8 (0.1–5.8)	
Gallbladder	3	4.1 (1.4–12.0)	
Aged 20–59	1	6.3 (1.1–36.6)	
Aged ≥ 60	2	3.5 (0.9–13.3)	
Sawmill workers (n = 139)		**Herbicides, chlorophenols**	
Gallbladder	2	2.3 (0.6–9.1)	
SWEDEN			
Incident stomach cancer cases 1961–1973 with agriculture as economic activity in 1960 census		99% CI	Wiklund, 1983
Liver (primary)	103	0.3 (0.3–0.4)	
Biliary tract	169	0.6 (0.5–0.7)	
Liver (unspecified)	67	0.9 (0.7–1.3)	

TABLE 6 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides**	Blair et al., 1993
		PCMRs	
Men			
Whites (n = 119,648)	326	1.0 (0.9–1.1)	
Nonwhites (n = 11,446)	24	0.7 (0.5–1.1)	
Women			
Whites (n = 2,400)	6	0.7 (0.3–1.6)	
Nonwhites (n = 2,066)	2	0.4 (0.0–1.3)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006		SIRs	Koutros et al., 2010a
Liver			
Private applicators	32	0.7 (0.5–1.0)	
Commercial applicators	1	nr	
Spouses	6	0.8 (0.3–1.7)	
Gallbladder			
Private applicators	8	1.3 (0.6–2.6)	
Commercial applicators	0	nr	
Spouses	7	1.1 (0.4–2.3)	
Enrollment through 2002			Alavanja et al., 2005
Liver			
Private applicators (men, women)	35	1.0 (0.7–1.4)	
Spouses of private applicators (> 99% women)	3	0.9 (0.2–2.5)	
Commercial applicators (men, women)	nr	0.0 (0.0–4.2)	
Gallbladder			
Private applicators (men, women)	8	2.3 (1.0–4.5)	
Spouses of private applicators (> 99% women)	3	0.9 (0.2–2.5)	
Commercial applicators (men, women)	nr	0.0 (0.0–35.8)	
Mortality			
Enrollment through 2007, vs state rates (liver and gallbladder)			Waggoner et al., 2011
Applicators (n = 1,641)	50	0.7 (0.5–0.9)	
Spouses (n = 676)	18	0.8 (0.5–1.3)	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Liver			
Private applicators (men, women)	8	0.6 (0.2–1.1)	
Spouses of private applicators (> 99% women)	4	1.7 (0.4–4.3)	
Rectum			
Private applicators (men, women)	3	2.0 (0.4–5.7)	
Spouses of private applicators (> 99% women)	2	1.3 (0.1–4.6)	

continued

TABLE 6 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Incidence			
20-year followup to 1996—men and women			Pesatori et al., 2009
Zone A			
Liver	0		
Biliary	0		
Zone B			
Liver	14	1.3 (0.8–2.2)	
Biliary	6	2.3 (1.0–5.2)	
Zone R			
Liver	56	0.7 (0.6–1.0)	
Biliary	16	0.8 (0.5–1.4)	
10-year followup to 1991—men			Bertazzi et al., 1993
Zone B			
Liver	4	2.1 (0.8–5.8)	
Gallbladder (ICD-9 156)	1	2.3 (0.3–17.6)	
Zone R			
Liver	3	0.2 (0.1–0.7)	
Gallbladder (ICD-9 156)	3	1.0 (0.3–3.4)	
10-year followup to 1991—women			Bertazzi et al., 1993
Zone B			
Gallbladder (ICD-9 156)	4	4.9 (1.8–13.6)	
Zone R			
Liver	2	0.5 (0.1–2.1)	
Gallbladder (ICD-9 156)	7	1.0 (0.5–2.3)	
Mortality			
25-year followup to 2001—men and women			Consonni et al., 2008
Zone A			
Liver	3	1.0 (0.3–3.2)	
Biliary	0	0.0 (nr)	
Zone B			
Liver	16	0.9 (0.5–1.4)	
Biliary	2	0.6 (0.1–2.3)	
Zone R			
Liver	107	0.8 (0.7–1.0)	
Biliary	31	1.2 (0.8–1.7)	
20-year followup to 1996			Bertazzi et al., 2001
Zones A and B—men			
Liver, gallbladder	6	0.5 (0.2–1.0)	
Liver	6	0.5 (0.2–1.1)	
Zones A and B—women			
Liver, gallbladder	7	1.0 (0.5–2.2)	
Liver	6	1.3 (0.6–2.9)	

TABLE 6 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
15-year followup to 1991—men			Bertazzi et al., 1997
Zone B			
Liver, gallbladder	4	0.6 (0.2–1.4)	
Liver	4	0.6 (0.2–1.6)	
Zone R			
Liver, gallbladder	35	0.7 (0.5–1.0)	
Liver	31	0.7 (0.5–1.0)	
15-year followup to 1991—women			Bertazzi et al., 1997
Zone B			
Liver, gallbladder	4	1.1 (0.3–2.9)	
Liver	3	1.3 (0.3–3.8)	
Zone R			
Liver, gallbladder	25	0.8 (0.5–1.3)	
Liver	12	0.6 (0.3–1.1)	
10-year followup to 1986—men			Bertazzi et al., 1989b
Zone B—liver	3	1.2 (0.4–3.8)	
Zone R—liver	7	0.4 (0.2–0.8)	
10-year followup to 1986—women			Bertazzi et al., 1989b
Zone A—gallbladder (ICD-9 156)	1	12.1 (1.6–88.7)	
Zone B—gallbladder (ICD-9 156)	2	3.9 (0.9–16.2)	
Zone R			
Liver	3	0.4 (0.1–1.4)	
Gallbladder (ICD-9 156)	5	1.2 (0.5–3.1)	
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995a
Incidence			
East coast	1	0.5 (0.0–2.7)	
West coast	9	0.9 (0.4–1.7)	
Mortality			
East coast	6	1.3 (0.5–2.9)	
West coast	24	1.0 (0.6–1.5)	
UNITED STATES			
Quail Run Mobile Home Cohort		**TCDD**	Hoffman et al., 1986
154 exposed residents vs 155 unexposed area residents	0	nr	
VIETNAM			
Risk factor for hepatocellular carcinoma in Hanoi		**Herbicides**	Cordier et al., 1993
Military service in South Vietnam for ≥ 10 years after 1960	11	8.8 (1.9–41.0)	
CASE-CONTROL STUDIES			
International Case-Control Studies			
Swedish patients (25–80 years of age) diagnosed with liver cancer (ICD-7 155, 156) between 1974–June 1981 vs national rates	102	**Phenoxy acids, chlorophenols** 1.8 (0.9–4.0)	Hardell et al., 1984

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; ICDA, *International*

continued

TABLE 6 Continued

Classification of Diseases, Adapted for Use in the United States; JEM, job-exposure matrix; MCPA, methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; n, number; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCP, pentachlorophenol; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs; VAMC, US Department of Veterans Affairs Medical Center.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

TABLE 7 Selected Epidemiologic Studies—Pancreatic Cancer (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Mortality			
1965–2000	5	1.0 (0.3–3.5)	Boehmer et al., 2004
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1982			Breslin et al., 1988
Army, deployed (n = 19,708) vs nondeployed (n = 22,904)	82	0.9 (0.6–1.2)	
Marine Corps, deployed (n = 4,527) vs nondeployed (n = 3,781)	18	1.6 (0.5–5.8)	
US VA Cohort of Female Vietnam-era Veterans served in Vietnam (n = 4,586; nurses only = 3,690); nondeployed (n = 5,325; nurses only = 3,282)		**All COIs**	
Mortality			
Through 2010—Vietnam-era veterans	50	1.7 (1.0–3.1)	Kang et al., 2014
Vietnam nurses only	35	2.1 (1.0–4.3)	
Through 2004—Vietnam-era veterans	17	2.1 (1.0–4.5)	Cypel and Kang, 2008
Vietnam-veteran nurses	14	2.5 (1.0–6.0)	
Through 1991—Vietnam-era veterans	7	2.8 (0.8–10.2)	Dalager et al., 1995a
Vietnam nurses only	7	5.7 (1.2–27.0)	
Through 1987—Vietnam-era veterans (Vietnam nurses not reported separately)	5	2.7 (0.9–6.2)	Thomas et al., 1991
State Studies of US Vietnam Veterans			
Michigan Vietnam-era veterans, PM study of deaths (1974–1989)—deployed vs nondeployed	14	1.0 (0.6–1.7)	Visintainer et al., 1995
Non-black	9	0.7 (0.3–1.3)	
Black	5	9.1 (2.9–21.2)	
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans	4	nr	Anderson et al., 1986a,b
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	86	1.2 (0.9–1.4)	ADVA, 2005b
Navy	14	0.9 (0.5–1.5)	
Army	60	1.2 (0.9–1.5)	
Air Force	12	1.3 (0.7–2.3)	
Mortality			
All branches, return–2001	101	1.2 (1.0–1.5)	ADVA, 2005a
Navy	18	1.0 (0.6–1.6)	
Army	71	1.3 (1.0–1.6)	
Air Force	11	1.1 (0.5–1.8)	
1980–1994	38	1.4 (0.9–1.8)	CDVA, 1997a

continued

TABLE 7 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Incidence			
1982–2000	17	2.5 (1.0–6.3)	ADVA, 2005c
Mortality			
1966–2001	19	3.1 (1.3–8.3)	ADVA, 2005c
1982–1994	6	1.5 (nr)	CDVA, 1997b
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008)	6	0.7 (0.3–1.6)	
Mortality (1988–2008)	5	0.7 (0.2–1.6)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores)		**All COIs**	
		HRs	
Incidence (1992–2003)—pancreas (C25) categorized high (n = 100) vs low (n = 84)	100	1.1 (0.8–1.5)	Yi and Ohrr, 2014
Mortality (1992–2005)—pancreas (C25) categorized high (n = 141) vs low (n = 114)			Yi et al., 2014b
HR per unit of log EOI (n = 180,639)	255	1.0 (1.0–1.1)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	47	0.9 (0.7–1.3)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	30	1.0 (0.7–1.4)	
7,553 not exposed to highly chlorinated PCDDs	16	0.9 (0.5–1.4)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	26	1.1 (0.7–1.6)	Saracci et al., 1991
British MCPA Plant—All manual employees employed January 1947–December 1975 (n = 1,146), ever potentially exposed to phenoxy herbicides (n = 1,544), potentially exposed to phenoxy herbicides ≥ 1 year (n = 848) (not included in IARC cohort)		**MCPA**	
Mortality through 2012, all workers			Coggon et al., 2015
Pancreas (ICD-10 C25)	54	1.04 (0.78–1.35)	
Mortality through 2012, workers ever exposed to phenoxy herbicides			
Pancreas (ICD-10 C25)	39	1.03 (0.73–1.40)	
Mortality through 2012, workers ever exposed to phenoxy herbicides ≥ 1 year			
Pancreas (ICD-10 C25)	13	0.74 (0.39–1.26)	
Mortality through 1983	9	0.7 (0.3–1.4)	Coggon et al., 1986
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence			
Incidence 1943–1982			Lynge, 1985
Men	3	0.6 (nr)	
Women	0	nr	

TABLE 7 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Mortality			
Mortality 1955–2006	7	1.2 (0.8–1.7)	Boers et al., 2012
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–2006 (HR for lagged TCDD plasma levels)	6	0.9 (0.5–1.6)	Boers et al., 2012
Mortality 1955–2006	4	0.9 (0.2–4.2)	Boers et al., 2010
Mortality 1955–1991	4	2.5 (0.7–6.3)	Hooiveld et al., 1998
Mortality 1955–1985	3	2.9 (0.6–8.4)	Bueno de Mesquita et al., 1993
Dutch production workers in Plant B (414 men exposed during production 1965–1986; 723 unexposed) (in IARC cohort)		**2,4-D; MCPA; MCP; highly chlorinated dioxins unlikely**	
Mortality 1965–2006	1	nr	Boers et al., 2010
Mortality 1965–1986	0	0.0 (0.0–10.9)	Bueno de Mesquita et al., 1993
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 month in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992	0	—	Becher et al., 1996
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 month in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1965–1989	0	—	Becher et al., 1996
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 month in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1956–1989	2	1.7 (0.2–6.1)	Becher et al., 1996
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 month in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–2007 (ICD-9 157)	10	0.9 (0.4–1.7)	Manuwald et al., 2012
Men	7	0.9 (0.4–1.9)	
Women	3	1.0 (0.2–2.9)	
Mortality 1952–1989	2	0.6 (0.1–2.3)	Becher et al., 1996
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	3	1.3 (0.3–3.9)	
Never-exposed workers	0	0.0 (0.0–4.9)	
Production Workers (713 men and 100 women worked > 1 month in 1969–1984)			
Mortality 1969–2000			't Mannetje et al., 2005
Phenoxy herbicide producers (men, women)	3	2.1 (0.4–6.1)	
Phenoxy herbicide sprayers (> 99% men)	0	0.0 (0.0–2.1)	

continued

TABLE 7 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993	16	1.0 (0.6–1.6)	Steenland et al., 1999
Through 1987	10	0.8 (0.4–1.6)	Fingerhut et al., 1991
≥ 1-year exposure, ≥ 20-year latency	4	1.0 (0.3–2.5)	
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, Michigan) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)	6	0.7 (0.2–1.4)	Collins et al., 2009b
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, Washington, and Wichita, Kansas) and workers who made PCP and TCP at two additional plants (in Midland, Michigan, and Sauget, Illinois)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122)	18	1.3 (0.8–2.0)	
PCP and TCP (n = 720)	6	1.4 (0.5–3.0)	
PCP (no TCP) (n = 1,402)	12	1.3 (0.7–2.2)	
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)	2	0.4 (0.1–1.5)	Burns CJ et al., 2011
Dow PCP Production Workers (1937–1989 in Midland, Michigan) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
1937–2011 Potential dioxin exposure (n = 2,192), TCP production (n = 1,419), PCP production (n = 577), Both TCP and PCP (n = 196)			Collins et al., 2016
TCP or PCP, Pancreas (ICD-10 C25)	10	0.58 (0.28–1.07)	
TCP, Pancreas (ICD-10 C25)	7	0.55 (0.22–1.14)	
PCP, Pancreas (ICD-10 C25)	6	1.00 (0.37–5.25)	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	5	1.1 (0.3–2.5)	Collins et al., 2009c
Mortality 1940–1989 (n = 770)			Ramlow et al., 1996
0-year latency	2	0.7 (0.1–2.7)	
15-year latency	2	0.9 (0.1–3.3)	
Other Studies of Industrial Workers (not related to IARC or NIOSH phenoxy cohorts)			
1,412 white male US Flavor and fragrance chemical plant workers (1945–1965)	6	**Dioxin, 2,4,5-T** 1.4 (nr)	Thomas, 1987
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	67	0.8 (0.7–1.1)	
Ever	69	1.1 (0.9–1.4)	
Danish paper workers			Rix et al., 1998
Men	30	1.2 (0.8–1.7)	
Women	2	0.3 (0.0–1.1)	

TABLE 7 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
New Hampshire pulp and paper workers, 883 white men working ≥ 1 year, mortality through July 1985	9	1.9 (0.9–3.6)	Henneberger et al., 1989
United Paperworkers International, 201 white men employed ≥ 10 year and dying 1970–1984	1	0.4 (0.0–2.1)	Solet et al., 1989
Northwestern US paper and pulp workers—5 mills in Washington, Oregon, and California, 3,523 worked ≥ 1 year 1945–1955, mortality through March 1977	4	90% CI 0.3 (0.1–0.8)	Robinson et al., 1986
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	137	0.6 ($p < 0.05$)	
Employee	23	0.6 ($p < 0.05$)	
Women			
Self-employed	7	1.2 (nr)	
Employee	4	1.3 (nr)	
Family workers	27	0.7 ($p < 0.05$)	
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	5	1.2 (0.4–2.7)	Swaen et al., 2004
Through 1987	3	2.2 (0.4–6.4)	Swaen et al., 1992
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	32	0.7 (0.5–1.0)	Torchio et al., 1994
Italian rice growers with documented phenoxy use (n = 1,487)	7	**Phenoxy herbicides** 0.9 (0.4–1.9)	Gambini et al., 1997
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of incident pantreatic cancer cases vs remainder of 19,904 men with any incident cancer		**Herbicides**	Reif et al., 1989
Forestry workers (n = 134)	6	1.8 (0.8–4.1)	
Aged 20–59	0	—	
Aged ≥ 60	6	2.4 (1.1–5.4)	
		Herbicides, chlorophenols	
Sawmill workers (n = 139)	2	0.5 (0.1–1.8)	
SWEDEN			
Incident pancreatic cancer cases 1961–1973 with agriculture as economic activity in 1960 census	777	99% CI 0.8 (0.8–0.9)	Wiklund, 1983
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	1,133	1.1 (1.1–1.2)	
Nonwhites (n = 11,446)	125	1.2 (1.0–1.4)	
Women			
Whites (n = 2,400)	23	1.0 (0.6–1.5)	
Nonwhites (n = 2,066)	16	0.7 (0.4–1.2)	

continued

TABLE 7 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	80	0.7 (0.6–0.9)	
Commercial applicators	5	1.0 (0.3–2.3)	
Spouses	32	0.7 (0.5–1.0)	
Nested case-control (applicators, spouses combined)			Andreotti et al., 2009
2,4-D	48	0.9 (0.5–1.5)	
Dicamba	23	0.9 (0.6–1.6)	
Enrollment through 2002			Alavanja et al., 2005
Private applicators	46	0.7 (0.5–1.0)	
Spouses of private applicators (> 99% women)	20	0.9 (0.6–1.4)	
Commercial applicators	3	1.1 (0.2–3.2)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	171	0.8 (0.7–1.0)	
Spouses (n = 676)	1	nr	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	29	0.6 (0.4–0.9)	
Spouses of private applicators (> 99% women)	10	0.7 (0.3–1.2)	
US Department of Agriculture Workers—nested case-control study of white men dying 1970–1979 of pancreatic cancer		**Herbicides**	
Agricultural extension agents	21	1.3 (0.8–1.9)	Alavanja et al., 1988
Forest conservationists	22	1.5 (0.9–2.3)	Alavanja et al., 1989
Florida Licensed Pesticide Applicators (common phenoxy use assumed but not documented; had been listed by Blair et al., 1983)		**Herbicides**	
Pesticide applicators in Florida licensed 1965–1966 (n = 3,827)—mortality through 1976		*Expected exposed cases*	Blair et al., 1983
Any pesticide (dose-response by length of licensure)	4	4.0	
White Male Residents of Iowa—pancreatic cancer on death certificate, usual occupation: farmers vs not		**Herbicides**	
> 20 years old when died 1971–1978—PMR	416	1.1 (nr)	Burmeister, 1981

TABLE 7 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group)		**TCDD**	
Incidence			
20-year followup to 1996—men and women			
Zone A	1	1.2 (0.2–8.2)	Pesatori et al., 2009
Zone B	3	0.6 (0.2–1.7)	
Zone R	38	1.0 (0.7–1.4)	
10-year followup to 1991—men			Pesatori et al., 1992
Zone A, B	2	1.0 (0.3–4.2)	
10-year followup to 1991—women			Pesatori et al., 1992
Zone A, B	1	1.6 (0.2–12.0)	
Mortality			
25-year followup to 2001—men and women			Consonni et al., 2008
Zone A	2	1.2 (0.3–4.7)	
Zone B	5	0.5 (0.2–1.1)	
Zone R	76	1.0 (0.7–1.7)	
20-year followup to 1996			Bertazzi et al., 2001
Zones A and B—men	4	0.7 (0.3–1.9)	
Zones A and B—women	1	0.3 (0.0–2.0)	
15-year followup to 1991—men			Bertazzi et al., 1997
Zone A	1	1.9 (0.0–10.5)	
Zone B	2	0.6 (0.1–2.0)	
Zone R	20	0.8 (0.5–1.2)	
15-year followup to 1991—women			Bertazzi et al., 1997
Zone B	1	0.5 (0.0–3.1)	
Zone R	11	0.7 (0.4–1.3)	
10-year followup to 1986—men			Bertazzi et al., 1989a,b
Zone A, B, R	9	0.6 (0.3–1.2)	
Zone B	2	1.1 (0.3–2.7)	
10-year followup to 1986—women			Bertazzi et al., 1989a
Zone A, B, R	4	1.0 (0.3–2.7)	
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995a,b
Incidence			
East coast	4	0.6 (0.2–1.6)	
West coast	37	1.0 (0.7–1.4)	
Mortality			
East coast	5	0.7 (0.2–1.6)	
West coast	33	0.8 (0.6–1.2)	

continued

TABLE 7 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
CASE-CONTROL STUDIES			
International Case-Control Studies			
UK men, 18–35 years of age from counties with particular chemical manufacturing—mortality		**Herbicides, Chlorophenols**	Magnani et al., 1987
Herbicides	nr	0.7 (0.3–1.5)	
Chlorophenols	nr	0.8 (0.5–1.4)	
Australia Queensland [Australia] Pancreatic Cancer Study. January 2007 to June 2011 504 confirmed pancreatic cancer cases and 643 controls exposure to nitrosamines and occupational use of pesticides.		**Phenoxy herbicide**	Fritschi et al., 2015
Pancreatic cancer ever occupationally exposed to phenoxy herbicides vs never exposed	19	0.93 (0.50–1.74)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,5-DCP, 2,5-dichlorophenol; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job-exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; n, number; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCDF, polychlorinated dibenzofuran; PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; PM, proportionate mortality; PMR, proportionate mortality ratio; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; UK, United Kingdom; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

TABLE 8 Selected Epidemiologic Studies—Laryngeal Cancer (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Mortality			
1965–2000	0	0.0 (nr)	Boehmer et al., 2004
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1988	50	1.3 (nr)	Watanabe and Kang, 1996
Army, deployed (n = 27,596) vs nondeployed (n = 31,757)	50	1.4 ($p < 0.05$)	
Marine Corps, deployed (n = 6,237) vs nondeployed (n = 5,040)	4	0.7 (nr)	
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	97	1.5 (1.2–1.8)	ADVA, 2005b
Navy	21	1.5 (0.9–2.1)	
Army	69	1.6 (1.2–1.9)	
Air Force	7	0.8 (0.3–1.7)	
Mortality			
All branches, return–2001	28	1.1 (0.7–1.5)	ADVA, 2005a
Navy	6	1.1 (0.4–2.4)	
Army	19	1.1 (0.7–1.7)	
Air Force	3	0.9 (0.2–2.5)	
1980–1994	12	1.3 (0.7–2.2)	CDVA, 1997a
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Incidence			
1982–2000	8	0.7 (0.2–1.6)	ADVA, 2005c
Mortality			
1966–2001	2	0.4 (0.0–2.4)	ADVA, 2005c
1982–1994	0	0 (0– > 10)	CDVA, 1997b
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008)	5	1.2 (0.4–2.8)	
Mortality (1988–2008)	2	2.0 (0.2–7.4)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores)		**All COIs**	
		HRs	
Incidence (1992–2003)—larynx (C32) categorized high (n = 87) vs low (n = 67)	87	1.2 (0.9–1.7)	Yi and Ohrr, 2014
Mortality (1992–2005)—larynx (C32) categorized high (n = 50) vs low (n = 32)		1.3 (0.8–2.0)	Yi et al., 2014b
HR per unit of log EOI (n = 180,639)	82	1.1 (1.0–1.3)	

continued

TABLE 8 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	21	1.6 (1.0–2.5)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	15	1.7 (1.0–2.8)	
7,553 not exposed to highly chlorinated PCDDs	5	1.2 (0.4–2.9)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	8	1.5 (0.6–2.9)	Saracci et al., 1991
British MCPA Plant—All manual employees employed January 1947–December 1975 (n = 1,146), ever potentially exposed to phenoxy herbicides (n = 1,544), potentially exposed to phenoxy herbicides ≥ 1 year (n = 848) (not included in IARC cohort)		**MCPA**	
Mortality through 2012, all workers			
Larynx (ICD-10 C32)	7	0.66 (0.26–1.35)	Coggon et al., 2015
Mortality through 2012, workers ever exposed to phenoxy herbicides			
Larynx (ICD-10 C32)	7	0.91 (0.36–1.87)	
Mortality through 2012, workers ever exposed to phenoxy herbicides ≥ 1 year			
Larynx (ICD-10 C32)	3	3.6 (0.17–2.44)	
Mortality through 1983	4	1.7 (0.5–4.5)	Coggon et al., 1986
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 month in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–2007	7	3.5 (1.4–7.2)	Manuwald et al., 2012
Men	6	3.8 (1.4–8.2)	
Women	1	2.5 (0.0–13.9)	
Mortality 1952–1989—stats on men only, 1,184 (tables all for 1,148 men, not necessarily German nationals) vs national rates (also vs gas workers); same observation period as Becher et al., 1966	2	2.0 (0.2–7.1)	Manz et al., 1991
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	1	2.5 (0.1–14.0)	
Never-exposed workers	1	9.7 (0.2–54.3)	
Production Workers (713 men and 100 women worked > 1 month in 1969–1984)			
Mortality 1969–2000	0	nr	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1987	7	2.1 (0.8–4.3)	Fingerhut et al., 1991
≥ 1-year exposure, ≥ 20-year latency	3	2.7 (0.6–7.8)	

TABLE 8 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, Michigan) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)	3	1.3 (0.3–3.9)	Collins et al., 2009b
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, Washington, and Wichita, Kansas) and workers who made PCP and TCP at two additional plants (in Midland, Michigan, and Sauget, Illinois)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122)	5	1.5 (0.5–3.4)	
PCP and TCP (n = 720)	1	0.9 (0.0–5.1)	
PCP (no TCP) (n = 1,402)	4	1.7 (0.5–4.3)	
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)	4	1.1 (0.3–2.9)	Burns CJ et al., 2011
Through 1982 (n = 878)	1	3.0 (0.0–16.8)	Bond et al., 1988
Dow PCP Production Workers (1937–1989 in Midland, Michigan) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	2	1.7 (0.2–6.2)	Collins et al., 2009c
Mortality 1940–1989 (n = 770)	2	2.9 (0.3–10.3)	Ramlow et al., 1996
0-year latency	2	2.9 (0.4–10.3)	
15-year latency	1	nr	
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	18	0.9 (0.5–1.5)	
Ever	20	1.2 (0.8–1.9)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish gardeners (n = 3,124) exposed to pesticides	9	0.7 (0.3–1.4)	Kenborg et al., 2012
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	25	0.5 (0.3–0.7)	Torchio et al., 1994
Italian rice growers with documented phenoxy use		**Phenoxy herbicides**	Gambini et al., 1997
(n = 1,487)	7	0.9 (0.4–1.9)	
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of 303 incident laryngeal cancer cases vs remainder of 19,904 men with any incident cancer		**Herbicides**	Reif et al., 1989
Forestry workers (n = 134)	2	1.1 (0.3–4.7)	

continued

TABLE 8 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
SWEDEN			
Swedish lumberjacks—Used phenoxys 1954–1967, Incidence 1958–1992			Thörn et al., 2000
Exposed (n = 154)			
Foremen (n = 15)	0	nr	
THE NETHERLANDS			
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	1	1.0 (0.0–5.1)	Swaen et al., 2004
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	162	0.7 (0.6–0.8)	
Nonwhites (n = 11,446)	32	1.1 (0.8–1.5)	
Women			
Whites (n = 2,400)	0	nr (0.0–3.3)	
Nonwhites (n = 2,066)	0	nr (0.0–4.8)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group)		**TCDD**	
Mortality			
25-year followup to 2001—men and women, all respiratory cancers (ICD-9 160–165) excluding lung cancers (ICD-9 162)			Consonni et al., 2008
Zone A	0	nr	
Zone B	≤ 8	nr	
Zone R	≤ 49	nr	
20-year followup to 1996—men and women, all respiratory cancers (ICD-9 160–165) excluding lung cancers (ICD-9 162)			Bertazzi et al., 2001
Zone A	0	nr	
Zone B	8	nr	
15-year followup to 1991—men			Bertazzi et al., 1997, 1998
Zone B	6	nr	
Zone R	32	nr	
15-year followup to 1991—women			Bertazzi et al., 1997, 1998
Zone B	0	nr	
Zone R	6	nr	
Ecological Study of Residents of Chapaevsk, Russia		**Dioxin**	Revich et al., 2001
Incidence— Crude incidence rate in 1998 vs			
Men			
Regional (Samara)		0	
National (Russia)		11.3	
Women			
Regional (Samara)		0	
National (Russia)		0.4	

TABLE 8 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Mortality—1995–1998 (SMR vs regional rates)			
Men	13	2.3 (1.2–3.8)	
Women	1	0.1 (0.0–0.6)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,5-DCP, 2,5-dichlorophenol; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job-exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; n, number; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; SMR, standardized mortality ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

TABLE 9 Selected Epidemiologic Studies—Lung, Bronchus, or Trachea Cancer (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Incidence			
1982–2003—White SEA comparison veterans only (n = 1,482). Serum TCDD (pg/g) based on model with exposure variable $\log_e$(TCDD)			Pavuk et al., 2005
Per unit increase of –$\log_e$(TCDD) (pg/g) Quartiles (pg/g):	36	1.7 (0.9–3.2)	
0.4–2.6	6	1.0 (nr)	
2.6–3.8	8	1.1 (0.3–3.4)	
3.8–5.2	9	1.2 (0.4–3.5)	
> 5.2	13	1.9 (0.7–5.5)	
Number of years served in SEA (per year of service)			
Quartiles (years in SEA):	36	1.1 (0.9–1.2)	
0.8–1.3	8	1.0 (nr)	
1.3–2.1	4	0.5 (0.2–1.8)	
2.1–3.7	11	0.7 (0.3–2.0)	
3.7–16.4	13	0.7 (0.3–2.0)	
Through 1999—White subjects vs national rates			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	33	1.1 (0.8–1.6)	
With tours between 1966–1970	26	1.1 (0.7–1.6)	
SEA comparison veterans (n = 1,776)	48	1.2 (0.9–1.6)	
With tours between 1966–1970	37	1.2 (0.9–1.6)	
Mortality			
Through 1999—White subjects vs national rates			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	21	0.9 (0.6–1.3)	
SEA comparison veterans (n = 1,776)	38	1.1 (0.8–1.5)	
US VA Cohort of Army Chemical Corps—Expanded as of 1997 to include all Army men with chemical MOS (2,872 deployed vs 2,737 nondeployed) serving during Vietnam era (July 1, 1965–March 28, 1973)		**All COIs**	
Mortality—Respiratory system cancers			
Through 2005			Cypel and Kang, 2010
Deployed veterans (2,872) vs nondeployed (2,737)	60 vs 26	1.3 (0.8–2.1)	
ACC deployed men in Kang et al. (2006) reported sprayed herbicide vs did not spray	19	1.4 (0.5–3.4)	
Through 1991	11	1.4 (0.4–5.4)	Dalager and Kang, 1997
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Mortality—trachea, bronchus, lung			
1965–2000	41	1.0 (0.6–1.5)	Boehmer et al., 2004
Low grade pay at time of discharge	nr	1.6 (0.9–3.0)	

TABLE 9 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1988 (lung)			Watanabe and Kang, 1996
Army, deployed (n = 27,596) vs nondeployed (n = 31,757)	1,139	1.1 (nr) ($p < 0.05$)	
Marine Corps, deployed (n = 6,237) vs nondeployed (n = 5,040)	215	1.2 (1.0–1.3)	
US VA Study of Marine Post-service Mortality—sample of Marines serving 1967–1969, deployed (n = 10,716) vs nondeployed (n = 9,346)		**All COIs**	
Mortality (lung), earlier of discharge or April 1973 through 1991	42	1.3 (0.8–2.1)	Watanabe and Kang, 1995
US VA Cohort of Female Vietnam-era Veterans served in Vietnam (n = 4,586; nurses only = 3,690); nondeployed (n = 5,325; nurses only = 3,282)		**All COIs**	
Mortality			
Through 2004—lung	195	1.1 (0.8–1.5)	Kang et al., 2014
Vietnam nurses only	137	0.9 (0.7–1.3)	
Through 2004—lung	50	1.0 (0.7–1.4)	Cypel and Kang, 2008
Vietnam veteran nurses	35	0.8 (0.5–1.2)	
Through 1991—lung	15	0.9 (0.4–1.7)	Dalager et al., 1995a
Vietnam veteran nurses	9	0.5 (0.2–1.2)	
Through 1987—lung (Vietnam nurses not reported separately)	8	0.6 (0.3–1.5)	Thomas et al., 1991
US VA using the Patient Treatment Files—329 Vietnam-era veterans and 269 non-cancer controls and 111 colon cancer controls (1983–1990)	134	**All COIs** 1.4 (1.0–1.9)	Mahan et al., 1997
State Studies of US Vietnam Veterans			
Michigan Vietnam-era veterans, PM study of deaths (1974–1989)—deployed vs nondeployed	80	0.9 (0.7–1.1)	Vistainer et al., 1995
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	576	1.2 (1.1–1.3)	ADVA, 2005b
Navy	141	1.4 (1.2–1.7)	
Army	372	1.2 (1.1–1.3)	
Air Force	63	1.0 (0.7–1.2)	
Histologic type—all service branches combined			
Adenocarcinoma	188	1.5 (1.2–1.7)	
Squamous	152	1.2 (1.0–1.4)	
Small-cell	87	1.2 (0.97–1.5)	
Large-cell	79	1.1 (0.8–1.3)	
Other	70	1.1 (0.8–1.3)	

continued

TABLE 9 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Validation Study		*Expected number of exposed cases*	AIHW, 1999
	46	65 (49–81)	
Men—self-report	120	65 (49–89)	CDVA, 1998a
Mortality			
All branches, return–2001	544	1.2 (1.1–1.3)	ADVA, 2005a
Navy	135	1.4 (1.2–1.6)	
Army	339	1.1 (1.0–1.3)	
Air Force	71	1.1 (0.9–1.4)	
1980–1994			CDVA, 1997a
Lung (ICD-9 162)	212	1.3 (1.1–1.4)	
Respiratory systems (ICD-9 163–165)	13	1.8 (1.0–3.0)	
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Incidence			
1982–2000	78	1.2 (1.0–1.5)	ADVA, 2005c
Histologic type			
Adenocarcinoma	27	1.4 (0.8–1.9)	
Squamous	19	1.5 (0.9–2.3)	
Small-cell	14	1.4 (0.8–2.4)	
Large-cell	8	0.7 (0.3–1.3)	
Other	10	1.2 (0.6–2.2)	
Mortality			
1966–2001	67	1.8 (1.2–2.7)	ADVA, 2005c
1982–1994	27	2.2 (1.1–4.3)	CDVA, 1997b
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008)	58	1.1 (0.9–1.5)	
Mortality (1988–2008)	50	1.2 (0.9–1.5)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores)		**All COIs**	
		HRs	
Incidence (1992–2003)—Lung cancer (C33–C34) categorized high (n = 649) vs low (n = 505)		1.1 (1.0–1.3)	Yi and Ohrr, 2014
Mortality (1992–2005)—Lung cancer (C33–C34) categorized high (n = 673) vs low (n = 497)		1.2 (1.0–1.3)	Yi et al., 2014b
HR per unit of log EOI (n = 180,639)	1,170	1.0 (1.0–1.1)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992			Kogevinas et al., 1997
Lung (ICD-9 162)	380	1.1 (1.0–1.2)	
Other respiratory organs (ICD-9 163–165)	12	2.3 (1.2–3.9)	
13,831 exposed to highly chlorinated PCDDs			
Lung (ICD-9 162)	225	1.1 (1.0–1.3)	
Other respiratory organs (ICD-9 163–165)	9	3.2 (1.5–6.1)	

TABLE 9 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
7,553 not exposed to highly chlorinated PCDDs			
Lung (ICD-9 162)	148	1.0 (0.9–1.2)	
Other respiratory organs (ICD-9 163–165)	3	1.2 (0.3–3.6)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort			Saracci et al., 1991
Trachea, bronchus, lung (ICD-9 162)	173	1.0 (0.9–1.2)	
Mortality, incidence of women in production (n = 699) and spraying (n = 2) compared to national death rates and cancer incidence rates (lung)	2	**TCDD** 1.4 (0.2–4.9)	Kogevinas et al., 1993
British MCPA Plant—All manual employees employed January 1947–December 1975 (n = 1,146), ever potentially exposed to phenoxy herbicides (n = 1,544), potentially exposed to phenoxy herbicides ≥ 1 year (n = 848) (not included in IARC cohort)		**MCPA**	
Mortality through 2012, all workers			Coggon et al., 2015
Lung (ICD-10 C33–34)	392	1.01 (0.91–1.11)	
Mortality through 2012, workers ever exposed to phenoxy herbicides			
Lung (ICD-10 C33–34)	298	1.07 (0.95–1.20)	
Mortality through 2012, workers ever exposed to phenoxy herbicides ≥ 1 year			
Lung (ICD-10 C33–34)	138	1.05 (0.88–1.24)	
Mortality through 1983 (lung, pleura, mediastinum, ICD-8 162–164)	117	1.2 (1.0–1.4)	Coggon et al., 1986
Background exposure	39	1.0 (0.7–1.4)	
Low-grade exposure	35	1.1 (0.8–1.6)	
High-grade exposure	43	1.3 (1.0–1.8)	
British Production Workers at 4 plants (included in IARC cohort) (lung)		**Dioxins, but TCDD unlikely; MCPA**	Coggon et al., 1991
	19	1.3 (0.8–2.1)	
Workers with exposure above background	14	1.2 (0.7–2.1)	
Chinese Automobile Foundry Factory Workers (n = 3,529)		**PCDD/F**	Wang et al., 2013
Lung cancer mortality (1980–2005); comparison with Chinese general population	43	2.1 (1.6–2.9)	
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence			
Incidence 1943–1987 (lung, men only)	13	1.6 (0.9–2.8)	Lynge, 1993
Incidence 1943–1982			Lynge, 1985
Men	38	1.2 (nr)	
Women	6	2.2 (nr)	

continued

TABLE 9 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Dutch production workers in Plant A and Plant B, combined (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–2006 (Plant A, 1,020 workers; Plant B, 1,036 workers) (respiratory cancers)	54	1.0 (0.9–1.2)	Boers et al., 2012
TCDD plasma level (HRs, by tertile) (trachea, bronchus, lung)	52	1.0 (0.8–1.2)	
Background (≤ 0.4)	24	Referent	
Low (0.4–4.1)	11	0.5 (0.3–1.1)	
Medium (4.1–20.1)	12	1.2 (0.6–2.3)	
High (≥ 20.1)	5	1.2 (0.5–3.1)	
963 men exposed during production 1955–1985 vs 1,317 unexposed; mortality in 1986 (respiratory system cancers, ICD-8 160–163)	9 vs 3	1.7 (0.5–6.3)	Bueno de Mesquita et al., 1993
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–2006 (hazard ratios for lagged TCDD plasma levels)			Boers et al., 2012
Respiratory cancer	30	1.1 (0.9–1.3)	
Trachea, bronchus, lung cancers	28	1.1 (0.9–1.3)	
Mortality 1955–2006			Boers et al., 2010
Respiratory cancer	21	1.1 (0.5–2.5)	
Trachea, bronchus, lung cancers	20	1.2 (0.5–2.8)	
Mortality 1955–1985			Bueno de Mesquita et al., 1993
Trachea, bronchus, lung cancers	9	1.0 (0.5–1.9)	
Dutch production workers in Plant B (414 men exposed during production 1965–1986; 723 unexposed) (in IARC cohort)		**2,4-D; MCPA; MCPP; highly chlorinated dioxins unlikely**	
Mortality 1965–2006			Boers et al., 2010
Respiratory cancer	12	1.2 (0.6–2.7)	
Trachea, bronchus, lung cancers	12	1.2 (0.6–2.7)	
Mortality 1965–1986			Bueno de Mesquita et al., 1993
Trachea, bronchus, lung cancers	0	0.0 (0.0–1.3)	
German Production Workers—2,479 workers at 4 plants (in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
All for plants	47	1.4 (1.1–1.9)	Becher et al., 1996
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 month in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992	2	0.7 (0.0–2.5)	Becher et al., 1996
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 month in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1965–1989	3	1.6 (0.3–4.6)	Becher et al., 1996
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 month in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1956–1989	11	1.5 (0.7–2.6)	Becher et al., 1996

TABLE 9 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Mortality			
1953–1992			Ott and Zober, 1996a
Respiratory system	13	1.2 (0.6–2.0)	
TCDD 0.1–0.99 μg/kg of body weight	2	0.7 (0.1–2.5)	
TCDD ≥ 1 μg/kg of body weight	8	2.0 (0.9–3.9)	
Lung, bronchus	11	1.1 (0.6–2.0)	
TCDD 0.1–0.99 μg/kg of body weight	2	0.8 (0.1–2.8)	
TCDD ≥ 1 μg/kg of body weight	8	2.2 (1.0–4.3)	
		90% CI	Zober et al., 1990
Through 1987	4	2.0 (0.7–4.6)	
German Production Workers at Boehringer–Ingelheim Plant in Hamburg—1,144 men working > 1 month in 1952–1984 (generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–2007	73	1.4 (1.1–1.8)	Manuwald et al., 2012
Men	68	1.5 (1.2–1.9)	
Women	5	0.8 (0.3–1.9)	
Mortalilty 1952–1989	31	1.5 (1.0–2.1)	Becher et al., 1996
Mortality (lung) 1952–1989—stats on men only, 1,184 (tables all for 1,148 men, not necessarily German nationals) vs national rates (also vs gas workers); same observation period as Becher et al., 1966	26	1.7 (1.1–2.4)	Manz et al., 1991
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers			
Respiratory cancer	13	0.9 (0.5–1.6)	
Trachea, bronchus, lung	11	0.8 (0.4–1.5)	
Never-exposed workers			
Respiratory cancer	5	1.2 (0.4–2.7)	
Trachea, bronchus, lung	4	1.0 (0.3–2.5)	
Production Workers (713 men and 100 women worked > 1 month in 1969–1984); mortality (1969–2000)			
Trachea, bronchus, lung (ICD-9 162)	12	1.4 (0.7–2.4)	't Mannetje et al., 2005
Other respiratory system sites (ICD-9 163–165)	1	3.9 (0.1–21.5)	
Sprayers (697 men and 2 women on register of New Zealand applicators, 1973–1984); mortality 1973–2000			
Trachea, bronchus, lung (ICD-9 162)	5	0.5 (0.2–1.1)	't Mannetje et al., 2005
Other respiratory system sites (ICD-9 163–165)	1	2.5 (0.1–13.7)	

continued

TABLE 9 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993	125	1.1 (0.9–1.3)	Steenland et al., 1999
Chloracne subcohort (n = 608)	30	1.5 (0.98–2.1)	
Through 1987 (Entire cohort)			Fingerhut et al., 1991
Trachea, bronchus, lung (ICD-9 162)	89	1.1 (0.9–1.4)	
Respiratory system (ICD-9 160–165	96	1.1 (0.9–1.4)	
≥ 1-year exposure, ≥ 20-year latency			
Trachea, bronchus, lung (ICD-9 162)	40	1.4 (1.0–1.9)	
Respiratory system (ICD-9 160–165)	43	1.4 (1.0–1.9)	
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, Michigan) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1937–2011 Potential dioxin exposure (n = 2,192), TCP production (n = 1,419), PCP production (n = 577), Both TCP and PCP (n = 196)			Collins et al., 2016
TCP or PCP, Respiratory system (C30–C39)	110	0.94 (0.77–1.13)	
TCP, Respiratory system (C30–C39)	77	0.88 (0.69–1.10)	
PCP, Respiratory system (C30–C39)	42	1.05 (0.76–1.42)	
TCP or PCP, Bronchus, trachea, lung (C33–C34)	103	0.92 (0.75–1.11)	
TCP, Bronchus, trachea, lung (C33–C34)	72	0.86 (0.67–1.08)	
PCP, Bronchus, trachea, lung (C33–C34)	39	1.02 (0.73–1.40)	
1942–2003 (n = 1,615) (bronchus, trachea, lung)	46	0.7 (0.5–0.9)	Collins et al., 2009b
1940–1994 (n = 2,187 men) (lung)	54	0.8 (0.6–1.1)	Bodner et al., 2003
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, Washington, and Wichita, Kansas) and workers who made PCP and TCP at two additional plants (in Midland, Michigan, and Sauget, Illinois)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
Respiratory cancer (ICD-9 160–165)			
1940–2005 (n = 2,122)	133	1.4 (1.2–1.6)[c]	
PCP and TCP (n = 720)	28	0.9 (0.6–1.3)	
PCP (no TCP) (n = 1,402)	105	1.6 (1.3–1.9)[c]	
Trachea, bronchus, lung (ICD-9 162)			
1940–2005 (n = 2,122)	126	1.4 (1.1–1.6)[c]	
PCP and TCP (n = 720)	27	0.9 (0.6–1.3)	
PCP (no TCP) (n = 1,402)	99	1.6 (1.3–1.9)[c]	
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3) (lung, bronchus)	36	0.9 (0.6–1.3)	Burns CJ et al., 2011
Through 1994 (n = 1,517) (respiratory system, ICD-8 160–163)	31	0.9 (0.6–1.3)	Burns et al., 2001
Through 1986 (n = 878) vs national vs 36,804 "unexposed" workers at same location			Bloemen et al., 1993
Respiratory system (ICD-8 162–163)	9	0.8 (0.4–1.5)	

TABLE 9 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Through 1982 (n = 878)			Bond et al., 1988
Lung (ICD-8 162–163)	8	1.0 (0.5–2.0)	
Respiratory (ICD-8 160–163) (exposure lagged 15 years)			
Low cumulative exposure	1	0.7 (nr)	
Medium cumulative exposure	2	1.0 (nr)	
High cumulative exposure	5	1.7 (nr)	
Dow PCP Production Workers (1937–1989 in Midland, Michigan) (**not** in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP) (bronchus, trachea, lung)	30	1.0 (0.6–1.4)	Collins et al., 2009c
Mortality 1940–1989 (n = 770)			
0-year latency			Ramlow et al., 1996
Respiratory system (ICD-8 160–163)	18	1.0 (0.6–1.5)	
Lung (ICD-8 162)	16	0.9 (0.5–1.5)	
15-year latency			
Respiratory system (ICD-8 160–163)	17	1.1 (0.6–1.8)	
Lung (ICD-8 162)	16	1.1 (0.6–1.8)	
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Lung (ICD-9 162)			
Never	356	1.0 (0.9–1.1)	
Ever	314	1.0 (0.9–1.2)	
Pleura (ICD-9 163)			
Never	17	2.8 (1.6–4.5)	
Ever	4	0.8 (0.2–2.0)	
Other respiratory (ICD-9 164–165)			
Never	8	2.1 (0.9–4.2)	
Ever	2	0.7 (0.1–2.4)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Ontario Forestry Workers—1,222 men working ≥ 6 months 1950–1982		**Herbicides**	
80 deaths through 1982; 18 cancers (lung greatest with 5)	5	nr	Green, 1991
DENMARK			
Danish gardeners (n = 3,124) exposed to pesticides	139	1.0 (0.9–1.2)	Kenborg et al., 2012
Danish gardeners—incidence from 3,156 male and 859 female gardeners			Hansen et al., 2007
25-year followup (1975–2001)		**Herbicides**	
Born before 1915 (high exposure)	34	0.9 (0.6–1.3)	
Born 1915–1934 (medium exposure)	72	1.0 (0.8–1.2)	
Born after 1934 (low exposure)	8	0.8 (0.4–1.7)	
10-year followup (1975–1984) of male gardeners	41	1.0 (0.7–1.3)	Hansen et al., 1992

continued

TABLE 9 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000 (trachea, lung)	27	0.7 (0.5–1.0)	Swaen et al., 2004
Through 1987 (trachea, lung)	12	1.1 (0.6–1.9)	Swaen et al., 1992
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 weeks) not IARC		**Phenoxy herbicides**	
Incidence			Asp et al., 1994
Trachea, bronchus, lung (ICD-8 162)	39	0.9 (0.7–1.3)	
Other respiratory (ICD-8 160, 161, 163)	4	1.1 (0.7–1.3)	
Mortality 1972–1989			
Trachea, bronchus, lung (ICD-8 162)	37	1.0 (0.7–1.4)	
Other respiratory (ICD-8 160, 161, 163)	1	0.5 (0.0–2.9)	
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401) (lung)	155	0.5 (0.4–0.5)	Torchio et al., 1994
Italian rice growers with documented phenoxy use (n = 1,487)		**Phenoxy herbicides**	Gambini et al., 1997
Lung	45	0.8 (0.6–1.1)	
Pleura	2	2.2 (0.2–7.9)	
ITALIAN Electric Arc Furnance Workers—males employed who worked for at least 1-year (n = 331 exposed)		**PCDD/Fs**	
Mortality 1979–2009 malignant tumors of the larynx, trachea, bronchi, lungs compared with regional population	8	3.35 (1.45–6.60)	Cappelletti et al., 2016
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of 4,224 incident lung cancer cases vs remainder of 19,904 men with any incident cancer		**Herbicides**	Reif et al., 1989
Forestry workers (n = 134)	30	1.3 (0.8–1.9)	
SWEDEN			
Swedish pesticide applicators—incidence			Wiklund et al., 1989a
Trachea, bronchus, lung	38	0.5 (0.4–0.7)	
348 Swedish railroad workers (1957–October 1978)—total exposure to herbicides (lung)	3	**Phenoxy acids** 1.4 (nr)	Axelson et al., 1980
Swedish lumberjacks—Used phenoxys 1954–1967, Incidence 1958–1992			Thörn et al., 2000
Exposed (n = 154)			
Foremen (n = 15)	1	4.2 (0.0–23.2)	
Lumberjacks (n = 139)	0	—	
Unexposed lumberjacks (n = 241)	5	1.2 (0.4–2.7)	
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	6,473	0.9 (0.9–0.9)	
Nonwhites (n = 11,446)	664	1.0 (0.9–1.1)	
Women			
Whites (n = 2,400)	57	0.8 (0.6–1.1)	
Nonwhites (n = 2,066)	24	0.6 (0.4–0.9)	

TABLE 9 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Vital stats updated 2011			Bonner et al., 2017
Dicamba—lifetime days exposure, adjusted for age, smoking status and pack-years, sex, and total lifetime pesticide use			
Quartile 1	38	0.64 (0.44–0.92)	
Quartile 2	45	0.57 (0.40–0.83)	
Quartile 3	45	0.75 (0.55–1.04)	
Quartile 4	36	0.86 (0.60–1.24)	
		p-trend = 0.007	
Dicamba—intensity weighted lifetime exposure days, adjusted for age, smoking status and pack-years, sex, and total lifetime pesticide use			
Quartile 1	39	0.57 (0.40–0.82)	
Quartile 2	44	0.66 (0.47–0.95)	
Quartile 3	36	0.73 (0.48–1.10)	
Quartile 4	44	0.81 (0.59–1.13)	
		p-trend = 0.001	
Dicamba—5-year lag, adjusted for age, smoking status and pack-years, sex, and total lifetime pesticide use			
Quartile 1	38	0.62 (0.44–0.88)	
Quartile 2	43	0.54 (0.38–0.77)	
Quartile 3	45	0.73 (0.53–1.00)	
Quartile 4	33	0.79 (0.55–1.14)	
		p-trend = 0.001	
Dicamba—15-year lag, intensity weighted lifetime exposure days, adjusted for age, smoking status and pack-years, sex, and total lifetime pesticide use			
Quartile 1	35	0.52 (0.37–0.74)	
Quartile 2	34	0.47 (0.33–0.67)	
Quartile 3	37	0.61 (0.43–0.86)	
Quartile 4	21	0.59 (0.38–0.93)	
		p-trend = < 0.001	
Enrollment through 2006—SIRs for participants (lung, bronchus)			Koutros et al., 2010a
Private applicators	436	0.5 (0.4–0.5)	
Commercial applicators	26	0.8 (0.5–1.1)	
Spouses	133	0.4 (0.4–0.5)	

continued

TABLE 9 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Enrollment through 2002			Samanic et al., 2006
Dicamba—lifetime days exposure			
None	95	1.0	
1– < 20	14	0.8 (0.5–1.5)	
20– < 56	11	0.6 (0.3–1.3)	
56– < 116	12	1.0 (0.5–1.9)	
≥ 116	15	1.5 (0.8–2.7)	
		p-trend = 0.13	
Enrollment through 2002			Alavanja et al., 2005
Private applicators			
Lung	266	0.5 (0.4–0.5)	
Respiratory system	294	0.5 (0.4–0.5)	
Spouses of private applicators (> 99% women)			
Lung	68	0.4 (0.3–0.5)	
Respiratory system	71	0.4 (0.3–0.5)	
Commercial applicators			
Lung	12	0.6 (0.3–1.0)	
Respiratory system	14	0.6 (0.3–1.0)	
Mortality			
Enrollment through 2007, vs state rates			
Respiratory			Waggoner et al., 2011
Applicators (n = 1,641)	422	0.4 (0.4–0.5)	
Spouses (n = 676)	110	0.4 (0.3–0.5)	
Trachea, bronchus, lung			
Applicators (n = 1,641)	417	0.4 (0.4–0.5)	
Spouses (n = 676)	108	0.4 (0.3–0.5)	
Other respiratory system			
Applicators (n = 1,641)	5	0.2 (0.1–0.3)	
Spouses (n = 676)	2	nr	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	129	0.4 (0.3–0.4)	
Years handled pesticides			
≤ 10 years	25	0.4 (nr) ($p < 0.05$)	
≥ 10 years	80	0.3 (nr) ($p < 0.05$)	
Spouses of private applicators (> 99% women)	29	0.3 (0.2–0.5)	
Florida Licensed Pesticide Applicators (common phenoxy use assumed but not documented)		**Herbicides**	
Pesticide applicators in **Florida** licensed 1965–1966 (n = 3,827)—mortality through 1976		**Herbicides**	Blair et al., 1983
Any pesticide (dose-response by length of licensure)			
Only for lawn and ornamentals (lung, ICD-8 162–163)	7	0.9 (nr)	
Minnesota Highway Maintenance Workers (n = 4,849) who worked ≥ 1 day for the Department of Transportation and ≥ 1 day after January 1, 1945 (1984–1986)		**Herbicides**	Bender et al., 1989
Trachea, bronchus, lung (ICD-9 162.0–162.8)	54	0.7 (0.5–0.9)	
All respiratory (ICD-9 160.0–165.9)	57	0.7 (0.5–0.9)	

TABLE 9 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Incidence			
20-year followup to 1996—men and women (lung ICD-9 162)			Pesatori et al., 2009
Zone A	7	1.1 (0.5–2.4)	
Zone B	37	1.0 (0.7–1.3)	
Zone R	280	1.0 (0.9–1.2)	
10-year followup to 1991—men			Bertazzi et al., 1993
Zone A	2	0.8 (0.2–3.4)	
Zone B	18	1.1 (0.7–1.8)	
Zone R	96	0.8 (0.7–1.0)	
10-year followup to 1991—women			Bertazzi et al., 1993
Zone R	16	1.5 (0.8–2.5)	
Mortality			
25-year followup to 2001—men and women (lung ICD-9 162)			Consonni et al., 2008
Zone A	11	1.1 (0.6–2.0)	
Zone B	62	1.1 (0.9–1.4)	
Zone R	383	1.0 (0.8–1.1)	
20-year followup to 1996 (lung)			Bertazzi et al., 2001
Zones A, B—men	57	1.3 (1.0–1.7)	
Zones A, B—women	4	0.6 (0.2–1.7)	
15-year followup to 1991—men (lung)			Bertazzi et al., 1998
Zone A	4	1.0 (0.4–2.6)	
Zone B	34	1.2 (0.9–1.7)	
Zone R	176	0.9 (0.8–1.1)	
15-year followup to 1991—women (lung)			Bertazzi et al., 1998
Zone A	0	nr	
Zone B	2	0.6 (0.1–2.3)	
Zone R	29	1.0 (0.7–1.6)	
Ecological Study of Residents of Chapaevsk, Russia		**Dioxin**	Revich et al., 2001
Incidence—Crude incidence rate in 1998 vs			
Men			
Regional (Samara)	nr	102.4 (nr)	
National (Russia)	nr	89.4 (nr)	
Women			
Regional (Samara)	nr	11.1 (nr)	
National (Russia)	nr	9.8 (nr)	
Mortality—1995–1998 (SMR vs regional rates)			
Men	168	3.1 (2.6–3.5)	
Women	40	0.4 (0.3–0.6)	
Other International Environmental Studies			
FINLAND			
Finnish fishermen (n = 6,410) and spouses (n = 4,260) registered between 1980 and 2002 compared to national statistics (larynx, trachea, lung, combined)		**Serum dioxin**	Turunen et al., 2008
Fisherman	72	0.8 (0.6–1.0)	
Spouses	8	0.7 (0.3–1.4)	

continued

TABLE 9 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
JAPAN			
Residents of municipalities with and without waste incineration plants (cross-sectional)		**Dioxin emissions** age-adjusted mortality (per 100,000)	Fukuda et al., 2003
Men			
With		39.0 ± 6.7 vs	
Without		41.6 ± 9.1 (p = 0.0001)	
Women			
With		13.7 ± 3.8 vs	
Without		14.3 ± 4.6 (p = 0.11)	
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995a
Incidence			
East coast (lung)	24	1.2 (0.8–1.8)	
West coast (lung)	73	0.9 (0.7–1.1)	
Mortality			
East coast	16	0.8 (0.5–1.3)	
West coast	77	0.9 (0.7–1.1)	
CASE-CONTROL STUDIES			
International Case-Control Studies			
Saskatchewan, Canada farmers (604 men, 223 women) diagnosed with lung cancer between November 1983 and July 1986		**Herbicides**	McDuffie et al., 1990
Interviews with lung cancer patients (273 men and 103 women) who sprayed herbicides	103	0.6 (nr)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,5-DCP, 2,5-dichlorophenol; ACC, Army Chemical Corps; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job-exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; MOS, military occupational specialty; n, number; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; PM, proportionate mortality; SEA, Southeast Asia; SIR, standardized incidence ratio; SMR, standardized mortality ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

[c]99% CI.

TABLE 10 Selected Epidemiologic Studies—Bone and Joint Cancer (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1982			Breslin et al., 1986, 1988
Army, deployed (n = 19,708) vs nondeployed (n = 22,904)	27	0.8 (0.4–1.7)	
Marine Corps, deployed (n = 4,527) vs nondeployed (n = 3,781)	11	1.4 (0.1–21.5)	
State Studies of US Vietnam Veterans			
Massachusetts Vietnam-era veterans			
Veterans aged 35–64 years in 1993—cases diagnosed 1988–1993 vs non-exposed veterans with gastrointestinal cancers	4	0.9 (0.1–11.3)	Clapp, 1997
New York			
Deployed vs nondeployed veterans	8	1.0 (0.3–3.0)	Lawrence et al., 1985
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans	1	nr	Anderson et al., 1986a,b
International Vietnam-Veteran Studies			
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence—bone and cartilage (1988–2008)	2	2.8 (0.3–10.0)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs)		**All COIs**	
Incidence (1992–2003)—bone cancer (C40–C41) categorized high (n = 8) vs low (n = 11)	8	0.7 (0.3–1.8)	Yi and Ohrr, 2014
Mortality (1992–2005)—bone cancer (C40–C41) categorized high (n = 5) vs low (n = 11)		0.5 (0.2–1.5)	Yi et al., 2014b
HR per unit of log EOI (n = 180,639)	16	0.8 (0.6–1.0)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	5	1.2 (0.4–2.8)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	3	1.1 (0.2–3.1)	
7,553 not exposed to highly chlorinated PCDDs	2	1.4 (0.2–5.2)	
British MCPA Plant—Production 1947–1982 (n = 1,545) (included in IARC cohort) and spraying 1947–1972 (n = 2,561) (not included in IARC cohort)		**MCPA**	
Mortality through 1983	1	0.9 (0.0–5.0)	Coggon et al., 1986
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Mortality			
Through 1987	0	90% CI 0.0 (0.0–65.5)	Zober et al., 1990

continued

TABLE 10 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004	0	0.0 (0.0–21.8)	McBride et al., 2009a
Production Workers (713 men and 100 women worked > 1 month in 1969–1984)			
Mortality 1969–2000	0	nr	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1987	2	2.3 (0.3–8.2)	Fingerhut et al., 1991
≥ 1-year exposure, ≥ 20-year latency	1	5.5 (0.1–29.0)	
Mortality—754 Monsanto workers, among most highly exposed workers from Fingerhut et al. (1991)	2	5.0 (0.6–18.1)	Collins et al., 1993
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3) (bone, soft tissue)	1	0.8 (0.0–4.5)	Burns et al., 2011
Through 1982 (n = 878)	0	nr (0.0–31.1)	Bond et al., 1988
Dow PCP Production Workers (1937–1989 in Midland, Michigan) (**not** in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–1989 (n = 770)	0	nr	Ramlow et al., 1996
0-year latency	0	nr	
15-year latency	0	nr	
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			
Danish paper workers			Rix et al., 1998
Men	1	0.5 (0.0–2.7)	
Women	0	nr	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Sawmill Workers in British Columbia—23,829 workers for ≥ 1 year at 11 mills using chlorophenates 1940–1985		**Chlorophenates, not TCDD**	
Incidence 1969–1989	4	1.1 (0.4–2.4)	Hertzman et al., 1997
Mortality 1950–1989	5	1.3 (0.5–2.7)	
No exposed to highly chlorinated PCDDs	2	1.4 (0.2–5.2)	
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	9	0.9 (nr)	
Employee	0	nr	

TABLE 10 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Women			
Self-employed	0	0.0	
Employee	1	6.3 ($p < 0.05$)	
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	0	nr	Swaen et al., 2004
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	10	0.8 (0.4–1.4)	Torchio et al., 1994
Italian rice growers with documented phenoxy use (n = 1,487)	1	**Phenoxy herbicides** 0.5 (0.0–2.6)	Gambini et al., 1997
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of incident bone cancer cases vs remainder of 19,904 men with any incident cancer		**Herbicides**	Reif et al., 1989
Forestry workers (n = 134)	1	1.7 (0.2–13.3)	
SWEDEN			
Incident bone cancer cases 1961–1973 with agriculture as economic activity in 1960 census	44	99% CI 1.0 (0.6–1.4)	Wiklund, 1983
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	49	1.3 (1.0–1.8)	
Nonwhites (n = 11,446)	4	1.0 (0.3–2.5)	
Women			
Whites (n = 2,400)	1	1.2 (0.0–6.6)	
Nonwhites (n = 2,066)	0	0.0 (0.0–6.3)	
White Male Residents of Iowa—bone cancer on death certificate, usual occupation: farmers vs not		**Herbicides**	
> 20 years old when died 1971–1978—PMR	56	1.1 (nr)	Burmeister, 1981
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Mortality			
15-year followup to 1991—men			Bertazzi et al., 1998
Zone R	2	0.5 (0.1–2.0)	
15-year followup to 1991—women			Bertazzi et al., 1998
Zone B	1	2.6 (0.3–19.4)	
Zone R	7	2.4 (1.0–5.7)	
Ecological Study of Residents of Chapaevsk, Russia		**Dioxin**	Revich et al., 2001
Mortality—1995–1998 (SMR vs regional rates)			
Men	7	2.1 (0.9–4.4)	
Women	7	1.4 (0.6–3.0)	

continued

TABLE 10 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
CASE-CONTROL STUDIES			
International Case-Control Studies			
European Multicentric study of association between occupational exposure and risk of bone sarcoma		**Herbicides, pesticides**	Merletti et al., 2005
(96 cases, 35–69 years of age vs 2,632 hospital- and population-based controls)	18	2.6 (1.5–4.6)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; GI, gastrointestinal; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job-exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; PMR, proportionate mortality ratio; SMR, standardized mortality ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

TABLE 11 Selected Epidemiologic Studies—Soft-Tissue Sarcomas (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Mortality			
Through 1987—Ranch Hand personnel (n = 1,261) vs SEA veterans (n = 19,102)	1	nr	Michalek et al., 1990
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1984			
Army, deployed (n = 24,145) vs nondeployed (n = 27,917)	43	1.1	Watanabe et al., 1991
Served in I Corps (n = 6,668)	10	0.9 (0.4–1.6)	Bullman et al., 1990
Marine Corps, deployed (n = 5,501) vs nondeployed (n = 4,505)	11	0.7	Watanabe et al., 1991
1965–1982			Breslin et al., 1986, 1988
Army, deployed (n = 19,708) vs nondeployed (n = 22,904)	30	1.0 (0.8–1.2)	
Marine Corps, deployed (n = 4,527) vs nondeployed (n = 3,781)	8	0.7 (0.4–1.3)	
US VA Study of Marine Post-service Mortality—sample of Marines serving 1967–1969, deployed (n = 10,716) vs nondeployed (n = 9,346)		**All COIs**	
Mortality, earlier of discharge or April 1973 through 1991	0	nr	Watanabe and Kang, 1995
US VA Case-control study			
234 Vietnam veterans vs 13,496 Vietnam-era veterans	86	0.8 (0.6–1.1)	Kang et al., 1986
State Studies of US Vietnam Veterans			
Massachusetts Vietnam-era veterans			
Veterans aged 35–65 years in 1993—cases diagnosed 1988–1993 vs gastrointestinal cancers	18	1.6 (0.5–5.4)	Clapp, 1997
Diagnosed 1972–1983	9	5.2 (2.4–11.1)	Kogan and Clapp, 1988
Michigan Vietnam-era veterans, PM study of deaths (1974–1989) deployed vs nondeployed	8	1.1 (0.5–2.2)	Vistainer et al., 1995
New York			
deployed vs nondeployed	2	1.1 (0.2–6.7)	Lawrence et al., 1985
281 STS cases with service in Vietnam vs live matched controls	10	0.5 (0.2–1.3)	Greenwald et al., 1984
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans	4	nr	Anderson et al., 1986a,b
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/ 23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	35	1.0 (0.7–1.3)	ADVA, 2005b
Navy	6	0.8 (0.3–1.7)	
Army	29	1.2 (0.8–1.6)	
Air Force	0	0.0 (0.0–1.1)	

continued

TABLE 11 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Validation Study		*Expected number of exposed cases*	AIHW, 1999
	14	27 (17–37)	
Men	398	27 (17–37)	CDVA, 1998a
Women	2	0 (0–4)	CDVA, 1998b
Mortality			
All branches, return–2001	12	0.8 (0.4–1.3)	ADVA, 2005a
Navy	3	0.9 (0.2–2.4)	
Army	9	0.8 (0.4–1.5)	
Air Force	0	0.0 (0.0–2.3)	
1980–1994	9	1.0 (0.4–1.8)	CDVA, 1997a
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Incidence			
1982–2000	10	1.0 (0.4–2.4)	ADVA, 2005c
Mortality			
1966–2001	3	0.5 (0.1–2.0)	ADVA, 2005c
1982–1994	2	0.7 (0.6–4.5)	CDVA, 1997b
1983–1985	1	1.3 (0.1–20.0)	Fett et al., 1987b
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence–connective and soft-tissue (1988–2008)	3	1.0 (0.2–3.0)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores)		**All COIs**	
		HRs	
Incidence (1992–2003)—connective and soft tissue (C47, C49) categorized high (n = 13) vs low (n = 20)	13	0.6 (0.3–1.3)	Yi and Ohrr, 2014
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992			Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	6	2.0 (0.8–4.4)	
7,553 not exposed to highly chlorinated PCDDs	2	1.4 (0.2–4.9)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	4	2.0 (0.6–5.2)	Saracci et al., 1991
Nested case-control study			
IARC cohort (men and women)—incidence			Kogevinas et al., 1995
Exposed to 2,4,5-T	5	4.3 (0.7–26.3)	
Exposed to TCDD	5	5.2 (0.9–31.9)	
Mortality—IARC cohort (16,863 men and 1,527 women) 10–19 years since first exposure	4	6.1 (1.7–15.5)	Kogevinas et al., 1992
British MCPA Plant—All manual employees employed January 1947–December 1975 (n = 1,146), ever potentially exposed to phenoxy herbicides (n = 1,544), potentially exposed to phenoxy herbicides ≥ 1 year (n = 848) (not included in IARC cohort)		**MCPA**	
Mortality through 2012, all workers			Coggon et al., 2015
Soft tissue sarcoma (ICD-10 C46, C47, C49)	4	0.92 (0.25–2.36)	

TABLE 11 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Mortality through 2012, workers ever exposed to phenoxy herbicides			
Soft tissue sarcoma (ICD-10 C46, C47, C49)	4	1.22 (0.33–3.13)	
Mortality through 2012, workers ever exposed to phenoxy herbicides ≥ 1 year			
Soft tissue sarcoma (ICD-10 C46, C47, C49)	3	2.05 (0.42–5.98)	
Nested case control study by exposure level			
None	3	referent	
< 1 year	6	0.77 (0.17–3.50)	
≥ 1 year	6	1.30 (0.30–5.62)	
None	3	referent	
Low	5	1.38 (0.30–6.21)	
High	3	0.45 (0.08–2.62)	
Mortality through 1983	1	1.1 (0.0–5.9)	Coggon et al., 1986
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence 1943–1987 (men only)	5	2.0 (0.7–4.8)	Lynge, 1993
Incidence 1943–1982			Lynge, 1985
Men	5	2.7 (0.9–6.3)	
Women	0	nr	
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–1991	0	nr	Hooiveld et al., 1998
Mortality 1955–1985	0	0.0 (0.0–18.4)	Bueno de Mesquita et al., 1993
Dutch production workers in Plant B (414 men exposed during production 1965–1986; 723 unexposed) (in IARC cohort)		**2,4-D; MCPA; MCPP; highly chlorinated dioxins unlikely**	
Mortality 1965–1986	0	0.0 (0.0–73.8)	Bueno de Mesquita et al., 1993
German Production Workers—2,479 workers at 4 plants (in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Incidence			
1960–1992			Ott and Zober, 1996a,b
TCDD < 0.1 μg/kg of body weight	0	nr	
TCDD 0.1–0.99 μg/kg of body weight	0	nr	
TCDD > 1 μg/kg of body weight	0	nr	
Mortality		90% CI	Zober et al., 1990
Through 1987	0	nr	

continued

TABLE 11 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 month in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–1989—stats on men only, 1,184 (tables all for 1,148 men, not necessarily German nationals) vs national rates (also vs gas workers); same observation period as Becher et al., 1966	0	nr	Manz et al., 1991
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	1	3.4 (0.1–19.5)	
Never-exposed workers	0	0.0 (0.0–34.9)	
Production Workers (713 men and 100 women worked > 1 month in 1969–1984)			
Mortality 1969–2000	0	0.0 (0.0–19.3)	't Mannetje et al., 2005
Sprayers (697 men and 2 women registered any time 1973–1984)			
Mortality 1973–2000	1	4.3 (0.1–23.8)	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993	4	2.3 (0.6–5.9)	Steenland et al., 1999
Chloracne subcohort (n = 608)	3	11.3 (2.3–33.1)	
Through 1987	4	3.4 (0.9–8.7)	Fingerhut et al., 1991
≥ 1-year exposure, ≥ 20-year latency	3	9.2 (1.9–27.0)	
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, Michigan) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)	4	4.1 (1.1–10.5)	Collins et al., 2009b
1940–1994 (n = 2,187 men)	2	2.4 (0.3–8.6)	Bodner et al., 2003
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, Washington, and Wichita, Kansas) and workers who made PCP and TCP at two additional plants (in Midland, Michigan, and Sauget, Illinois) (connective tissue and soft tissue)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122) (connective tissue and soft tissue)	2	1.5 (0.2–5.5)	
PCP and TCP (n = 720)	1	2.3 (0.1–12.6)	
PCP (no TCP) (n = 1,402)	1	1.1 (0.0–6.4)	
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3) (bone, soft tissue)	1	0.8 (0.0–4.5)	Burns CJ et al., 2011
Through 1982 (n = 878)	0	nr	Bond et al., 1988

TABLE 11 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Dow PCP Production Workers (1937–1989 in Midland, Michigan) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
1937–2011 Potential dioxin exposure (n = 2,192), TCP production (n = 1,419), PCP production (n = 577), Both TCP and PCP (n = 196)			Collins et al., 2016
TCP or PCP, soft tissue sarcoma	4	2.31 (0.63–5.91)	
TCP, soft tissue sarcoma	4	3.08 (0.84–7.87)	
PCP, soft tissue sarcoma	1	1.73 (0.04–9.62)	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	1	2.2 (0.0–12.1)	Collins et al., 2009c
		Expected number of exposed cases	Ramlow et al., 1996
Mortality 1940–1989 (n = 770)	0	0.2	
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	8	1.2 (0.5–2.4)	
Ever	4	0.8 (0.2–2.0)	
Danish paper-mill workers			Rix et al., 1998
Men employed in sorting and packing	12	1.2 (0.6–2.0)	
Women employed in sorting and packing	8	4.0 (1.7–7.8)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Sawmill Workers in British Columbia—23,829 workers for ≥ 1 year at 11 mills using chlorophenates 1940–1985		**Chlorophenates, not TCDD**	
Incidence 1969–1989	11	1.0 (0.6–1.7)	Hertzman et al., 1997
Mortality 1950–1989	6	1.2 (0.5–2.3)	
DENMARK			
Danish gardeners—incidence from 3,156 male and 859 female gardeners			Hansen et al., 2007
25-year followup (1975–2001)		**Herbicides**	
Born before 1915 (high exposure)	3	5.9 (1.9–18.2)	
Born 1915–1934 (medium exposure)	0	0.0 (0.0–3.8)	
Born after 1934 (low exposure)	1	1.8 (0.3–12.9)	
10-year followup (1975–1984) of male gardeners	3	5.3 (1.1–15.4)	Hansen et al., 1992
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	2	1.0 (0.1–3.5)	Torchio et al., 1994
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of 142 incident STS cases vs remainder of 19,904 men with any incident cancer			
Forestry workers (n = 134)		**Herbicides**	Reif et al., 1989
Aged 20–59	4	3.2 (1.2–9.0)	
Aged ≥ 60	0	—	

continued

TABLE 11 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
SWEDEN		99% CI	
Swedish pesticide applicators—incidence (n = 20,245)	7	0.9 (0.8–1.1)	Wiklund et al., 1988b, 1989a
354,620 Swedish agricultural and forestry workers identified from 1960 census, followed 1961–1979; compared to reference population	331	0.9 (0.8–1.0)	Wiklund and Holmes, 1986
Incident STS cases 1961–1973 with agriculture as economic activity in 1960 census (connective tissue and muscle)	162	1.1 (0.9–1.3)	Wiklund, 1983
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	98	0.9 (0.8–1.1)	
Nonwhites (n = 11,446)	10	1.5 (0.7–2.8)	
Women			
Whites (n = 2,400)	3	1.2 (0.2–3.5)	
Nonwhites (n = 2,066)	0	0.0 (0.0–1.9)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2002			Alavanja et al., 2005
Private applicators	10	0.7 (0.3–1.2)	
Spouses of private applicators (> 99% women)	3	0.5 (0.1–1.4)	
Commercial applicators	nr	0.0 (0.0–3.8)	
Mortality			
Enrollment through 2007, vs state rates (connective tissue)			Waggoner et al., 2011
Applicators (n = 1,641)	9	0.7 (0.3–1.5)	
Spouses (n = 676)	6	1.0 (0.4–2.2)	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	4	0.7 (0.2–1.8)	
Spouses of private applicators (> 99% women)	3	1.4 (0.3–4.1)	
US Department of Agriculture Workers—nested case-control study of white men dying 1970–1979 of STS		**Herbicides**	
USDA forest and soil	2	1.0 (0.1–3.6)	Alavanja et al., 1989
Florida Pesticide Applicators licensed 1965–1966 (n = 3,827)—mortality through 1976		**Herbicides**	Blair et al., 1983
Any pesticide (dose-response by length of licensure)	0	nr	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Incidence			
20-year followup to 1996—men and women			
Zone A	0	nr	Pesatori et al., 2009
Zone B	0	nr	
Zone R	9	1.3 (0.6–2.7)	

TABLE 11 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
10-year followup to 1991—men			Bertazzi et al., 1993; Pesatori et al., 1992
Zone A	0	nr	
Zone B	0	nr	
Zone R	6	2.8 (1.0–7.3)	
10-year followup to 1991—women			Bertazzi et al., 1993; Pesatori et al., 1992
Zone A	0	nr	
Zone B	0	nr	
Zone R	2	1.6 (0.3–7.4)	
Mortality			
25-year followup to 2001—men and women			Consonni et al., 2008
Zone A	0	nr	
Zone B	0	nr	
Zone R	4	0.8 (0.3–2.1)	
20-year followup to 1996			Bertazzi et al., 2001
Zone A—men and women	0	nr	
Zone B—men and women	0	nr	
Zones A and B—men	0	nr	
Zones A and B—women	0	nr	
15-year followup to 1991—men			Bertazzi et al., 1997, 1998
Zone A	—	nr	
Zone B	0	nr	
Zone R	4	2.1 (0.7–6.5)	
15-year followup to 1991—women			Bertazzi et al., 1997, 1998
Zone A	—	nr	
Zone B	0	nr	
Zone R	0	nr	
10-year followup to 1986—men			Bertazzi et al., 1989a
Zone A, B, R	2	5.4 (0.8–38.6)	
Zone R	2	6.3 (0.9–45.0)	Bertazzi et al., 1989b
10-year followup to 1986—women			Bertazzi et al., 1989a
Zone A, B, R	1	2.0 (0.2–1.9)	
Zone B	1	17.0 (1.8–163.6)	Bertazzi et al., 1989b
FINLAND			
Finnish community exposed to chlorophenol contamination (men and women)	6	**Chlorophenol** 1.6 (0.7–3.5)	Lampi et al., 1992
FRANCE			
Residents near French solid-waste incinerator—incidence		**Dioxin**	Viel et al., 2000
Spatial cluster	45	1.4 (p = 0.004)	
1994–1995	12	3.4 (p = 0.008)	
ITALY			
Italian rice growers	1	**Chlorophenoxy acids, chlorophenols** 4.0 (0.1–22.3)	Gambini et al., 1997
NEW ZEALAND			
Residents of New Plymouth Territorial Authority, New Zealand near plant manufacturing 2,4,5-T in 1962–1987		**2,4,5-T**	Read et al., 2007
Incidence	56	1.0 (0.8–1.4)[c]	
1970–1974	7	1.0 (0.4–2.1)	
1975–1979	3	0.4 (0.1–2.1)	

continued

TABLE 11 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
1980–1984	10	1.3 (0.6–2.4)	
1985–1989	11	1.2 (0.6–2.2)	
1990–1994	9	0.9 (0.4–1.7)	
1995–1999	14	1.3 (0.7–2.2)	
2000–2001	2	0.8 (0.1–3.0)	
Mortality	27	1.2 (0.8–1.8)[c]	
1970–1974	5	1.8 (0.6–4.3)	
1975–1979	1	0.4 (0.0–2.0)	
1980–1984	4	1.1 (0.3–2.9)	
1985–1989	5	1.5 (0.5–3.6)	
1990–1994	5	1.3 (0.4–3.0)	
1995–1999	5	1.3 (0.4–3.0)	
2000–2001	2	0.9 (0.1–3.1)	
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995a
Incidence			
East coast	0	0.0 (0.0–2.6)	
West coast	3	0.5 (0.1–1.4)	
Mortality			
East coast	0	nr	
West coast	0	nr	
CASE-CONTROL STUDIES			
US Case-Control Studies			
Kansas residents—duration and frequency of herbicide use—incidence		**Phenoxy herbicides, 2,4-D**	Hoar et al., 1986
All farmers	95	1.0 (0.7–1.6)	
Farm-use of herbicides	22	0.9 (0.5–1.6)	
Washington state residents—incidence (1983–1985)		**Phenoxy herbicides, chlorinated phenols**	Woods et al., 1987
High phenoxy exposure	nr	0.9 (0.4–1.9)	
Self-reported chloracne	nr	3.3 (0.8–14.0)	
International Case-Control Studies			
Australian residents in Victorian Cancer Registry (1982–1987)	30	**Phenoxy compounds** 1.0 (0.3–3.1)	Smith and Christophers, 1992
British agricultural workers		**Herbicides**	Balarajan and Acheson, 1984
Overall	42	1.7 (1.0–2.9)	
Under 75 years old	33	1.4 (0.8–2.6)	
Cross-Canada Study of Pesticides and Health—Men (≥ 19 years of age) diagnosed September 1991–December 1994 (n = 357) vs matched population-based controls (n = 1,506); exposure to:			Pahwa et al., 2011
Phenoxy herbicides	80 vs 321	1.1 (0.8–1.5)	
2,4-D	69 vs 293	1.0 (0.7–1.4)	
Mecoprop	26 vs 81	1.3 (0.8–2.2)	
MCPA	13 vs 46	1.1 (0.6–2.2)	
Diclofop-methyl	8 vs 25	1.2 (0.4–2.9)	

TABLE 11 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Cross-Canada Study of Pesticides and Health—Men (≥ 19 years of age) diagnosed September 1991–December 1994 (n = 357) vs matched population-based controls (n = 1,506); exposure to:		**Phenoxy herbicides**	Pahwa et al., 2006
Any phenoxyherbicide	80 vs 321	1.1 (0.7–1.5)	
2,4-D	69 vs 293	1.0 (0.6–1.5)	
Mecoprop	26 vs 81	1.0 (0.5–1.9)	
MCPA	13 vs 46	1.1 (0.5–2.2)	
Finnish STS patients vs controls matched on age and area; adjusted for sex, PCDD/F TEQ in fat		**Dioxin**	Tuomisto et al., 2017
Reported exposure to wood preservatives	8	0.96 (0.60–1.54)	
Reported exposure to fungicides and herbicides	7	0.87 (0.50–1.51)	
Reported exposure to insecticides	6	0.90 (0.54–1.49)	
Reported exposure to any of the three chemical groups	15	0.84 (0.49–1.42)	
Finnish STS patients vs controls within quintiles based on TEQ in subcutaneous fat—incidence	110	**Dioxin**	Tuomisto et al., 2004
Quintile 1 (median, ~12 ng/kg TEQ)	nr	1.0	
Quintile 2 (median, ~20 ng/kg TEQ)	nr	0.4 (0.2–1.1)	
Quintile 3 (median, ~28 ng/kg TEQ)	nr	0.6 (0.2–1.7)	
Quintile 4 (median, ~40 ng/kg TEQ)	nr	0.5 (0.2–1.3)	
Quintile 5 (median, ~62 ng/kg TEQ)	nr	0.7 (0.2–2.0)	
Italy			
Population-based Veneto Tumour Registry, Italy, average exposure based on duration and distance of residence from 33 industrial sources—incidence		**Dioxin**	Zambon et al., 2007
Sarcoma (ICD-9 158, 171, 173, visceral sites)			
Men			
< 4 TCDD (fg/m^3)	31	1.0	
4–6	39	1.1 (0.6–2.0)	
≥ 6	17	1.9 (0.9–4.0)	
Women		p-trend = 0.15	
< 4 TCDD (fg/m^3)	24	1.0	
4–6	44	1.5 (0.8–2.7)	
≥ 6	17	2.4 (1.0–5.6)	
Men, women combined		p-trend = 0.04	
Connective, other soft tissue (ICD-9 171)			
< 4 TCDD (fg/m^3)	25	1.0	
4–6	39	1.4 (0.7–2.5)	
≥ 6	17	3.3 (1.4–7.9)	
Skin (ICD-9 173)		p-trend = 0.01	
< 4 TCDD (fg/m^3)	5	1.0	
4–6	10	0.0 (0.3–4.7)[d]	
≥ 6	2	0.3 (0.0–3.4)	
		p-trend = 0.48	

continued

TABLE 11 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Retroperitoneum, peritoneum (ICD-9 158)			
< 4 TCDD (fg/m^3)	6	1.0	
4–6	12	1.1 (0.3–3.4)	
≥ 6	3	0.8 (0.1–4.5)	
		p-trend = 0.86	
Visceral sites		TCDD	
< 4 (fg/m^3)	19	1.0	
4–6	22	1.2 (0.6–2.6)	
≥ 6	12	2.5 (1.0–6.3)	
		p-trend = 0.08	
Residents near industrial-waste incinerator in Mantua, Italy—incidence		**Dioxin**	
Residence within 2 km of incinerator	5	31.4 (5.6–176.1)	Comba et al., 2003
Residents near chemical plant in Mantua, Italy—incidence	20	**TCDD emissions** 2.3 (1.3–3.5)	Costani et al., 2000
Italian rice weeders (1981–1983)		**Phenoxy herbicides**	Vineis et al., 1986
Among all living females (n = 31)	5	2.4 (0.4–16.1)	
New Zealand Pesticide Workers		**Phenoxy herbicides** 90% CI	
Update of New Zealand workers (1976–1982)	133	1.1 (0.7–1.8)	Smith and Pearce, 1986
Reanalysis of New Zealand workers (1976–1980)	17	1.6 (0.7–3.8)	Smith et al., 1984
New Zealand workers exposed to herbicides (1976–1980)	17	1.6 (0.8–3.2)	Smith et al., 1983
Swedish agricultural and forestry workers (1974–1979)		**Phenoxy acids, chlorophenols**	Eriksson et al., 1979, 1981
	25	(2.5–10.4) 5:1 matched	
Swedish patients (1970–1977)		**Phenoxy acids, chlorophenols**	Hardell, 1981; Hardell and Sandström, 1979
Exposed to phenoxy herbicides	13	5.5 (2.2–13.8)	
Exposed to chlorophenols	6	5.4 (1.3–22.5)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,5-DCP, 2,5-dichlorophenol; CATI, computer-assisted telephone interviewing; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job-exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; n, number; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; PM, proportionate mortality; SEA, Southeast Asia; STS, soft-tissue sarcoma; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; TEQ, toxicity equivalent; USDA, US Department of Agriculture; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

[c]Committee computed total SMR and SIR by dividing sum of observed values by sum of expected values over all years; 95% CIs on these total ratios were computed with exact methods.

[d]There appears to be an error in this entry because lower 95% CI (0.3) is not smaller than odds ratio (0.0).

TABLE 12 Selected Epidemiologic Studies—Melanoma (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk(95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Incidence			
1982–2003—White SEA comparison veterans only (n = 1,482). Serum TCDD (pg/g) based on model with exposure variable $\log_e$(TCDD)			Pavuk et al., 2005
Per unit increase of –$\log_e$(TCDD) (pg/g) Quartiles (pg/g):	25	2.7 (1.1–6.3)	
0.4–2.6	3	1.0	
2.6–3.8	5	2.1 (0.4–11.0)	
3.8–5.2	8	3.2 (0.7–15.5)	
> 5.2	9	3.6 (0.7–17.2)	
Number of years served in SEA (per year of service)			
Quartiles (years in SEA):	25	1.1 (0.9–1.3)	
0.8–1.3	3	1.0	
1.3–2.1	4	1.9 (0.3–10.3)	
2.1–3.7	8	3.2 (0.7–15.3)	
3.7–16.4	10	4.1 (0.9–19.7)	
Through 1999—White subjects vs national rates			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	17	2.3 (1.4–3.7)	
With tours between 1966–1970	16	2.6 (1.5–4.1)	
SEA comparison veterans (n = 1,776)	15	1.5 (0.9–2.4)	
With tours between 1966–1970	12	1.5 (0.8–2.6)	
White AFHS subjects			
Veterans who spent at most 2 years in SEA			
Per unit increase of –$\log_e$(TCDD) (pg/g)	14	2.2 (1.3–3.9)	
Comparison group	3	1.0	
Ranch Hand— < 10 TCDD pg/g in 1987	4	3.0 (0.5–16.8)	
Ranch Hand < 118.5 TCDD pg/g at end of service	4	7.4 (1.3–41.0)	
Ranch Hand > 118.5 TCDD pg/g at end of service	3	7.5 (1.1–50.2)	
Only Ranch Hands with 100% service in Vietnam, comparisons with no Vietnam service			
Per unit increase of –$\log_e$(TCDD) (pg/g)	14	1.7 (1.0–2.8)	
Comparison group	2	1.0	
Ranch Hand— < 10 TCDD pg/g in 1987	5	3.9 (0.4–35.3)	
Ranch Hand < 118.5 TCDD pg/g at end of service	4	7.2 (0.9–58.8)	
Ranch Hand > 118.5 TCDD pg/g at end of service	3	5.5 (0.6–46.1)	
Ranch Hand veterans, comparisons through June 1997			Ketchum et al., 1999
Ranch Hand background exposure	4	1.1 (0.3–4.5)	
Ranch Hand low exposure	6	2.6 (0.7–9.1)	
Ranch Hand high exposure	2	0.9 (0.2–5.6)	
Comparisons	9	1.0	
Attended 1987 exam—Rand Hand personnel (n = 995) vs SEA veterans (n = 1,299)	4	1.3 (0.3–5.2)	Wolfe et al., 1990

continued

TABLE 12 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk(95% CI)[b]	Reference
US VA Cohort of Army Chemical Corps—Expanded as of 1997 to include all Army men with chemical MOS (2,872 deployed vs 2,737 nondeployed) serving during Vietnam era (July 1, 1965–March 28, 1973)		**All COIs**	
Through 2005 (mortality)			Cypel and Kang, 2010
Deployed veterans (2,872) vs nondeployed (2,737)	5 vs 4	1.5 (0.4–6.2)	
ACC deployed men in Kang et al. (2006) reported sprayed herbicide vs did not spray			
Vietnam cohort	5	1.3 (0.4–3.1)	
Non-Vietnam cohort	4	1.3 (0.4–3.4)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
1965–2000 (mortality)	6	1.4 (0.4–4.9)	Boehmer et al., 2004
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1982			Breslin et al.,1986, 1988
Army, deployed (n = 19,708) vs nondeployed (n = 22,904)	145	1.0 (0.9–1.1)	
Marine Corps, deployed (n = 4,527) vs nondeployed (n = 3,781)	36	0.9 (0.6–1.5)	
State Studies of US Vietnam Veterans			
Massachusetts Vietnam-era veterans			
Veterans aged 35–65 years in 1993—melanoma cases diagnosed 1988–1993 vs gastrointestinal cancers	21	1.4 (0.7–2.9)	Clapp, 1997
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	756	1.3 (1.2–1.4)	ADVA, 2005b
Navy	173	1.4 (1.2–1.6)	
Army	510	1.2 (1.2–1.4)	
Air Force	73	1.4 (1.1–1.7)	
Validation Study		*Expected number of exposed cases*	
	483	380 (342–418)	
Men	2,689	380 (342–418)	CDVA, 1998a
Women	7	3 (1–8)	CDVA, 1998b
Mortality			
All branches, return–2001	111	1.1 (0.9–1.3)	ADVA, 2005a
Navy	35	1.6 (1.0–2.1)	
Army	66	1.0 (0.7–1.2)	
Air Force	10	1.0 (0.5–1.8)	
1980–1994	51	1.3 (0.9–1.7)	CDVA, 1997a
Sample of 1,000 Male Australian Vietnam Veterans— prevalence		**All COIs**	
450 interviewed 2005–2006 vs respondents to 2004–2005 national survey	nr	4.7 (1.3–8.2)	O'Toole et al., 2009

TABLE 12 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk(95% CI)[b]	Reference
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Incidence			
1982–2000	204	1.1 (0.9–1.4)	ADVA, 2005c
Mortality			
1966–2001	14	0.6 (0.3–1.1)	ADVA, 2005c
1982–1994	16	0.5 (0.2–1.3)	CDVA, 1997b
International Vietnam-Veteran Studies			
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008)	33	0.7 (0.5–1.0)	
Mortality (1988–2008)	4	0.6 (0.2–1.4)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores)		**All COIs**	
		HRs	
Incidence (1992–2003)—categorized high (n = 9) vs low (n = 10)	9	0.9 (0.4–2.3)	Yi and Ohrr, 2014
Mortality (1992–2005)—categorized high (n = 6) vs low (n = 5)		1.5 (0.4–5.4)	Yi et al., 2014b
HR per unit of $\log_{10}$ EOI (n = 180,639)	11	1.3 (0.9–1.8)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	9	0.6 (0.3–1.2)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	5	0.5 (0.2–3.2)	
7,553 not exposed to highly chlorinated PCDDs	4	0.0 (0.3–2.4)	
British MCPA Plant—All manual employees employed January 1947–December 1975 (n = 1,146), ever potentially exposed to phenoxy herbicides (n = 1,544), potentially exposed to phenoxy herbicides ≥ 1 year (n = 848) (not included in IARC cohort)		**MCPA**	
Mortality through 2012, all workers			Coggon et al., 2015
Melanoma (ICD-10 C43)	7	0.66 (0.26–1.35)	
Mortality through 2012, workers ever exposed to phenoxy herbicides			
Melanoma (ICD-10 C43)	6	0.73 (0.27–1.59)	
Mortality through 2012, workers ever exposed to phenoxy herbicides ≥ 1 year			
Melanoma (ICD-10 C43)	2	0.55 (0.07–2.00)	
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence			
Incidence 1943–1987 (men only)	4	4.3 (1.2–10.9)	Lynge, 1993
Mortality			
Mortality 1955–2006	7	1.3 (0.9–1.8)	Boers et al., 2012

continued

TABLE 12 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk(95% CI)[b]	Reference
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–2006 (HRs for lagged TCDD plasma levels)	5	1.3 (0.8–2.2)	Boers et al., 2012
Mortality 1955–1991	1	2.9 (0.1–15.9)	Hooiveld et al., 1998
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	2	1.0 (0.1–3.7)	
Production Workers (713 men and 100 women worked > 1 month in 1969–1984)			
Mortality 1969–2000	0	0.0 (0.0–3.0)	't Mannetje et al., 2005
Sprayers (697 men and 2 women registered any time 1973–1984)			
Mortality 1973–2000	1	0.6 (0.0–3.4)	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
1937–2011 Potential dioxin exposure (n = 2,192), TCP production (n =1,419), PCP production (n = 577), Both TCP and PCP (n = 196)			Collins et al., 2016
TCP or PCP, malignant melanoma (C43)	2	0.36 (0.04–1.30)	
TCP, malignant melanoma (C43)	2	0.47 (0.06–1.71)	
PCP, malignant melanoma (C43)	1	0.56 (0.01–3.09)	
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, Michigan) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)	2	0.6 (0.1–2.3)	Collins et al., 2009b
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)	8	1.2 (0.5–2.3)	Burns CJ et al., 2011
Dow PCP Production Workers (1937–1989 in Midland, Michigan) (**not** in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	1	0.7 (0.0–4.0)	Collins et al., 2009c
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	20	0.8 (0.5–1.3)	
Ever	21	1.2 (0.7–1.8)	

TABLE 12 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk(95% CI)[b]	Reference
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Canadian Farm Operator Study—156,242 men farming in Manitoba, Saskatchewan, and Alberta in 1971; mortality from melanoma June 1971–December 1987			
Deaths among Saskatchewan farmers ≥ 35 years of age, 1971–1985	24	1.1 (0.7–1.6)	Wigle et al., 1990
Sawmill Workers in British Columbia—23,829 workers for ≥ 1 year at 11 mills using chlorophenates 1940–1985		**Chlorophenates, not TCDD**	
Incidence 1969–1989	38	1.0 (0.7–1.3)	Hertzman et al., 1997
Mortality 1950–1989	17	1.4 (0.9–2.0)	
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Self-employed	72	0.7 ($p < 0.05$)	
Employee	17	0.6 (nr)	
Danish gardeners—incidence from 3,156 male and 859 female gardeners		**Herbicides**	Hansen et al., 2007
25-year followup (1975–2001)	31	1.3 (0.9–1.8)	
Born before 1915 (high exposure)	28	0.9 (0.6–1.4)	
Born 1915–1934 (medium exposure)	36	0.6 (0.4–0.9)	
Born after 1934 (low exposure)	5	0.3 (0.1–0.7)	
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	5	3.6 (1.2–8.3)	Swaen et al., 2004
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	9	1.2 (0.6–2.3)	Torchio et al., 1994
SWEDEN			
Incident melanoma cases 1961–1973 with agriculture as economic activity in 1960 census	268	0.8 (0.7–1.0)	Wiklund, 1983
Swedish lumberjacks—Used phenoxys 1954–1967, Incidence 1958–1992			Thörn et al., 2000
Exposed (n = 154)	0	nr	
Foremen (n = 15)	0	nr	
Lumberjacks (n = 139)	0	nr	
Unexposed lumberjacks (n = 241)	0	nr	
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	244	1.0 (0.8–1.1)	
Nonwhites (n = 11,446)	5	1.2 (0.4–2.9)	
Women			
Whites (n = 2,400)	5	1.1 (0.4–2.7)	
Nonwhites (n = 2,066)	1	1.2 (0.0–6.6)	

continued

TABLE 12 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk(95% CI)[b]	Reference
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	173	0.9 (0.8–1.0)	
Commercial applicators	13	1.1 (0.6–1.9)	
Spouses	92	1.2 (0.9–1.4)	
Licensed, male pesticide applicators—150 cutaneous melanomas among 24,704 pesticide applicators			Dennis et al., 2010
Ever-exposed to arsenic-based pesticides vs never exposed	11	1.3 (0.7–2.4)	
Ever used lead arsenate insecticide	10	1.2 (0.6–2.3)	
Enrollment through 2002			Samanic et al., 2006
Dicamba—lifetime days exposure			
None	32	1.0	
1– < 20	10	1.0 (0.5–2.1)	
20– < 56	18	1.6 (0.8–3.0)	
56– < 116	6	0.7 (0.3–1.8)	
≥ 116	6	0.8 (0.3–2.1)	
		p-trend = 0.51	
Enrollment through 2002			Alavanja et al., 2005
Private applicators	100	1.0 (0.8–1.2)	
Spouses of private applicators (> 99% women)	67	1.6 (1.3–2.1)	
Commercial applicators	7	1.1 (0.4–2.2)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	38	0.8 (0.5–1.1)	
Spouses (n = 676)	10	0.8 (0.4–1.4)	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	13	0.7 (0.4–1.3)	
Spouses of private applicators (> 99% women)	2	0.4 (0.1–1.6)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Incidence			
20-year followup to 1996—men and women			
Zone A	1	1.6 (0.2–11.6)	Pesatori et al., 2009
Zone B	2	0.5 (0.1–2.0)	
Zone R	19	0.7 (0.4–1.1)	

TABLE 12 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk(95% CI)[b]	Reference
Mortality			
25-year followup to 2001—men and women			Consonni et al., 2008
Zone A	1	3.1 (0.4–22.0)	
Zone B	2	1.0 (0.2–3.9)	
Zone R	12	0.8 (0.4–1.5)	
20-year followup to 1996			Bertazzi et al., 2001
Zones A and B—men	1	1.5 (0.2–12.5)	
Zones A and B—women	2	1.8 (0.4–7.3)	
15-year followup to 1991—men			Bertazzi et al., 1997
Zone A	0	0.0 (0.0–60.2)	
Zone B	0	0.0 (0.0–9.1)	
Zone R	3	1.1 (0.2–3.2)	
15-year followup to 1991—women			Bertazzi et al., 1997
Zone A	1	9.4 (0.1–52.3)	
Zone B	0	0.0 (0.0–5.4)	
Zone R	3	0.6 (0.1–1.8)	
10-year followup to 1986—men			Bertazzi et al., 1989a
Zone A, B, R	3	3.3 (0.8–13.9)	
10-year followup to 1986—women			Bertazzi et al., 1989a,b
Zone A, B, R	1	0.3 (0.1–2.5)	
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995a
Incidence			
East coast	0	0.0 (0.0–0.7)	
West coast	20	0.8 (0.5–1.2)	
Mortality			
East coast	0	0.0 (0.0–1.7)	
West coast	6	0.7 (0.3–1.5)	
CASE-CONTROL STUDIES			
International Case-Control Studies			
British Columbia—melanoma cases recruited for a study evaluating effects of ultraviolet exposure and gene variants using plasma specimens and sun-exposure data (80 cases vs 310 controls)		**PCBs**	Gallagher et al., 2011
Highest PCB-exposure quintile	29	6.0 (2.0–18.2)	
Dioxin-like PCBs	25	2.8 (1.0–8.0)	
Non-dioxin-like PCBs	30	7.0 (2.3–21.4)	
European—uveal melanoma patients (n = 323), diagnosed 1994–1997, identified from hospital records (diagnosed 1994–1995) in nine countries and matched controls (n = 3,198)		**Herbicides**	Behrens et al., 2012
Personal application of herbicides	8	0.5 (0.2–1.3)	
Personal mixing of herbicides	6	0.5 (0.2–1.5)	

continued

TABLE 12 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk(95% CI)[b]	Reference
UK men, 18–35 years of age from counties with particular chemical manufacturing—mortality		**Herbicides, Chlorophenols**	Magnani et al., 1987
Herbicides	nr	1.2 (0.4–4.0)	
Chlorophenols	nr	0.9 (0.4–2.3)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; ACC, Army Chemical Corps; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job-exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; MOS, military occupational specialty; n, number; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; SEA, Southeast Asia; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Cohorts are male and outcome mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

TABLE 13 Selected Epidemiologic Studies—Other Nonmelanoma (Basal-Cell and Squamous-Cell) Skin Cancers (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Incidence—basal cell, squamous cell			
1982–2003—White SEA comparison veterans only (n = 1,482). Serum TCDD (pg/g) based on model with exposure variable $\log_e$(TCDD)	253	1.2 (0.9–1.4)	Pavuk et al., 2005
Per unit increase of –$\log_e$(TCDD) (pg/g) Quartiles (pg/g):			
0.4–2.6	50	nr	
2.6–3.8	59	1.2 (0.8–1.8)	
3.8–5.2	71	1.5 (1.1–2.3)	
> 5.2	73	1.4 (0.9–2.0)	
Number of years served in SEA (per year of service)	253	1.0 (0.9–1.1)	
Quartiles (years in SEA):			
0.8–1.3	55	nr	
1.3–2.1	50	0.9 (0.6–1.4)	
2.1–3.7	73	1.1 (0.8–1.6)	
3.7–16.4	75	1.2 (0.8–1.7)	
Attended 1987 exam—Rand Hand personnel (n = 995) vs SEA veterans (n = 1,299)			Wolfe et al., 1990
Basal cell carcinoma	78	1.5 (1.0–2.1)	
Squamous cell carcinoma	6	1.6 (0.5–5.1)	
VA Hospital Retrospective Chart Review—1,024 skin cancer patients with biopsied skin lesions from Richard L. Roudebush VA Medical Center from 2003–2013		**All COIs**	
Incidence—basal cell carcinoma, exposed vs unexposed	66	36.1% vs 30.3% p = 0.36	Nosrati et al., 2014
Incidence—squamous cell carcinoma, exposed vs unexposed	34	53.6% vs 57.2% p = 0.18	
Total exposed vs unexposed		43.0% vs 41.4% p = 0.28	
International Vietnam-Veteran Study			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
Validation Study (expected number of exposed cases)			
Men	6,936	nr	CDVA, 1998a
Women	37	nr	CDVA, 1998b
International Vietnam-Veteran Studies			
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs)		**All COIs**	
Incidence (1992–2003)—"other skin" (C44) categorized high (n = 40) vs low (n = 38)		1.0 (0.6–1.6)	Yi and Ohrr, 2014

continued

TABLE 13 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates	4	0.9 (0.3–2.4)	
Mortality 1939–1992			Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	4	1.3 (0.3–3.2)	
7,553 not exposed to highly chlorinated PCDDs	0	0.0 (0.0–3.4)	
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
British MCPA Plant—All manual employees employed January 1947–December 1975 (n = 1,146), ever potentially exposed to phenoxy herbicides (n = 1,544), potentially exposed to phenoxy herbicides ≥ 1 year (n = 848) (not included in IARC cohort)		**MCPA**	
Mortality through 2012, all workers			Coggon et al., 2015
Other skin (ICD-10 C44)	4	1.15 (0.31–2.93)	
Mortality through 2012, workers ever exposed to phenoxy herbicides			
Other skin (ICD-10 C44)	2	0.81 (0.10–2.91)	
Mortality through 2012, workers ever exposed to phenoxy herbicides ≥ 1 year			
Other skin (ICD-10 C44)	0	0.0 (0.00–3.15)	
Mortality through 1983	3	3.1 (0.6–9.0)	Coggon et al., 1986
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Through 1994 (n = 1,517)	0	nr	Burns et al., 2001
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	493	0.7 ($p < 0.05$)	
Employee	98	0.7 ($p < 0.05$)	
Women			
Self-employed	5	0.3 ($p < 0.05$)	
Employee	10	0.9 (nr)	
Family worker	90	0.6 ($p < 0.05$)	
Danish gardeners—incidence from 3,156 male and 859 female gardeners (skin, ICD-7 190–191)	31	**Herbicides** 1.3 (0.9–1.8)	Hansen et al., 2007
25-year followup (1975–2001)			
Born before 1915 (high exposure)	28	0.9 (0.6–1.4)	
Born 1915–1934 (medium exposure)	36	0.6 (0.4–0.9)	
Born after 1934 (low exposure)	5	0.3 (0.1–0.7)	

TABLE 13 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000—melanoma, squamous-cell carcinoma, unknown skin cancer (mortality presumably attributable to melanoma)	5	3.6 (1.2–8.3)	Swaen et al., 2004
ICELANDIC pesticide users (n = 2,449, 1,860 men and 589 women), 2,4-D used most often, little 2,4,5-T			Zhong and Rafnsson, 1996
Men	5	2.8 (0.9–6.6)	
Men, women combined	5	2.6 (0.8–6.1)	
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	3	0.6 (0.1–1.8)	Torchio et al., 1994
SWEDEN			
Incident melanoma cases 1961–1973 with agriculture as economic activity in 1960 census	708	99% CI 1.1 (1.0–1.2)	Wiklund, 1983
Swedish lumberjacks—Used phenoxys 1954–1967, Incidence 1958–1992			Thörn et al., 2000
Exposed (n = 154)			
Foremen (n = 15)	1	16.7 (0.2–92.7)	
Lumberjacks (n = 139)	0	—	
Unexposed lumberjacks (n = 241)	3	2.0 (0.4–5.8)	
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states (skin, including melanoma)		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	425	1.1 (1.0–1.2)	
Nonwhites (n = 11,446)	13	1.0 (0.5–1.7)	
Women			
Whites (n = 2,400)	6	1.0 (0.4–2.1)	
Nonwhites (n = 2,066)	3	1.8 (0.4–5.4)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group)		**TCDD**	
Incidence			
20-year followup to 1996—men and women			Pesatori et al., 2009
Zone A	3	1.4 (0.5–4.3)	
Zone B	5	0.4 (0.2–0.9)	
Zone R	88	0.9 (0.8–1.2)	
10-year followup to 1991—men			Bertazzi et al., 1993
Zone A	1	2.4 (0.3–17.2)	
Zone B	2	0.7 (0.2–2.9)	
Zone R	20	1.0 (0.6–1.6)	
10-year followup to 1991—women			Bertazzi et al., 1993
Zone A	1	3.9 (0.5–28.1)	
Zone B	2	1.3 (0.3–5.1)	
Zone R	13	1.0 (0.6–1.9)	

continued

TABLE 13 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Other International Environmental Study			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995
Incidence			
East coast	22	2.3 (1.5–3.5)	
West coast	69	1.1 (0.9–1.4)	
Mortality			
East coast	0	0.0 (0.0–15.4)	
West coast	5	3.1 (1.0–7.1)	
CASE-CONTROL STUDIES			
International Case-Control Studies			
Alberta, **Canada** residents—squamous-cell carcinoma—incidence		**Herbicides**	Gallagher et al., 1996
All herbicide exposure	79	1.5 (1.0–2.3)	
Low herbicide exposure	33	1.9 (1.0–3.6)	
High herbicide exposure	46	3.9 (2.2–6.9)	
Alberta, **Canada** residents—basal-cell carcinoma		**Herbicides**	Gallagher et al., 1996
All herbicide exposure	70	1.1 (0.8–1.7)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; MCPA, 2-methyl-4-chlorophenoxyacetic acid; n, number; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

TABLE 14 Selected Epidemiologic Studies—Breast Cancer (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Mortality			
1965–2000	0	nr	Boehmer et al., 2004
US VA Cohort of Female Vietnam-era Veterans served in Vietnam (n = 4,586; nurses only = 3,690); nondeployed (n = 5,325; nurses only = 3,282)		**All COIs**	
Incidence			
Breast cancer	170	1.2 (0.9–1.5)	Kang et al., 2000b
Mortality			
Through 2010	170	1.1 (0.8–1.4)	Kang et al., 2014
Vietnam nurses only	118	0.9 (0.6–1.3)	
Through 2004	57	1.0 (0.7–1.4)	Cypel and Kang, 2008
Vietnam nurses only	44	0.9 (0.6–1.4)	
Through 1991 (Vietnam nurses not reported separately)	26	1.0 (0.6–1.8)	Dalager et al., 1995a
Through 1987 (Vietnam nurses not reported separately)	17	1.2 (0.6–2.5)	Thomas et al., 1991
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	7	0.9 (0.4–1.9)	ADVA, 2005b
Navy	1	0.6 (0.0–3.3)	
Army	5	1.0 (0.3–2.2)	
Air Force	1	1.1 (0.0–6.3)	
Validation Study		*Expected number of exposed cases*	
Women	17	5 (2–11)	CDVA, 1998b
Mortality			
All branches, return–2001	4	2.2 (0.6–5.4)	ADVA, 2005a
Navy	1	2.5 (0.0–13.5)	
Army	3	2.5 (0.5–7.2)	
Air Force	0	0.0 (0.0–14.6)	
1980–1994 (men)	3	5.5 (1.0– > 10.0)	CDVA, 1997a
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Incidence			
1982–2000	0	0.0 (0.0–2.4)	ADVA, 2005c
Mortality			
1966–2001	nr		ADVA, 2005c
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores)		**All COIs**	
		HRs	
Incidence (1992–2003)—breast cancer (C50) categorized high (n = 3) vs low (n = 5)		0.5 (0.1–2.3)	Yi and Ohrr, 2014

continued

TABLE 14 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992 (13,831 exposed to highly chlorinated PCDDs vs 7,553 unexposed)		**Phenoxy herbicides**	Kogevinas et al., 1997
Men	2	1.6 (0.2–2.1)	
Exposed to highly chlorinated PCDDs	2	2.6 (0.3–9.3)	
Not exposed to highly chlorinated PCDDs	0	nr	
Women	12	1.2 (0.6–2.1)	
Exposed to highly chlorinated PCDDs	9	2.2 (1.0–4.1)	
Not exposed to highly chlorinated PCDDs	3	0.5 (0.1–1.6)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort			Saracci et al., 1991
Men	2	3.5 (0.4–12.5)	
Women	1	0.3 (0.0–1.7)	
Mortality, incidence of women in production (n = 699) and spraying (n = 2) compared to national death rates and cancer incidence rates	7	**TCDD** 0.9 (0.4–1.9)	Kogevinas et al., 1993
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence 1943–1982 (women)	13	0.9 (nr)	Lynge, 1985
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 month in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–2007			Manuwald et al., 2012
Women	19	1.9 (1.1–2.9)	
Mortality 1952–1989—stats on men only, 1,184 (tables all for 1,148 men, not necessarily German nationals) vs national rates (also vs gas workers); same observation period as Becher et al., 1966	9	2.2 (1.0–4.1)	Manz et al., 1991
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	2	1.4 (0.2–5.0)	
Production Workers (713 men and 100 women worked > 1 month in 1969–1984)			
Mortality 1969–2000			't Mannetje et al., 2005
Phenoxy herbicide producers			
Men	1	32 (0.8–175)	
Women	1	1.3 (0.0–7.2)	
Phenoxy herbicide sprayers (> 99% men)			
Men	0	0.0 (0.0–214)	
Women	0	0.0 (0.0–86.0)	

TABLE 14 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, Washington, and Wichita, Kansas) and workers who made PCP and TCP at two additional plants (in Midland, Michigan, and Sauget, Illinois)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122)	1	0.5 (0.0–2.9)	
PCP and TCP (n = 720)	0	nr	
PCP (no TCP) (n = 1,402)	1	0.6 (0.0–3.1)	
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)	0	nr	Burns CJ et al., 2011
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	21	0.9 (0.6–1.4)	
Ever	32	0.9 (0.6–1.3)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	5	0.5 (nr)	
Employee	3	1.4 (nr)	
Women			
Self-employed	41	0.9 (nr)	
Employee	25	0.6 ($p < 0.05$)	
Family worker	429	0.8 ($p < 0.05$)	
SWEDEN			
Incident breast cancer cases 1961–1973 with agriculture as economic activity in 1960 census			Wiklund, 1983
Men, women		99% CI	
	444	0.8 (0.7–0.9)	
Men	nr	1.0 (nr)	
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	18	0.7 (0.4–1.2)	
Nonwhites (n = 11,446)	4	1.7 (0.5–4.4)	
Women			
Whites (n = 2,400)	71	1.0 (0.8–1.3)	
Nonwhites (n = 2,066)	30	0.7 (0.5–1.0)	

continued

TABLE 14 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	33	1.0 (0.7–1.3)	
Commercial applicators	0	nr	
Spouses	770	1.0 (0.9–1.1)	
Enrollment through 2002			Alavanja et al., 2005
Private applicators	27	1.1 (0.7–1.6)	
Spouses of private applicators (> 99% women)	474	1.0 (0.9–1.1)	
Commercial applicators	1	0.6 (0.1–3.5)	
Enrollment through 2001			Engel et al., 2005
Wives' own use of phenoxy herbicides	41	0.8 (0.6–1.1)	
2,4-D	41	0.8 (0.6–1.1)	
Husbands' own use of phenoxy herbicides	110	1.1 (0.7–1.8)	
2,4-D	107	0.9 (0.6–1.4)	
2,4,5-T	44	1.3 (0.9–1.9)	
2,4,5-TP	19	2.0 (1.2–3.2)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	11	0.9 (0.5–1.7)	
Spouses (n = 676)	136	0.8 (0.7–0.9)	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	3	0.9 (0.2–2.7)	
Spouses of private applicators (> 99% women)	54	0.9 (0.7–1.1)	
ENVIRONMENTAL			
United States, National Health and Nutrition Examination Survey—Females > 20 years of age, 1999–2004			Morgan et al., 2017
Estimated ORs for risk of having breast cancer, adjusted for age, race/ethnicity, BMI		**PCB 118**	
< LOD to 50%	6	1.00 (reference)	
50% to 75%	9	1.27 (0.21–7.79)	
> 75%	28	1.45 (0.26–7.92)	
Estimated ORs for risk of having breast cancer, adjusted for age, race/ethnicity, BMI, age at menarche, lactation		**Dioxin-like PCBs**	
< LOD to 50%	4	reference	
≥ 50%	39	1.58 (0.29–8.53)	

TABLE 14 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
France, E3N (Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale)—98,995 females born between 1925 and 1950.			Danjou et al., 2015
Estimated HRs according to quartiles of estimated dietary dioxin exposure (n = 63,830) adjusted for age, height, body mass index, energy intake, education, physical activity, smoking status, menopausal status, use of menopausal hormone treatment, alcohol intake, age at menarche, use of oral contraceptives, use of progestin, age at menopause, age at first full-term pregnancy and number of live births, breastfeeding, family history of breast cancer, history of personal benign breast disease and mammography		**Estimated dietary dioxin**	
Premenopausal women			
< 0.98 pg/kg body weight/day	104	1.00 (reference)	
0.98 to 1.23	105	0.84 (0.63–1.11)	
1.23 to 1.52	117	0.83 (0.62–1.11)	
≥ 1.52	120	0.77 (0.54–1.08)	
Postmenopausal women			
< 0.98 pg/kg body weight/day	775	1.00 (reference)	
0.98 to 1.23	749	0.94 (0.84–1.04)	
1.23 to 1.52	731	0.90 (0.80–1.01)	
≥ 1.52	764	0.93 (0.82–1.06)	
ER+/PR+			
< 0.98 pg/kg body weight/day	354	1.00 (reference)	n = 787 invasive breast cancer cases with missing hormone receptor status
0.98 to 1.23	336	0.91 (0.78–1.06)	
1.23 to 1.52	325	0.86 (0.73–1.02)	
≥ 1.52	350	0.91 (0.75–1.10)	
ER+/PR–			
< 0.98 pg/kg body weight/day	117	1.00 (reference)	
0.98 to 1.23	136	1.16 (0.89–1.49)	
1.23 to 1.52	125	1.07 (0.81–1.41)	
≥ 1.52	135	1.19 (0.86–1.63)	
ER–/PR–			
< 0.98 pg/kg body weight/day	98	1.00 (reference)	
0.98 to 1.23	91	0.84 (0.63–1.13)	
1.23 to 1.52	89	0.77 (0.56–1.07)	
≥ 1.52	81	0.65 (0.45–0.96)	
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group)		**TCDD**	
Incidence			
20-year followup to 1996—men and women			
Zone A	8	1.4 (0.7–2.9)	Pesatori et al., 2009
15+ years after accident	5	2.6 (1.1–6.2)	
10–14 years after accident	2	1.4 (0.4–5.7)	
5–9 years after accident	1	0.8 (0.1–5.7)	
Zone B	30	0.9 (0.6–1.2)	
Zone R	249	1.0 (0.9–1.2)	

continued

TABLE 14 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
10-year followup to 1991—men			Bertazzi et al., 1993
Zone R	1	1.2 (0.1–10.2)	
10-year followup to 1991—women			Bertazzi et al., 1993
Zone A	1	0.5 (0.1–3.3)	
Zone B	10	0.7 (0.4–1.4)	
Zone R	106	1.1 (0.9–1.3)	
Mortality			
25-year followup to 2001—men and women			Consonni et al., 2008
Zone A	2	0.6 (0.2–2.4)	
Zone B	13	0.6 (0.3–1.2)	
Zone R	133	0.9 (0.7–1.1)	
20-year followup to 1996			Bertazzi et al., 2001
Zones A and B—women	14	0.7 (0.4–1.3)	
15-year followup to 1991—women			Bertazzi et al., 1997
Zone A	1	0.6 (0.0–3.1)	
Zone B	9	0.8 (0.4–1.5)	
Zone R	67	0.8 (0.6–1.0)	
10-year followup to 1986—women			Bertazzi et al., 1989a,b
Zone A	1	1.1 (0.1–7.5)	
Zone B	5	0.9 (0.4–2.1)	
Zone R	28	0.6 (0.4–0.9)	
Seveso (Italy) Women's Health Study—981 women who were infants to 40 years of age when exposed—incidence		**TCDD**	
Hazard ratios for 10-fold increase in TCDD [$\log_{10}$ lipid adjusted TCDD (ppt)]			Warner et al., 2011
1976–2009	33	1.4 (0.9–2.3)	
Years from accident to diagnosis			
0–10 years (1976–1986)	3	2.9 (0.9–9.4)	
11–20 years (1987–1996)	10	2.2 (1.1–4.6)	
21–32 years (1997–2009)	20	1.1 (0.6–1.9)	
1976–1997	15	2.1 (1.0–4.6)	Warner et al., 2002
Ecological Study of Residents of Chapaevsk, Russia		**Dioxin**	Revich et al., 2001
Women			
Regional (Samara)	nr	50.7 (nr)	
National (Russia)	nr	46.2 (nr)	
Mortality—1995–1998 (SMR vs regional rates)			
Women	58	2.1 (1.6–2.7)	
FINLAND			
Finnish fishermen (n = 6,410) and spouses (n = 4,260) registered between 1980 and 2002 compared to national statistics		**Serum dioxin**	Turunen et al., 2008
Fisherman's wives	18	0.8 (0.5–1.3)	

TABLE 14 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
CASE-CONTROL STUDIES			
US Case-Control Studies			
California—Women undergoing breast biopsies in San Francisco area hospitals—79 breast cancer cases vs 52 controls with benign breasts conditions—incidence		**PCDDs, PCDFs**	Reynolds et al., 2005
Total TEQs (pg/g) in adipose breast tissue			
≤ 14.0	24	1.0	
14.1–20.9	22	0.7 (0.3–1.9)	
≤ 21.0	33	0.3 (0.3–2.0)	
		p-trend = 0.99	
California—Registry-based study of 128 Hispanic agricultural farm workers (women) diagnosed 1988–2001 and 640 cancer-free controls.		**Herbicides**	Mills and Yang, 2005
Cancer diagnosis 1987–1994			
Low 2,4-D use	12	0.6 (0.2–1.9)	
High 2,4-D use	8	0.6 (0.2–1.7)	
Cancer diagnosis 1995–2001			
Low 2,4-D use	19	2.2 (1.0–4.9)	
High 2,4-D use	21	2.1 (1.1–4.3)	
California Teachers Study Cohort—residential proximity to use of "endocrine disruptors" (including 2,4-D, cacodylic acid)		**2,4-D, cacodylic acid**	Reynolds et al., 2004
Quartiles of use (lb/mi^2)			
< 1	1,027	1.0	
1–21	274	1.0 (0.8–1.1)	
22–323	114	0.9 (0.7–1.1)	
≥ 324	137	1.0 (0.9–1.3)	
California women (n = 146) receiving medical care in Woodland Hills (1995–1996), 73 breast cancer cases vs 73 controls undergoing mammoplasty	73	**Organochlorines** nr	Bagga et al., 2000
New York—Population-based study of lifetime residential pesticide use in Long Island; 1,508 newly diagnosed cases and 1,556 matched controls (1996–1997)		**Pesticides**	Teitelbaum et al., 2007
Used lawn and garden pesticides			
Never	240	1.0	
Ever	1,254	1.3 (1.1–1.6)	
Product for weeds	1,109	1.4 (1.2–1.8)	
North Carolina—862 female farm workers, residents diagnosed 1993–1996 and 790 controls		**Herbicides**	Duell et al., 2000
Used pesticides in garden	228	2.3 (0.7–3.1)	
Laundered clothes for pesticide user	119	4.1 (2.8–5.9)	
Connecticut patient at Yale–New Haven hospital with breast related surgery; dioxin-like congener 156	nr	**dioxin-like PCBs** 0.9 (0.8–1.0)	Holford et al., 2000

continued

TABLE 14 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
International Case-Control Studies			
Canadian women in Quebec City—315 newly diagnosed breast cancer cases (and plasma concentrations) vs hospital- and population-based controls	314	**Organochlorines,** nr	Demers et al., 2000
Denmark females with breast cancer in Copenhagen City Heart Study (n = 195), 2 blood samples taken (1987–1978, 1981–1983)	195	**Organochlorines** *Overall survival RR* 2.8 (1.4–5.6)	Høyer et al., 2000
France—Besançon residents in zones of dioxin exposure around solid-waste incinerator (434 incident breast cancer cases; 2,170 randomly selected controls) (1996–2002)		**Dioxin**	Viel et al., 2008a
Women, 20–59 years of age			
Very low	41	1.0	
Low	81	1.1 (0.7–1.6)	
Intermediate	64	1.3 (0.8–1.9)	
High	11	0.9 (0.4–1.8)	
Women, 20–59 years of age			
Very low	50	1.0	
Low	111	0.9 (0.6–1.3)	
Intermediate	72	1.0 (0.7–1.4)	
High	4	0.3 (0.1–0.9)	
Tunisia—Non-metatstatic breast cancer cases at two cancer centers (n = 69) vs controls (n = 56)		**Dioxin (Heptachlor)**	Arrebola et al., 2015
Estimated OR adjusted for age, body mass index, occupational class, residence, education, accumulated lactation time, parity, menopausal status, family history of breast cancer, total serum lipids			
β-HCH (ng/dL)			
< LOD		1.0 (reference)	
> LOD		3.44 (1.30–9.72)	
HCB (ng/dL)			
Tertile 1		1.0 (reference)	
Tertile 2		1.21 (0.36–4.15)	
Tertile 3		1.03 (1.00–1.08)	
Heptachlor (ng/dL)			
Tertile 1		1.0 (reference)	
Tertile 2		1.27 (0.40–4.07)	
Tertile 3		2.87 (0.93–10.63)	
Greenland Inuit women with breast cancer (n = 31) vs 115 matched controls, 2000–2003		**POPs, dioxin-like PCBs**	Bonefeld-Jorgensen and Long, 2011
Dioxin-like PCBs in serum (mediam: cases vs controls)		56.8 vs 65.4 pg/g lipid p = 0.0009	

TABLE 14 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
China hospital-based case-control study comparing levels of organochlorine pesticides in serum and breast adipose tissue and infiltrating ductal carcinomas (n = 75) benign conditions (n = 79), healthy women (n = 80)		**Organochlorine pesticides**	Yang et al., 2015
β-HCH (serum) cases vs controls		3.42 μg/L (cases) vs 0.60 μg/L (benign) vs 0.58 μg/L (healthy) $p < 0.05$	
β-HCH (serum) IDC degrees		2.32 μg/L (degree 1) vs 3.22 μg/L (degree 2) 4.92 μg/L (degree 3) $p < 0.05$	
β-HCH (serum) ER+/ER–		2.31 μg/L (ER-) vs 3.72 μg/L (ER+) $p < 0.05$	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,4,5-TP, 2 (2,4,5-trichlorophenoxy) propionic acid; 2,5-DCP, 2,5-dichlorophenol; CATI, computer-assisted telephone interviewing; CC, case-control; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HCH, hexachlorohexane; HR, hazard ratio; IARC, International Agency for Research on Cancer; JEM, job-exposure matrix; LOD, limit of detection; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; n, number; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCDF, polychlorinated dibenzofurans; PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; PM, proportionate mortality; POP, persistent organic pollutant; ppt, parts per trillion; RR, relative risk; SIR, standardized incidence ratio; SMR, standardized mortality rate; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; TEQ, toxicity equivalent; VA, US Department of Veterans Affairs.

[a]Subjects are female and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

TABLE 15 Selected Epidemiologic Studies—Cervical Cancer (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US VA Cohort of Female Vietnam-era Veterans who served in Vietnam (n = 4,586; nurses only = 3,690); nondeployed (n = 5,325; nurses only 3,282)			
Incidence		**All COIs**	
Female Vietnam veterans	57	1.1 (0.7–1.7)	Kang et al., 2000b
Mortality		**All COIs**	
Through 2010	11	1.0 (0.3–3.5)	Kang et al., 2014
Vietnam nurses only	7	1.2 (0.3–5.2)	
International Vietnam-Veterans Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence		*Expected number of exposed cases*	CDVA, 1998b
Validation Study			
Self-reported cervical cancer	8	1 (0–5)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates		**Dioxin, phenoxy herbicides**	
Mortality 1939–1992	3	1.1 (0.2–3.3)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	0	0.0 (0.0–3.8)	
7,553 not exposed to highly chlorinated PCDDs	3	1.8 (0.4–5.2)	
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence 1943–1987	7	3.2 (1.3–6.6)	Lynge, 1993
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Cervix uteri (ICD-10 C53)	0	0.0 (0.0–14.6)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Self-employed	7	0.5 ($p < 0.05$)	
Employees	12	0.8 (nr)	
Family workers	100	0.5 ($p < 0.05$)	
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Incident cervical cancer cases 1961–1973 with agriculture as economic activity in 1960 census	82	99% CI 0.6 (0.4–0.8)	Wiklund, 1983

TABLE 15 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Women			
Whites (n = 2,400)	6	0.9 (0.3–2.0)	
Nonwhites (n = 2,066)	21	2.0 (1.3–3.1)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Incidence			
20-year followup to 1996—men and women			
Zone A	2	2.7 (0.7–10.8)	Pesatori et al., 2009
Zone B	7	1.5 (0.7–3.1)	
Zone R	28	0.8 (0.6–1.3)	
Ecological Study of Residents of Chapaevsk, Russia		**Dioxin**	Revich et al., 2001
Incidence—Crude incidence rate in 1998 vs			
Regional (Samara)	nr	11.7 (nr)	
National (Russia)	nr	13.2 (nr)	
Mortality—1995–1998 (SMR vs regional rates)	13	1.8 (1.0–3.1)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; n, number; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; SMR, standardized mortality rate; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VA, US Department of Veterans Affairs.

[a]Subjects are female and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

TABLE 16 Selected Epidemiologic Studies—Uterine Cancer (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans		**All COIs**	
US VA Cohort of Female Vietnam-era Veterans who served in Vietnam (n = 4,586; nurses only = 3,690); nondeployed (n = 5,325; nurses only 3,282)			
Incidence			
Female Vietnam veterans	41	1.0 (0.6–1.6)	Kang et al., 2000b
Mortality			
Through 2010	21	0.9 (0.4–2.2)	Kang et al., 2014
Vietnam nurses only	17	0.9 (0.4–2.5)	
Through 2004—US non-Vietnam veterans	5	0.8 (0.2–2.8)	Cypel and Kang, 2008
vs non-Vietnam nurses	5	1.3 (0.3–5.0)	
Through 1991—US Vietnam veterans	4	2.1 (0.6–5.4)	Dalager et al., 1995a
International Vietnam-Veterans Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence		*Expected number of exposed cases*	
Validation Study			
Self-reported uterine cancer	4	1 (0–5)	CDVA, 1998b
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates		**Dioxin, phenoxy herbicides**	
Mortality 1939–1992	3	3.4 (0.7–10.0)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	1	1.2 (0.0–6.5)	
7,553 not exposed to highly chlorinated PCDDs	4	2.3 (0.6–5.9)	
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Corpus uteri (ICD-10 C54–C55)	0	0.0 (0.0–30.6)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Self-employed	8	0.6 (nr)	
Employees	9	0.9 (nr)	
Family workers	103	0.8 ($p < 0.05$)	
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Incident NHL cases 1961–1973 with agriculture as economic activity in 1960 census	135	99% CI 0.9 (0.7–1.1)	Wiklund, 1983

TABLE 16 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Women			
Whites (n = 2,400)	15	1.2 (0.7–2.1)	
Nonwhites (n = 2,066)	17	1.4 (0.8–2.2)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	4	nr	
Commercial applicators	1	nr	
Spouses	148	0.9 (0.8–1.1)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group)		**TCDD**	
Incidence			
20-year followup to 1996 (Uterus, ICD-9 179–182)			
Zone A	4	2.3 (0.9–6.3)	Pesatori et al., 2009
Zone B	10	0.9 (0.5–1.7)	
Zone R	61	0.8 (0.6–1.0)	
20-year followup to 1996 (Endometrium, ICD-9 182)			
Zone A	1	1.2 (0.2–8.8)	
Zone B	3	0.6 (0.2–1.9)	
Zone R	27	0.7 (0.5–1.1)	
Mortality			
25-year followup to 2001			
Zone A	0	0	Consonni et al., 2008
Zone B	2	0.5 (0.1–1.9)	
Zone R	41	1.3 (0.9–1.8)	
20-year followup to 1996			
Zone A, B	2	0.5 (0.1–1.9)	Bertazzi et al., 2001
15-year followup to 1991			
Zone B	1	0.3 (0.0–2.4)	Bertazzi et al., 1997, 1998
Zone R	27	1.1 (0.8–1.7)	

continued

TABLE 16 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
CASE-CONTROL STUDIES			
International Case-Control Studies			
Swedish women—endometrial cancer and serum concentrations of chlorinated pesticides and PCB congeners		**Pesticides, PCB congeners**	Weiderpass et al., 2000
	154	1.0 (0.6–2.0)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; CATI, computer-assisted telephone interviewing; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; n, number; NHL, non-Hodgkin lymphoma; nr, not reported; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VA, US Department of Veterans Affairs.

[a]Subjects are female and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

TABLE 17 Selected Epidemiologic Studies—Ovarian Cancer (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US VA Cohort of Female Vietnam-era Veterans who served in Vietnam (n = 4,586; nurses only = 3,690); nondeployed (n = 5,325; nurses only 3,282)			
Incidence		**All COIs**	
Female Vietnam veterans	16	1.8 (0.7–4.6)	Kang et al., 2000b
Mortality			
Through 2010	48	1.6 (0.8–3.1)	Kang et al., 2014
Vietnam nurses only	38	1.4 (0.7–2.6)	
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence		*Expected number of exposed cases*	
Validation Study			
Self-reported uterine cancer	1	0 (0–4)	CDVA, 1998b
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates		**Dioxin, phenoxy herbicides**	
Mortality 1939–1992	1	0.3 (0.0–1.5)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	0	0.0 (0.0–2.6)	
7,553 not exposed to highly chlorinated PCDDs	1	0.5 (0.0–2.5)	
Mortality, incidence of women in production (n = 699) and spraying (n = 2) compared to national death rates and cancer incidence rates	1	**TCDD** 0.7 (nr)	Kogevinas et al., 1993
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ovarian cancer (ICD-10 C56)	0	0.0 (0.0–9.5)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Self-employed	12	0.9 (nr)	
Employees	5	0.5 (nr)	
Family workers	104	0.8 ($p < 0.05$)	

continued

TABLE 17 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
UNITED STATES			
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010			
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	9	2.5 (1.1–4.7)	
Commercial applicators	0	nr	
Spouses	58	0.7 (0.6–0.9)	
Enrollment through 2002			Alavanja et al., 2005
Private applicators (men, women)	8	3.0 (1.3–5.9)	
Spouses of private applicators (> 99% women)	32	0.6 (0.4–0.8)	
Commercial applicators (men, women)	0	0.0 (0.0–16.0)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	5	1.6 (0.5–3.8)	
Spouses (n = 676)	45	0.7 (0.5–0.9)	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men, women)	4	3.9 (1.1–10.1)	
Spouses of private applicators (> 99% women)	13	0.7 (0.4–1.2)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Incidence			
20-year followup to 1996 (Uterus, ICD-9 179–182)			
Zone A	1	1.1 (0.2–7.9)	Pesatori et al., 2009
Zone B	1	0.2 (0.0–1.3)	
Zone R	45	1.1 (0.8–1.5)	
Mortality			
25-year followup to 2001			
Zone A	1	1.2 (0.2–8.5)	Consonni et al., 2008
Zone B	2	0.4 (0.1–1.6)	
Zone R	37	1.0 (0.7–1.4)	
20-year followup to 1996			
Zone A, B	3	0.7 (0.2–2.0)	Bertazzi et al., 2001
15-year followup to 1991			
Zone B	1	2.3 (0.3–16.5)	Bertazzi et al., 1997, 1998
Zone R	21	1.0 (0.6–1.6)	

TABLE 17 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
CASE-CONTROL STUDIES			
International Case-Control Studies			
Italian women—hospital-based study of women with primary mesothelial ovarian tumors (n = 60) and 127 subjects with non-ovarian malignancies	18	**Herbicides** 4.4 (1.9–16.1)	Donna et al., 1984

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; CATI, computer-assisted telephone interviewing; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; n, number; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VA, US Department of Veterans Affairs.

[a]Subjects are female and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

TABLE 18 Selected Epidemiologic Studies—Prostate Cancer (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Incidence			
2,516 veterans (1,019 Ranch Hand, 1,497 SEA veterans) who participated in ≥ 1 physical examination and had recorded serum TCDD measurements			Pavuk et al., 2006
20-year cumulative TCDD (ppt-year)			
Comparison group	81	1.0	
Ranch Hand low (≤ 434 ppt-year)	31	1.0 (0.7–1.6)	
Ranch Hand high (> 434 ppy-year)	28	1.2 (0.8–1.9)	
		p-trend = 0.42	
Last tour in SEA before 1969 (heavy spraying)			
Yes			
Comparison group	17	1.0	
Ranch Hand low (≤ 434 ppt-year)	9	1.0 (0.4–2.3)	
Ranch Hand high (> 434 ppy-year)	15	2.3 (1.1–4.7)	
		p-trend = 0.04	
No			
Comparison group	64	1.0	
Ranch Hand low (≤ 434 ppt-year)	22	1.1 (0.7–1.8)	
Ranch Hand high (> 434 ppy-year)	13	0.9 (0.5–1.6)	
		p-trend = 0.75	
Less than 2 years served in SEA			
Yes			
Comparison group	16	1.0	
Ranch Hand low (≤ 434 ppt-year)	20	1.9 (1.0–3.7)	
Ranch Hand high (> 434 ppy-year)	14	2.2 (1.0–4.5)	
		p-trend = 0.03	
No			
Comparison group	65	1.0	
Ranch Hand low (≤ 434 ppt-year)	11	0.8 (0.4–1.5)	
Ranch Hand high (> 434 ppy-year)	14	1.1 (0.6–1.9)	
		p-trend = 0.89	
1982–2003—White SEA comparison veterans only (n = 1,482). Serum TCDD (pg/g) based on model with exposure variable $\log_e$(TCDD)			Pavuk et al., 2005
Per unit increase of –$\log_e$(TCDD) (pg/g) Quartiles (pg/g):	83	1.1 (0.7–1.5)	
0.4–2.6	13	1.0	
2.6–3.8	24	1.7 (0.8–3.3)	
3.8–5.2	24	1.5 (0.7–2.9)	
> 5.2	22	1.2 (0.6–2.4)	
Number of years served in SEA (per year of service)	83	1.1 (1.0–1.2)	
Quartiles (years in SEA):			
0.8–1.3	8	1.0	
1.3–2.1	11	1.3 (0.5–3.2)	
2.1–3.7	28	2.2 (1.0–4.9)	
3.7–16.4	36	2.4 (1.1–5.2)	

TABLE 18 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Through 1999—White subjects vs national rates			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	36	1.5 (1.0–2.0)	
With tours between 1966–1970	34	1.7 (1.2–2.3)	
SEA comparison veterans (n = 1,776)	54	1.6 (1.2–2.1)	
With tours between 1966–1970	42	1.6 (1.2–2.2)	
White AFHS subjects who spent at most 2 years in SEA			
Per unit increase of $-\log_e$(TCDD)	28	1.5 (0.9–2.4)	
Comparison group	7	1.0	
Ranch Hand— < 10 TCDD pg/g in 1987	10	1.5 (0.5–4.4)	
Ranch Hand— < 118.5 TCDD pg/g at end of service	6	2.2 (0.7–6.9)	
Ranch Hand— > 118.5 TCDD pg/g at end of service	5	6.0 (0.4–24.6)	
Only Ranch Hands with 100% service in Vietnam and comparisons with no service in Vietnam			
Per unit increase of $-\log_e$(TCDD)	20	1.1 (0.6–1.8)	
Comparison group	3	1.0	
Ranch Hand— < 10 TCDD pg/g in 1987	9	2.5 (0.4–16.1)	
Ranch Hand— < 118.5 TCDD pg/g at end of service	4	2.4 (0.4–16.0)	
Ranch Hand— > 118.5 TCDD pg/g at end of service	4	4.7 (0.8–29.1)	
Mortality			
Through 1999—White subjects vs national rates			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	2	0.7 (0.1–2.3)	
SEA comparison veterans (n = 1,776)	3	0.8 (0.2–2.1)	
US VA Cohort of Army Chemical Corps—Expanded as of 1997 to include all Army men with chemical MOS (2,872 deployed vs 2,737 nondeployed) serving during Vietnam era (July 1, 1965–March 28, 1973)		**All COIs**	
Mortality—Prostate cancers			
Through 2005			Cypel and Kang, 2010
Deployed veterans (2,872) vs nondeployed (2,737)	5 vs 2	1.0 (0.2–5.6)	
ACC veterans vs US men			
Vietnam cohort	5	1.1 (0.3–2.5)	
Non-Vietnam cohort	2	1.0 (0.1–3.4)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Mortality			
1965–2000	1	0.4 (nr)	Boehmer et al., 2004
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1988			Watanabe and Kang, 1996
Army, deployed (n = 27,596) vs nondeployed (n = 31,757)	58	0.9 (nr)	
Marine Corps, deployed (n = 6,237) vs nondeployed (n = 5,040)	9	0.8 (nr)	
1965–1982			Breslin et al., 1986, 1988
Army, deployed (n = 19,708) vs nondeployed (n = 22,904)	30	0.9 (0.6–1.2)	
Marine Corps, deployed (n = 4,527) vs nondeployed (n = 3,781)	5	1.3 (0.2–10.3)	

continued

TABLE 18 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
State Studies of US Vietnam Veterans			
VA Hospital Medical Records—men who underwent radial prostatectomy between 1988 and 2011 (n = 1,882) with a self-reported AO exposure status	333 (total)	**All COIs** (supposed AO exposure)	Ovadia et al., 2015
OR for relationship between AO exposure and cancer, adjusted for age, biopsy Gleason Score, race, clinical stage, BMI, center, and preoperative PSA level (log transformed)			
Biochemical recurrence		1.21 (0.99–1.49)	
Secondary treatment		1.21 (0.97–1.51)	
Metastases		0.93 (0.30–2.66)	
Prostate cancer–specific death		0.89 (0.46–1.85)	
OR for relationship between AO exposure and cancer, adjusted for age, race, clinical stage, BMI, center, year of RP, and preoperative PSA level (log transformed)			
Biopsy Gleason Score ≥ 8		0.73 (0.46–1.14)	
Radical prostatectomy Gleason Score ≥ 8		0.60 (0.39–0.90)	
Extracapsular extension, positive lymph node, seminal vesicle invasion, or radical prostatectomy Gleason Score ≥ 8		0.74 (0.55–0.98)	
2005 and 2009 (n = 93); dioxin levels (TEQs) measured in subcutaneous adipose tissue		**All COIs** (supposed AO exposure)	Li et al., 2013
Proportion of TEQ levels for AO exposed (self-reported) vs non-exposed		27% vs 20% p = 0.68	
Proportion of higher TEQ levels vs lower TEQs		28% vs 17% p = 0.23	
Veterans with radical prostatectomies examined in VA Healthcare facilities (California, Georgia, North Carolina)			Shah et al., 2009
AO-exposed veterans with biochemical progression	nr	1.5 (1.1–2.0)	
Northern California—prostate cancer (self-reported [before diagnosis] of AO expo vs not)	239	**All COIs** 2.9 (2.3–3.6)	Chamie et al., 2008
Massachusetts veterans aged 35–65 years in 1993—prostate cases diagnosed 1988–1993 vs gastrointestinal cancers	15	**All COIs** 0.8 (0.4–1.6)	Clapp, 1997
Michigan Vietnam veterans using the VA Medical Center in Ann Arbor, Michigan (n = 47); 142 frequency-matched controls		**All COIs**	Giri et al., 2004
Cases reporting AO exposure	11	OR 2.1 (0.8–5.2)	
Cases in white veterans reporting AO exposure	nr	OR 2.7 (0.9–8.2)	
Michigan Vietnam-era veterans, PM study of deaths (1974–1989)—deployed vs nondeployed		**All COIs**	Vistainer et al., 1995
Male genital system	19	1.1 (0.6–1.7)	Clapp, 1997
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans	0	**All COIs** nr	Anderson et al., 1986a,b
Oregon: A cohort of 2,720 veterans who underwent biopsy at Portland VA Medical Center (896 prostate cancers)		**All COIs** (supposed AO exposure)	Ansbaugh et al., 2013
All prostate cancer	74	1.5 (1.1–2.1)	
High grade prostate cancer (Gleason score > 7)	40	1.8 (1.1–2.7)	
Gleason score > 8 prostate cancer	nr	2.1 (1.2–3.6)	

TABLE 18 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	692	1.3 (1.2–1.3)	ADVA, 2005b
Navy	137	1.2 (1.0–1.4)	
Army	451	1.3 (1.2–1.4)	
Air Force	104	1.3 (1.0–1.5)	
		Expected number of exposed cases	AIHW, 1999
Validation Study	212	147 (123–171)	
Men	428	147 (123–171)	CDVA, 1998a
Mortality			
All branches, return–2001	107	1.2 (1.0–1.5)	ADVA, 2005a
Navy	22	1.3 (0.8–1.8)	
Army	65	1.2 (0.9–1.5)	
Air Force	19	1.4 (0.8–2.1)	
Sample of 1,000 Male Australian Vietnam Veterans— prevalence		**All COIs**	
450 interviewed 2005–2006 vs respondents to 2004–2005 national survey	nr	1.3 (0.3–6.7)	O'Toole et al., 2009
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Incidence			
1982–2000	65	1.2 (0.9–1.5)	ADVA, 2005c
Mortality			
1966–2001	0	0.0 (0.0–0.7)	ADVA, 2005c
1982–1994	36	1.5 (1.0–2.0)	CDVA, 1997b
Other Australian Vietnam veterans		**All COIs**	
606 prostate cancer cases in Western Australia			Leavy et al., 2006
Vietnam service	25	2.1 (0.9–5.1)	
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008)	136	1.2 (1.0–1.4)	
Mortality (1988–2008)	13	1.0 (0.6–1.8)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores)		**All COIs**	
		HRs	
Incidence (1992–2003)—prostate cancer (C61) categorized high (n = 53) vs low (n = 71)	53	0.7 (0.5–1.0)	Yi and Ohrr, 2014
Mortality (1992–2005)—prostate cancer (C61) categorized high (n = 17) vs low (n = 21)		0.7 (0.4–1.3)	Yi et al., 2014b
HR per unit of log EOI (n = 180,639)	38	0.9 (0.8–1.1)	

continued

TABLE 18 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	68	1.1 (0.9–1.4)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	43	1.1 (0.8–1.5)	
7,553 not exposed to highly chlorinated PCDDs	25	1.1 (0.7–1.6)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	30	1.1 (0.8–1.6)	Saracci et al., 1991
British MCPA Plant—All manual employees employed January 1947–December 1975 (n = 1,146), ever potentially exposed to phenoxy herbicides (n = 1,544), potentially exposed to phenoxy herbicides ≥ 1 year (n = 848) (not included in IARC cohort)		**MCPA**	
Mortality through 2012, all workers			Coggon et al., 2015
Prostate (ICD-10 C61)	120	1.10 (0.91–1.32)	
Mortality through 2012, workers ever exposed to phenoxy herbicides			
Prostate (ICD-10 C61)	89	1.14 (0.92–1.41)	
Mortality through 2012, workers ever exposed to phenoxy herbicides ≥ 1 year			
Prostate (ICD-10 C61)	43	1.15 (0.83–1.55)	
Mortality through 1983	18	1.3 (0.8–2.1)	Coggon et al., 1986
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Mortality 1955–2006	14	1.1 (0.8–1.5)	Boers et al., 2012
Incidence 1943–1982	9	0.8 (nr)	Lynge, 1985
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–2006 (hazard-ratios for lagged TCDD plasma levels)	8	1.3 (0.9–1.9)	Boers et al., 2012
Mortality 1955–2006	6 vs 2	2.9 (0.6–14.2)	Boers et al., 2010
Mortality 1955–1985	2	2.2 (0.3–7.8)	Bueno de Mesquita et al., 1993
Dutch production workers in Plant B (414 men exposed during production 1965–1986; 723 unexposed) (in IARC cohort)		**2,4-D; MCPA; MCPP; highly chlorinated dioxins unlikely**	
Mortality 1965–2006	4 vs 2	2.7 (0.5–14.9)	Boers et al., 2010
Mortality 1965–1986	1	4.8 (0.1–26.5)	Bueno de Mesquita et al., 1993
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 month in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992	1	1.5 (0.0–8.5)	Becher et al., 1996
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 month in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1965–1989	0	—	Becher et al., 1996

TABLE 18 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 month in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1956–1989	1	0.7 (0.0–3.7)	Becher et al., 1996
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Incidence			
1960–1992			Ott and Zober, 1996a
TCDD < 0.1 μg/kg of body weight	3	2.5 (0.5–7.4)	
TCDD 0.1–0.99 μg/kg of body weight	1	1.1 (0.0–5.9)	
TCDD > 1 μg/kg of body weight	0	0.0 (0.0–2.5)	
Mortality			
1953–1992			Ott and Zober, 1996a
TCDD < 0.1 μg/kg of body weight	0	0.0 (0.0–5.7)	
TCDD 0.1–0.99 μg/kg of body weight	0	0.0 (0.0–7.5)	
TCDD > 1 μg/kg of body weight	0	0.0 (0.0–4.6)	
		90% CI	Zober et al., 1990
Through 1987	0	0.0 (0.0–6.1)	
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 month in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–2007	19	1.4 (0.8–2.1)	Manuwald et al., 2012
Mortalilty 1952–1989	7	1.5 (0.6–3.0)	Becher et al., 1996
Mortality 1952–1989—stats on men only, 1,184 (tables all for 1,148 men, not necessarily German nationals) vs national rates (also vs gas workers); same observation period as Becher et al., 1966	7	1.4 (0.6–2.9)	Manz et al., 1991
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	1	0.2 (0.0–1.2)	
Never-exposed workers	2	1.9 (0.2–6.7)	
Production Workers (713 men and 100 women worked > 1 month in 1969–1984)			
Mortality 1969–2000	1	0.4 (0.0–2.1)	't Mannetje et al., 2005
Sprayers (697 men and 2 women on register of New Zealand applicators, 1973–1984)			
Mortality 1973–2000	2	0.6 (0.1–2.2)	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993	28	1.2 (0.8–1.7)	Steenland et al., 1999
Through 1987	17	1.2 (0.7–2.0)	Fingerhut et al., 1991
≥ 1-year exposure, ≥ 20-year latency	9	1.5 (0.7–2.9)	
Mortality—754 Monsanto workers, among most highly exposed workers from Fingerhut et al. (1991)	9	1.6 (0.7–3.0)	Collins et al., 1993

continued

TABLE 18 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, Michigan) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1937–2011 Potential dioxin exposure (n = 2,192), TCP production (n = 1,419), PCP production (n = 577), Both TCP and PCP (n = 196)			Collins et al., 2016
TCP or PCP, Prostate Cancer (ICD-10 C61)	31	1.07 (0.72–1.51)	
TCP, Prostate Cancer (ICD-10 C61)	21	1.01 (0.62–1.54)	
PCP, Prostate Cancer (ICD-10 C61)	11	1.05 (0.53–1.87)	
1942–2003 (n = 1,615)	21	1.4 (0.9–2.2)	Collins et al., 2009b
1940–1994 (n = 2,187 men)	nr	1.7 (1.0–2.6)	Bodner et al., 2003
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, Washington, and Wichita, Kansas) and workers who made PCP and TCP at two additional plants (in Midland, Michigan, and Sauget, Illinois)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122)	26	1.0 (0.7–1.5)	
PCP and TCP (n = 720)	8	1.1 (0.5–2.1)	
PCP (no TCP) (n = 1,402)	18	1.0 (0.6–1.6)	
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)	51	0.8 (0.6–1.0)	Burns CJ et al., 2011
Through 1994 (n = 1,517)	7	1.3 (0.5–2.8)	Burns et al., 2001
Through 1982 (n = 878)	1	1.0 (0.0–5.8)	Bond et al., 1988
Dow PCP Production Workers (1937–1989 in Midland, Michigan) (**not** in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	8	1.0 (0.4–1.9)	Collins et al., 2009c
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	117	0.9 (0.7–1.0)	
Ever	84	0.9 (0.7–1.2)	
New Hampshire pulp and paper workers, 883 white men working ≥ 1 year, mortality through July 1985	9	1.0 (0.5–1.9)	Henneberger et al., 1989
United Paperworkers International, 201 white men employed ≥ 10 year and dying 1970–1984	4	1.1 (0.3–2.9)	Solet et al., 1989
Northwestern US paper and pulp workers—5 mills in Washington, Oregon, and California, 3,523 worked ≥ 1 year 1945–1955, mortality through March 1977	17	90% CI 1.2 (0.7–1.7)	Robinson et al., 1986

TABLE 18 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Canadian Farm Operator Study—156,242 men farming in Manitoba, Saskatchewan, and Alberta in 1971; mortality from prostate cancer June 1971–December 1987		**Herbicides**	Morrison et al., 1993
Herbicides sprayed on ≥ 250 acres vs 0 acres	20	2.2 (1.3–3.8)	
Sawmill Workers in British Columbia—23,829 workers for ≥ 1 year at 11 mills using chlorophenates 1940–1985		**Chlorophenates, not TCDD**	
Incidence 1969–1989	282	1.0 (0.9–1.1)	Hertzman et al., 1997
Mortality 1950–1989	116	1.2 (1.0–1.4)	
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	399	0.9 ($p < 0.05$)	
Employee	63	0.8 ($p < 0.05$)	
Danish gardeners—incidence from 3,156 male and 859 female gardeners			Hansen et al., 2007
25-year followup (1975–2001)		**Herbicides**	
Born before 1915 (high exposure)	39	1.3 (1.0–1.8)	
Born 1915–1934 (medium exposure)	35	0.9 (0.6–1.2)	
Born after 1934 (low exposure)	3	0.4 (0.1–1.3)	
10-year followup (1975–1984) of male gardeners	20	1.2 (0.7–1.8)	Hansen et al., 1992
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	6	1.0 (0.4–2.2)	Swaen et al., 2004
Through 1987	1	1.3 (0.0–7.3)	Swaen et al., 1992
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 weeks) not IARC		**Phenoxy herbicides**	
Incidence	6	0.4 (0.1–0.8)	Asp et al., 1994
Mortality 1972–1989	5	0.8 (0.3–1.8)	
ICELAND			
Icelandic men (1,860), women (859) exposed to agricultural pesticides, primarily 2,4-D (other endocrine organs, ICD-9 194)—incidence	10	**2,4-D** 0.7 (0.3–1.3)	Zhong and Rafnsson, 1996
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	66	1.0 (0.7–1.2)	Torchio et al., 1994
Italian rice growers with documented phenoxy use (n = 1,487)	19	**Phenoxy herbicides** 1.0 (0.6–1.5)	Gambini et al., 1997
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of incident prostate cancer cases vs remainder of 19,904 men with any incident cancer		**Herbicides**	Reif et al., 1989
Forestry workers (n = 134)	12	0.7 (0.4–1.3)	

continued

TABLE 18 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
SWEDEN			
Swedish Cancer-Environment Registry—National cancer registry linked to census		**Herbicides**	Sharma-Wagner et al., 2000
36,269 incident prostate cancer cases 1961–1979 with 1960 census occupation of:			
Agriculture, stock raising	6,080	(1.0–1.1) ($p < 0.01$)	
Farmers, foresters, gardeners	5,219	(1.0–1.1) ($p < 0.01$)	
Paper-mill workers	304	0.9 (0.8–1.0)	
Pulp grinding	39	1.4 (1.0–1.9) ($p < 0.05$)	
Incident prostate cancer cases 1961–1973 with agriculture as economic activity in 1960 census	3,890	99% CI 1.0 (0.9–1.0)	Wiklund, 1983
Licensed Swedish Pesticide Sprayers—Incidence of prostate cancer	401	**Phenoxy herbicides** 1.1 (1.0–1.2)	Dich and Wiklund, 1998
Born 1935 or later	7	2.0 (0.8–4.2)	
Born before 1935	394	1.1 (1.0–1.2)	
Swedish lumberjacks—Used phenoxys 1954–1967, Incidence 1958–1992			Thörn et al., 2000
Exposed (n = 154)			
Foremen (n = 15)	2	4.7 (nr)	
Lumberjacks (n = 139)	3	0.9 (nr)	
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	3,765	1.2 (1.1–1.2)	
Nonwhites (n = 11,446)	564	1.1 (1.1–1.2)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Evaluation of whether single-nucleotide polymorphisms involved in hormone homeostasis alter the effect of pesticide exposure and prostate cancer risk			Christensen et al., 2016
2,4-D		No significant interaction robust to multiple comparison observed	
2,4,5-T		No significant interaction robust to multiple comparison observed	
Dicamba, low use and two wild-type genotype CC		0.62 (0.41–0.93)	
Dicamba, high use and two wild-type genotype CC		0.44 (0.29–0.68)	

TABLE 18 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	1,719	1.2 (1.1–1.3)	
Commercial applicators	73	1.3 (1.0–1.6)	
Spouses	7	1.1 (0.4–2.2)	
Enrollment through 2002			Samanic et al., 2006
Dicamba—lifetime days exposure			
None	343	1.0	
1– < 20	106	1.0 (0.8–1.3)	
20– < 56	102	0.9 (0.7–1.2)	
56– < 116	76	1.0 (0.7–1.3)	
≥ 116	67	(0.8–1.5)	
		p-trend = 0.45	
Enrollment through 2002			Alavanja et al., 2005
Private applicators	1,046	1.3 (1.2–1.3)	
Spouses of private applicators (> 99% women)	5	1.2 (0.4–2.8)	
Commercial applicators	41	1.4 (1.0–1.9)	
Enrollment through 1999 (n = 55,332)	566	1.1 (1.1–1.2)	Alavanja et al., 2003
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	171	0.8 (0.7–1.0)	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	48	0.7 (0.5–0.8)	
Spouses of private applicators (> 99% women)	0	0.0 (0.0–1.6)	
US Agricultural Health Study—Nested CC study (776 cases vs 1,444 controls)		**Herbicides**	Karami et al., 2013
2,4 D (ever exposed)	617	0.8 (0.7–1.1)	(supplementary table S1)
2,4 D (high exposure)	295	0.8 (0.6–1.1)	
2,4,5 T (ever exposed)	229	0.9 (0.7–1.1)	
2,4,5 T (high exposure)	56	0.7 (0.5–0.9)	
2,4,5 TP (ever exposed)	64	0.8 (0.6–1.1)	
2,4,5 TP (high exposure)	11	0.6 (0.3–1.1)	
US Department of Agriculture Workers—nested case-control study of white men dying 1970–1979 of prostate cancer		**Herbicides**	
Agricultural extension agents	nr	1.0 (0.7–1.5)	Alavanja et al., 1988
Forest conservationists	nr	p < 0.05	Alavanja et al., 1989
Soil conservationists	nr	p < 0.26	
Florida Licensed Pesticide Applicators (common phenoxy use assumed but not documented; had been listed by Blair et al., 1983)		**Herbicides**	
30,155 white men licensed 1975–1993			
Incidence 1975–1993	353	1.9 (1.7–2.1)	Fleming et al., 1999a
Mortality 1975–1993	64	2.4 (1.8–3.0)	Fleming et al., 1999b

continued

TABLE 18 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Pesticide applicators in Florida licensed 1965–1966 (n = 3,827)—mortality through 1976		**Herbicides** *Expected number of exposed cases*	Blair et al., 1983
Any pesticide (dose-response by length of licensure)	2	3.8 (nr)	
> 30 years old when died 1964–1978—case-control H_0: only for "modern methods" → born after 1900	4,827	1.2 ($p < 0.05$)	Burmeister et al., 1983
Born before 1880	1,539	1.5 (nr)	
Born 1980–1900	2,081	1.3 (nr)	
Born after 1900	1,207	0.8 (nr)	
> 20 years old when died 1971–1978—PMR	1,138	1.1 ($p < 0.01$)	Burmeister, 1981
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Incidence			
20-year followup to 1996—men and women			
Zone A	0		Pesatori et al., 2009
Zone B	7	0.9 (0.5–2.0)	
Zone R	39	0.8 (0.5–1.1)	
10-year followup to 1991—men			Bertazzi et al., 1993
Zone R	16	0.9 (0.5–1.5)	
Mortality			
25-year followup to 2001—men and women			Consonni et al., 2008
Zone A	1	0.9 (0.1–6.2)	
Zone B	8	0.9 (0.4–1.8)	
Zone R	65	1.1 (0.8–1.4)	
20-year followup to 1996			Bertazzi et al., 2001
Zones A, B—men	8	1.1 (0.5–2.2)	
15-year followup to 1991—men			Bertazzi et al., 1997
Zone B	6	1.2 (0.5–2.7)	
Zone R	39	1.2 (0.8–1.6)	
10-year followup to 1986—men			Bertazzi et al., 1989b
Zone B	3	2.2 (0.7–6.9)	
Zone R	16	1.6 (0.9–2.7)	
Other International Environmental Studies			
FINLAND			
Finnish fishermen (n = 6,410) and spouses (n = 4,260) registered between 1980 and 2002 compared to national statistics		**Serum dioxin**	Turunen et al., 2008
Fisherman	36	1.0 (0.7–1.4)	
Spouses	—	—	

TABLE 18 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995a
Incidence			
East coast	38	1.1 (0.8–1.5)	
West coast	224	1.0 (0.9–1.1)	
Mortality			
East coast	12	1.0 (0.5–1.8)	
West coast	123	1.1 (0.9–1.3)	
NORWAY			
Prediagnostic Serum Organochlorine Concentrations in the Norwegian Janus Serum Bank Cohort 150 cases matched to 314 controls on date and age of blood draw and region of residence		**Organochlorine compounds**	Kroutros et al., 2015 (supplementary table S3)
OR metastatic prostate cancer diagnosis			
PCB 118 Q4 vs Q1		1.07 (0.56–2.02)	
PCB 156 Q4 vs Q1		0.80 (0.42–1.52)	
PCB 157 Q4 vs Q1		0.86 (0.43–1.71)	
PCB 167 Q4 vs Q1		1.23 (0.67–2.29)	
PCB 189 Q4 vs Q1		0.92 (0.50–1.70)	
KOREA			
Case-cohort design of 110 incdicent cases and 256 controls of individuals who were participating in the Korean Cancer Prevention Study from 1994–2013		**Dioxin-like PCBs**	Lim et al., 2017 (supplementary table S3)
HR prostate cancer incidence			
Σ Dioxin-like PCBs continuous		1.39 (0.89–2.19)	
Σ Dioxin-like PCBs T2 vs T1	10	0.87 (0.34–2.20)	
Σ Dioxin-like PCBs T3 vs T1	90	1.73 (0.70–4.27)	
PCB 118 continuous		1.34 (0.86–2.07)	
PCB 118 T2 vs T1	16	2.68 (0.81–8.89)	
PCB 118 T3 vs T1	82	3.44 (1.01–11.69)	
PCB 156 continuous		2.17 (1.28–3.66)	
PCB 156 T2 vs T1	10	1.29 (0.54–3.11)	
PCB 156 T3 vs T1	94	2.26 (0.84–6.10)	
PCB 167 continuous		2.09 (1.26–3.47)	
PCB 167 T2 vs T1	11	0.54 (0.20–1.43)	
PCB 167 T3 vs T1	90	1.75 (0.71–4.29)	
CASE-CONTROL STUDIES			
CANADA—1,516 prostate cancer patients identified in the British Columbia Cancer Registry vs 4,994 matched controls; estimated lifetime exposure to:		**Pesticides**	Band et al., 2011
2,4-D	11	2.7 (1.1–6.6)	
2,4-DB	24	1.8 (1.0–3.0)	
MCPA	14	1.8 (1.0–3.2)	
Dicamba	22	2.0 (1.0–4.2)	
SINGAPORE—60 prostate cancer patients identified between April 2007 and May 2009 and 60 matched controls		**Pesticides**	Pi et al., 2016

continued

TABLE 18 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
PCB 118, ≤ LOD	0	1.00 (referent)	
PCB 118, ≤ 33	17	0.68 (0.32–1.47)	
PCB 118, 33–67	20	0.93 (0.44–1.98)	
PCB 118, ≥ 67	23	1.71 (0.79–3.71)	
PCB 156, ≤ LOD	6	1.00 (referent)	
PCB 156, ≤ 33	14	0.57 (0.25–1.26)	
PCB 156, 33–67	23	2.04 (0.92–4.51)	
PCB 156, ≥ 67	17	0.92 (0.42–2.03)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DB, 4-(2,4-dichlorophenoxy)butyric acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,5-DCP, 2,5-dichlorophenol; ACC, Army Chemical Corps; AFHS, Air Force Health Study; AO, Agent Orange; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job-exposure matrix; LOD, limit of detection; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; MOS, military occupation specialty; n, number; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; PM, proportionate mortality; PMR, proportionate mortality ratio; Q, quartile; SEA, Southeast Asia; SIR, standardized incidence ratio; T, tertile; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

TABLE 19 Selected Epidemiologic Studies—Testicular Cancer (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US VA Cohort of Army Chemical Corps—Expanded as of 1997 to include all Army men with chemical MOS (2,872 deployed vs 2,737 nondeployed) serving during Vietnam era (July 1, 1965–March 28, 1973)		**All COIs**	
Mortality			
Through 2005			Cypel and Kang, 2010
Deployed veterans (2,872) vs nondeployed (2,737)	2	—	
Through 1991	2	4.0 (0.5–14.5)	Dalager and Kang, 1997
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1988			Watanabe and Kang, 1996
Army, deployed (n = 27,596) vs nondeployed (n = 31,757)	114	1.1 (nr)	
Marine Corps, deployed (n = 6,237) vs nondeployed (n = 5,040)	28	1.0 (nr)	
1965–1984			Watanabe et al., 1991
Army, deployed (n = 24,145) vs nondeployed (n = 27,917)	109	1.2 (ns)	
Served in I Corps (n = 6,668)	12	2.6 (1.1–6.2)	Bullman et al., 1990
Marine Corps, deployed (n = 5,501) vs nondeployed (n = 4,505)	28	0.8 (ns)	Watanabe et al., 1991
1965–1982			Breslin et al., 1988
Army, deployed (n = 19,708) vs nondeployed (n = 22,904)	90	1.1 (0.8–1.5)	
Marine Corps, deployed (n = 4,527) vs nondeployed (n = 3,781)	26	1.3 (0.5–3.6)	
State Studies of US Vietnam Veterans			
District of Columbia patients (18–42 years of age) in 3 hospitals, diagnosed with testicular cancer (1976–June 30, 1981)	31	2.3 (1.0–5.5)	Tarone et al., 1991
Massachusetts Vietnam-era veterans			
Veterans aged 35–65 years in 1993—cases diagnosed 1988–1993 vs gastrointestinal cancers	30	1.2 (0.4–3.3)	Clapp, 1997
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans	9	1.0 (0.5–1.9)	Anderson et al., 1986a,b
International Vietnam-Veterans Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	54	0.9 (0.6–1.1)	ADVA, 2005b
Navy	17	1.2 (0.7–1.8)	
Army	34	0.8 (0.5–1.0)	
Air Force	3	0.8 (0.2–2.3)	

continued

TABLE 19 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Validation Study		*Expected number of exposed cases*	AIHW, 1999
	59	110 (89–139)	
Men	151	110 (89–131)	
Mortality			
All branches, return–2001	14	0.9 (0.4–1.4)	ADVA, 2005a
Navy	3	0.8 (0.2–2.4)	
Army	10	0.9 (0.4–1.7)	
Air Force	0	0.0 (0.0–3.3)	
1980–1994	4	ns	CDVA, 1997a
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Incidence			
1982–2000	17	0.7 (0.4–1.2)	ADVA, 2005c
Mortality			
1966–2001	4	0.8 (0.2–2.0)	ADVA, 2005c
1982–1994	1	1.3 (nr)	CDVA, 1997b
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores)		**All COIs** HRs	
Incidence (1992–2003)			Yi and Ohrr, 2014
Penis (C60) categorized high (n = 0) vs low (n = 1)		0.0 (nr)	
Testes (C62) categorized high (n = 2) vs low (n = 3)		0.5 (0.1–3.3)	
Other male genital organs (C63) categorized high (n = 1) vs low (n = 2)		1.0 (0.1–15.1)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	68	1.1 (0.9–1.4)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	43	1.1 (0.8–1.5)	
7,553 not exposed to highly chlorinated PCDDs	25	1.1 (0.3–1.6)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	7	2.3 (0.9–4.6)	Saracci et al., 1991
British MCPA Plant—All manual employees employed January 1947–December 1975 (n = 1,146), ever potentially exposed to phenoxy herbicides (n = 1,544), potentially exposed to phenoxy herbicides ≥ 1 year (n = 848) (not included in IARC cohort)		**MCPA**	
Mortality through 2012, all workers			Coggon et al., 2015
Testes (ICD-10 C21)	5	2.00 (0.65–4.67)	
Mortality through 2012, workers ever exposed to phenoxy herbicides			
Testes (ICD-10 C21)	4	2.10 (0.57–5.37)	
Mortality through 2012, workers ever exposed to phenoxy herbicides ≥ 1 year			
Testes (ICD-10 C21)	3	4.03 (0.83–11.78)	
Mortality through 1983	4	2.2 (0.6–5.7)	Coggon et al., 1986

TABLE 19 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	0	0.0 (0.0–15.6)	
Never-exposed workers			
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, Michigan) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1937–2011 Potential dioxin exposure (n = 2,192), TCP production (n = 1,419), PCP production (n = 577), Both TCP and PCP (n = 196)			Collins et al., 2016
TCP or PCP, Testes and other male genital	1	1.05 (0.03–5.85)	
TCP, Testes and other male genital	1	1.43 (0.04–7.96)	
PCP, Testes and other male genital	0	0.00 (0.0–10.99)	
1942–2003; testes and other male genital (n = 1,615)	1	1.6 (0.0–8.9)	Collins et al., 2009b
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Through 1994 (n = 1,517)	1	2.2 (0.0–12.5)	Burns et al., 2001
Through 1982 (n = 878)	1	4.6 (0.0–25.7)	Bond et al., 1988
Dow PCP Production Workers (1937–1989 in Midland, Michigan) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP); testes and other male genital	0	0.0 (0.0–12.5)	Collins et al., 2009c
Mortality 1940–1989 (n = 770)	0	nr	Ramlow et al., 1996
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	2	1.1 (0.1–4.1)	
Ever	5	3.6 (1.2–8.4)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Sawmill Workers in British Columbia—23,829 workers for ≥ 1 year at 11 mills using chlorophenates 1940–1985		**Chlorophenates, not TCDD**	
Incidence 1969–1989	18	1.0 (0.6–1.4)	Hertzman et al., 1997
Mortality 1950–1989 (male genital cancers)	116	1.0 (0.8–1.1)	
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	74	0.9 (nr)	
Employee	23	0.6 ($p < 0.05$)	
ICELANDIC men (1,860), women (859) exposed to agricultural pesticides, primarily 2,4-D—incidence	2	**2,4-D** 1.2 (0.1–4.3)	Zhong and Rafnsson, 1996

continued

TABLE 19 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of 339 incident testicular cancer cases vs remainder of 19,904 men with any incident cancer		**Herbicides**	Reif et al., 1989
Forestry workers (n = 134)	6	1.0 (0.4–2.6)	
SWEDEN			
Incident testicular cancer cases 1961–1973 with agriculture as economic activity in 1960 census	101	99% CI 1.0 (0.7–1.2)	Wiklund, 1983
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	32	0.8 (0.6–1.2)	
Nonwhites (n = 11,446)	6	1.3 (0.5–2.9)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	32	1.0 (0.7–1.4)	
Commercial applicators	6	1.2 (0.5–2.6)	
Spouses	0	nr	
Enrollment through 2002			Alavanja et al., 2005
Private applicators	23	1.1 (0.7–1.6)	
Spouses of private applicators (> 99% women)	nr	0.0 (0.0–50.2)	
Commercial applicators	4	1.2 (0.3–3.2)	
Mortality			
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	0	nr	
Spouses of private applicators (> 99% women)	0	nr	
Florida Licensed Pesticide Applicators (common phenoxy use assumed but not documented; had been listed by Blair et al., 1983)		**Herbicides**	
Mortality 1975–1993	23	2.5 (1.6–3.7)	Fleming et al., 1999b
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Incidence			
20-year followup to 1996—men and women			
Zone A	0		Pesatori et al., 2009
Zone B	2	0.8 (0.2–3.3)	
Zone R	22	1.4 (0.9–2.3)	
10-year followup to 1991—men			Bertazzi et al., 1993
Zone B	1	1.0 (0.1–7.5)	
Zone R	9	1.4 (0.7–3.0)	

TABLE 19 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Mortality			
20-year followup to 1996			Bertazzi et al., 2001
Zones A, B—men	17	1.0 (0.6–1.7)	
15-year followup to 1991—men			Bertazzi et al., 1998
Zone B	10	1.0 (0.5–1.8)	
Zone R	73	1.0 (0.8–1.3)	
CASE-CONTROL STUDIES			
International Case-Control Studies			
Swedish Cancer Registry (1989–1992)—testicular cancer patients (20–75 years old) (n = 148)		**Herbicides**	Hardell et al., 1998
Exposed to herbicides	4	0.3 (0.1–1.0)	
Italy—125 TC patients and 103 controls with			Paoli et al., 2015
PCBs or hexachlorobenzene detected and summed	17	$p < 0.001$	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; CATI, computer-assisted telephone interviewing; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job-exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MOS, military occupation specialty; n, number; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; ns, not significant; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

TABLE 20 Selected Epidemiologic Studies—Urinary Bladder Cancer (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Incidence			
Through 1999—White subjects vs national rates			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	14	1.1 (0.6–1.7)	
With tours between 1966–1970	14	1.3 (0.7–2.1)	
SEA comparison veterans (n = 1,776)	8	0.4 (0.2–0.8)	
With tours between 1966–1970	4	0.3 (0.1–0.7)	
Mortality			
Through 1999—White subjects vs national rates			
Ranch Hand veterans	1	0.9 (nr)	
SEA comparison veterans	1	0.6 (nr)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Mortality			
1965–2000	1	nr	Boehmer et al., 2004
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1982			Breslin et al., 1988
Army, deployed (n = 19,708) vs nondeployed (n = 22,904)	9	0.6 (0.3–1.2)	
Marine Corps, deployed (n = 4,527) vs nondeployed (n = 3,781)	4	2.4 (0.1–66.4)	
State Studies of US Vietnam Veterans			
Massachusetts Vietnam-era veterans			
Veterans served 1958–1973—cases diagnosed 1988–1993 (served in Vietnam) (updates Clapp et al., 1991)	80	0.6 (0.2–1.3)	Clapp, 1997
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans (includes lymphosarcoma, reticulosarcoma)	1	nr	Anderson et al., 1986a,b
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	164	1.0 (0.9–1.2)	ADVA, 2005b
Navy	34	1.0 (0.7–1.4)	
Army	104	1.0 (0.8–1.2)	
Air Force	26	1.3 (0.8–1.8)	
Mortality			
All branches, return–2001	22	0.7 (0.4–1.0)	ADVA, 2005a
Navy	4	0.6 (0.2–1.6)	
Army	13	0.7 (0.3–1.1)	
Air Force	5	1.1 (0.4–2.5)	
1980–1994	11	1.1 (0.6–1.9)	CDVA, 1997a

TABLE 20 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Incidence—1982–2000	19	0.7 (0.4–1.1)	ADVA, 2005c
Mortality			
1966–2001	1	0.3 (0.0–1.7)	
1982–1994	1	0.6 (nr)	CDVA, 1997b
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores)		**All COIs**	
		HRs	
Incidence (1992–2003)—bladder cancer (C67) categorized high (n = 133) vs low (n = 122)		1.0 (0.8–1.3)	Yi and Ohrr, 2014
Mortality (1992–2005)—bladder cancer (C67) categorized high (n = 85,809) vs low (n = 42)		2.0 (1.2–3.6)	Yi et al., 2014b
HR per unit of log EOI score (n = 19)	61	1.1 (1.0–1.3)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates		**Dioxins, phenoxy herbicides**	
Mortality 1939–1992	34	1.0 (0.7–1.5)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	24	1.4 (0.9–2.1)	
7,553 not exposed to highly chlorinated PCDDs	10	0.7 (0.3–1.2)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	13	0.8 (0.4–1.4)	Saracci et al., 1991
British MCPA Plant—All manual employees employed January 1947–December 1975 (n = 1,146), ever potentially exposed to phenoxy herbicides (n = 1,544), potentially exposed to phenoxy herbicides ≥ 1 year (n = 848) (not included in IARC cohort)		**MCPA**	
Mortality through 2012, all workers			Coggon et al., 2015
Bladder (ICD-10 C66–C68)	44	0.92 (0.67–1.23)	
Mortality through 2012, workers ever exposed to phenoxy herbicides			
Bladder (ICD-10 C66–C68)	30	0.87 (0.59–1.25)	
Mortality through 2012, workers ever exposed to phenoxy herbicides ≥ 1 year			
Bladder (ICD-10 C65–C68)	16	0.98 (0.56–1.59)	
Mortality through 1983	8	0.9 (0.4–1.7)	Coggon et al., 1986
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence 1943–1982 (men only)	11	0.8 (nr)	Lynge, 1985
Mortality 1955–2006	15	1.1 (0.8–1.4)	Boers et al., 2012
TCDD plasma level (hazard-ratios, by tertile)			
Background (≤ 0.4)	4	nr	
Low (0.4–4.1)	10	2.4 (0.8–8.3)	
Medium (4.1–20.1)	7	4.0 (1.1–14.3)	
High (≥ 20.1)	2	3.1 (0.6–17.0)	

continued

TABLE 20 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–2006 (hazard-ratios for lagged TCDD plasma levels)	11	1.0 (0.7–1.5)	Boers et al., 2012
Mortality 1955–2006	9 vs 2	2.3 (0.5–10.3)	Boers et al., 2010
Mortality 1955–1991	4	3.7 (1.0–9.5)	Hooiveld et al., 1998
Accidentally exposed subcohort	1	2.8 (0.1–15.5)	
Mortality 1955–1985	1	1.5 (0.0–8.8)	Bueno de Mesquita et al., 1993
Dutch production workers in Plant B (414 men exposed during production 1965–1986; 723 unexposed) (in IARC cohort)		**2,4-D; MCPA; MCPP; highly chlorinated dioxins unlikely**	
Mortality 1965–2006	2 vs 2	1.1 (0.2–7.2)	Boers et al., 2010
Mortality 1965–1986	0	0.0 (0.0–20.5)	Bueno de Mesquita et al., 1993
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 month in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Incidence			
1960–1992			Ott and Zober, 1996a
TCDD < 0.1 μg/kg of body weight	1	0.7 (0.0–4.0)	
TCDD 0.1–0.99 μg/kg of body weight	3	3.0 (0.6–8.9)	
TCDD > 1 μg/kg of body weight	1	0.8 (0.0–4.4)	
Mortality			
1960–1992			
TCDD < 0.1 μg/kg of body weight	0	0.0 (0.0–5.7)	
TCDD 0.1–0.99 μg/kg of body weight	2	4.1 (0.5–14.7)	
TCDD > 1 μg/kg of body weight	0	0.0 (0.0–5.4)	
		90% CI	Zober et al., 1990
Through 1987	0	nr (0.0–15.0)	
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 month in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–2007	13	1.8 (1.0–3.1)	Manuwald et al., 2012
Men	11	1.8 (0.9–3.3)	
Women	2	1.8 (0.2–6.6)	
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	0	0.0 (0.0–2.9)	
Production Workers (713 men and 100 women worked > 1 month in 1969–1984)			
Mortality 1969–2000	0	nr	't Mannetje et al., 2005

TABLE 20 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Sprayers (697 men and 2 women registered any time 1973–1984)			
Mortality 1973–2000	0	nr	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993	16	2.0 (1.1–3.2)	Steenland et al., 1999
Chloracne subcohort (n = 608)	6	3.0 (1.4–8.5)	
Through 1987 (bladder, other)	9	1.6 (0.7–3.0)	Fingerhut et al., 1991
≥ 1-year exposure, ≥ 20-year latency	4	1.9 (0.5–4.8)	
Mortality—754 Monsanto workers, among most highly exposed workers from Fingerhut et al. (1991)	16	6.8 (3.9–11.1)	Collins et al., 1993
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, Michigan) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1937–2011 Potential dioxin exposure (n = 2,192), TCP production (n = 1,419), PCP production (n = 577), Both TCP and PCP (n = 196)			Collins et al., 2016
TCP or PCP, Bladder and other urinary (ICD-10 C66–C68)	12	1.21 (0.63–2.11)	
TCP, Bladder and other urinary (ICD-10 C66–C68)	9	1.26 (0.57–2.38)	
PCP, Bladder and other urinary (ICD-10 C66–C68)	4	1.13 (0.31–2.90)	
1942–2003 (n = 1,615)	6	1.2 (0.5–2.7)	Collins et al., 2009b
1940–1994 (n = 2,187 men)	nr	0.7 (0.1–2.0)	Bodner et al., 2003
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, Washington, and Wichita, Kansas) and workers who made PCP and TCP at two additional plants (in Midland, Michigan, and Sauget, Illinois)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122) (bladder and other urinary organs, ICD-9 188, 189.3, 189.9)	8	1.1 (0.5–2.1)	
PCP and TCP (n = 720)	1	0.4 (0.0–2.3)	
PCP (no TCP) (n = 1,402)	7	1.4 (0.6–2.9)	
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)	19	1.2 (0.7–1.9)	Burns CJ et al., 2011
Through 1994 (n = 1,517)	1	0.5 (0.1–2.8)	Burns et al., 2001
Through 1982 (n = 878)	0	nr (0.0–7.2)	Bond et al., 1988
Dow PCP Production Workers (1937–1989 in Midland, Michigan) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	2	0.7 (0.1–2.7)	Collins et al., 2009c

continued

TABLE 20 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	50	1.0 (0.7–1.3)	
Ever	43	1.1 (0.8–1.5)	
New Hampshire pulp and paper workers, 883 white men working ≥ 1 year, mortality through July 1985	4	1.2 (0.3–3.2)	Henneberger et al., 1989
Pulp and Paper cohorts independent of IARC cohort			
Northwestern US paper and pulp workers—5 mills in Washington, Oregon, and California, 3,523 worked ≥ 1 year 1945–1955, mortality through March 1977	8	90% CI 1.2 (0.6–2.6)	Robinson et al., 1986
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Sawmill Workers in British Columbia—23,829 workers for ≥ 1 year at 11 mills using chlorophenates 1940–1985		**Chlorophenates, not TCDD**	
Incidence 1969–1989	33	0.9 (0.7–1.2)	Hertzman et al., 1997
Mortality 1950–1989	94	1.0 (0.8–1.2)	
Herbicide sprayers routinely exposed to herbicides for 6 months or more (1950–1982)		**Phenoxy herbicides**	Green, 1991
Diseases of genitourinary system	1	1.0 (0.0–5.6)	
DENMARK			
Danish gardeners (n = 3,124) exposed to pesticides	59	0.8 (0.6–1.1)	Kenborg et al., 2012
Danish farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	300	0.6 ($p < 0.05$)	
Employee	70	0.7 ($p < 0.05$)	
Women			
Self-employed	1	0.2 (nr)	
Employee	2	0.6 (nr)	
Family worker	25	0.6 ($p < 0.05$)	
Danish gardeners—incidence from 3,156 male and 859 female gardeners (urinary system, ICD-7 180–181)			Hansen et al., 2007
25-year followup (1975–2001)		**Herbicides**	
Born before 1915 (high exposure)	25	1.1 (0.7–1.6)	
Born 1915–1934 (medium exposure)	23	0.5 (0.4–0.8)	
Born after 1934 (low exposure)	1	0.2 (0.0–1.1)	
10-year followup (1975–1984) of male gardeners (lymphohematopoietic, ICD-7 200–2005)	18	0.9 (0.7–1.8)	Hansen et al., 1992
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	2	0.7 (0.1–2.4)	Swaen et al., 2004
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 weeks) not IARC		**Phenoxy herbicides**	
Incidence			Asp et al., 1994
No latency	12	1.6 (0.8–2.8)	
10-year latency	11	1.7 (0.8–3.0)	

TABLE 20 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Mortality			
No latency	1	0.5 (0.0–2.6)	
10-year latency	1	0.5 (0.0–3.0)	
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	31	0.5 (0.4–0.8)	Torchio et al., 1994
Italian rice growers with documented phenoxy use (n = 1,487)	12	**Phenoxy herbicides** 1.0 (0.5–1.8)	Gambini et al., 1997
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of incident stomach cancer cases vs remainder of 19,904 men with any incident cancer		**Herbicides**	Reif et al., 1989
Forestry workers (n = 134)	4	0.7 (0.3–1.8)	
UNITED STATES		**Phenoxy herbicides**	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010;			
Ever use of pesticides and risk of bladder cancer			Koutros et al., 2016
2,4,5-T (continuous, adjusted for age, race, state, pack-years of cigarettes and pipe smoking)	91	1.15 (0.84–0.59)	
2,4,5-T (never smokers with highest use, adjusted for age, race, and state)	9	2.64 (1.23–5.68)	
2,4,5-TP (continuous, adjusted for age, race, state, pack-years of cigarettes and pipe smoking)	40	1.07 (0.74–1.56)	
2,4-D (continuous, adjusted for age, race, state, pack-years of cigarettes and pipe smoking)	245	1.46 (0.98–2.18)	
2,4-D (never smokers with highest use, adjusted for age, race, and state)	23	1.88 (0.94–3.77)	
Dicamba (continuous, adjusted for age, race, state, pack-years of cigarettes and pipe smoking)	125	0.84 (0.62–1.14)	
Dicamba (never smokers with highest use, adjusted for age, race, and state)	13	1.12 (0.56–2.27)	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	191	0.6 (0.5–0.7)	
Commercial applicators	16	0.2 (0.7–1.9)	
Spouses	29	0.6 (0.4–0.9)	
Enrollment through 2002			Samanic et al., 2006
Dicamba—lifetime days exposure			
None	43	1.0	
1– < 20	6	0.5 (0.2–1.3)	
20– < 56	9	0.7 (0.3–1.4)	
56– < 116	6	0.6 (0.3–1.5)	
≥ 116	8	0.8 (0.4–1.9)	
		p-trend = 0.66	

continued

TABLE 20 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Enrollment through 2002			Alavanja et al., 2005
Private applicators	184	0.7 (0.6–0.8)	
Spouses of private applicators (> 99% women)	17	0.7 (0.4–1.1)	
Commercial applicators	13	1.1 (0.6–1.8)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	35	0.6 (0.4–0.8)	
Spouses (n = 676)	9	0.8 (0.4–1.6)	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	7	0.4 (0.1–0.7)	
Spouses of private applicators (> 99% women)	2	0.8 (0.1–2.7)	
US Department of Agriculture Workers—nested case-control study of white men dying 1970–1979 of NHL		**Herbicides**	
Agricultural extension agents	8	0.7 (0.4–1.4)	Alavanja et al., 1988
Forest conservationists	8	0.8 (0.3–1.6)	Alavanja et al., 1989
Florida Licensed Pesticide Applicators (common phenoxy use assumed but not documented; had been listed by Blair et al., 1983)		**Herbicides**	
Pesticide applicators in Florida licensed 1965–1966 (n = 3,827)—mortality through 1976		**Herbicides**	Blair et al., 1983
Any pesticide (dose-response by length of licensure)		*Expected number of exposed cases*	
	3	1.6 (nr)	
White Male Residents of Iowa—NHL cancer on death certificate, usual occupation: farmers vs not		**Herbicides**	
> 20 years old when died 1971–1978—PMR	274	0.9 (nr)	Burmeister, 1981
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Incidence			
20-year followup to 1996—men and women			
Zone A	3	1.4 (0.5–4.5)	Pesatori et al., 2009
Zone B	17	1.3 (0.8–2.2)	
Zone R	84	0.9 (0.8–1.2)	
10-year followup to 1991—men			Pesatori et al., 1992
Zone A, B	10	1.6 (0.9–3.1)	
Zone R	39	1.0 (0.7–1.4)	
10-year followup to 1991—women			
Zone A, B	1	0.9 (0.1–6.8)	
Zone R	4	0.6 (0.2–1.5)	
Mortality			
25-year followup to 2001—men and women			Consonni et al., 2008
Zone A	1	1.0 (0.2–7.4)	
Zone B	6	0.9 (0.4–2.0)	
Zone R	42	0.9 (0.6–1.2)	

TABLE 20 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
20-year followup to 1996			Bertazzi et al., 2001
Zones A and B—men	6	1.2 (0.5–2.7)	
15-year followup to 1991—men			Bertazzi et al., 1998
Zone B	1	2.4 (0.3–16.8)	
Zone R	21	0.9 (0.6–1.5)	
15-year followup to 1991—women			Bertazzi et al., 1998
Zone B	3	0.9 (0.3–3.0)	
Zone R	4	0.6 (0.2–1.8)	
Ecological Study of Residents of Chapaevsk, Russia		**Dioxin**	Revich et al., 2001
Mortality—1995–1998 (SMR vs regional rates)			
Men	31	2.6 (1.7–3.6)	
Women	17	0.8 (0.5–1.3)	
Other International Environmental Studies			
FINLAND			
Finnish community exposed to chlorophenol contamination (men and women)—incidence	14	**Chlorophenol** 1.0 (0.6–1.9)	Lampi et al., 1992
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995a
Incidence			
East coast	10	0.7 (0.4–1.3)	
West coast	55	0.9 (0.7–1.1)	
Mortality			
East coast	5	1.3 (0.4–3.1)	
West coast	20	1.0 (0..6–1.6)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,5-DCP, 2,5-dichlorophenol; CATI, computer-assisted telephone interviewing; CC, case-control; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job-exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; n, number; NHL, non-Hodgkin lymphoma; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; PMR, proportional mortality ratio; SEA, Southeast Asia; SIR, standardized incidence ratio; SMR, standardized mortality rate; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

TABLE 21 Selected Epidemiologic Studies—Renal Cancers (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veteran			
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Mortality			
1965–2000	1	nr	Boehmer et al., 2004
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1982			Breslin et al., 1988
Army, deployed (n = 19,708) vs nondeployed (n = 22,904)	55	0.9 (0.5–1.5)	
Marine Corps, deployed (n = 4,527) vs nondeployed (n = 3,781)	13	0.9 (0.5–1.5)	
State Studies of US Vietnam Veterans			
Massachusetts Vietnam veterans diagnosed 1972–1983	9	1.8 (1.0–3.5)	Kogan and Clapp, 1988
Michigan Vietnam-era veterans, PM study of deaths (1974–1989)—deployed vs nondeployed	21	1.4 (0.9–2.2)	Visintainer et al., 1995
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans (includes lymphosarcoma, reticulosarcoma)	2	nr	Anderson et al., 1986a,b
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	125	1.0 (0.8–1.2)	ADVA, 2005b
Navy	34	1.3 (0.9–1.7)	
Army	77	0.9 (0.7–1.1)	
Air Force	14	1.1 (0.6–1.8)	
Mortality			
All branches, return–2001	50	1.0 (0.7–1.2)	ADVA, 2005a
Navy	12	1.1 (0.6–1.9)	
Army	33	0.9 (0.6–1.3)	
Air Force	5	0.8 (0.3–1.8)	
1980–1994	22	1.2 (0.7–1.8)	
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Incidence—1982–2000	19	0.7 (0.4–1.0)	ADVA, 2005c
Mortality			
1966–2001	4	0.4 (0.1–1.1)	
1982–1994	3	3.9 (nr)	CDVA, 1997b

TABLE 21 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores)		**All COIs**	
		HRs	
Incidence (1992–2003)—categorized high (n = 85,809) vs low (n = 94,442)			Yi and Ohrr, 2014
Kidney cancer (C64) categorized high (n = 79) vs low (n = 102)		0.7 (0.6–1.0)	
Renal pelvis cancer (C65) categorized high (n = 11) vs low (n = 12)		1.1 (0.4–2.5)	
Ureter cancer (C66) categorized high (n = 11) vs low (n = 8)		1.3 (0.5–3.2)	
Mortality (1992–2005)—renal cancer (C64–C66) categorized high (n = 30) vs low (n = 33)		0.9 (0.5–1.5)	Yi et al., 2014b
HR per unit of EOI scores (n = 180,639)	63	1.0 (0.9–1.1)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates		**Dioxin, phenoxy herbicides**	
Mortality 1939–1992	29	1.1 (0.7–1.6)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	26	1.6 (1.1–2.4)	
7,553 not exposed to highly chlorinated PCDDs	3	0.3 (0.1–0.9)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	11	1.0 (0.5–1.7)	Saracci et al., 1991
British MCPA Plant—All manual employees employed January 1947–December 1975 (n = 1,146), ever potentially exposed to phenoxy herbicides (n = 1,544), potentially exposed to phenoxy herbicides ≥ 1 year (n = 848) (not included in IARC cohort)		**MCPA**	
Mortality through 2012, all workers			Coggon et al., 2015
Kidney (ICD-10 C64)	23	0.87 (0.55–1.31)	
Mortality through 2012, workers ever exposed to phenoxy herbicides			
Kidney (ICD-10 C64)	16	0.81 (0.46–1.32)	
Mortality through 2012, workers ever exposed to phenoxy herbicides ≥ 1 year			
Kidney (ICD-10 C64)	11	1.22 (0.61–2.19)	
Mortality through 1983	5	1.0 (0.3–2.3)	Coggon et al., 1986
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence 1943–1982 (men only)	3	0.6 (nr)	Lynge, 1985
Mortality 1955–2006	8	1.2 (0.8–1.6)	Boers et al., 2012
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–2006 (HRs for lagged TCDD plasma levels)	8	0.8 (0.5–1.5)	Boers et al., 2012
Mortality 1955–2006	8	HR = "infinitively large"	Boers et al., 2010
Mortality 1955–1991	4	3.7 (1.0–9.5)	Hooiveld et al., 1998
Total cohort—kidney cancer	4	4.1 (1.1–10.4)	
Total cohort—"urinary organs"	8	3.9 (0.7–7.6)	

continued

TABLE 21 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 month in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,4,5-TCP; 2,5-DCP**	
Mortality 1952–2007 (kidney and other and unspecified urinary organs)	9	2.1 (0.9–3.9)	Manuwald et al., 2012
Men	7	2.0 (0.8–4.1)	
Women	2	2.3 (0.3–8.1)	
Mortality 1952–1989—stats on men only, 1,184 (tables all for 1,148 men, not necessarily German nationals) vs national rates (also vs gas workers); same observation period as Becher et al., 1966	3	1.6 (0.3–4.6)	Manz et al., 1991
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	3	2.3 (0.5–6.7)	
Production Workers (713 men and 100 women worked > 1 month in 1969–1984)			
Mortality 1969–2000	1	1.2 (0.0–6.6)	't Mannetje et al., 2005
Sprayers (697 men and 2 women registered any time 1973–1984)			
Mortality 1973–2000	3	2.7 (0.6–8.0)	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993	13	1.6 (0.8–2.7)	Steenland et al., 1999
Through 1987 (bladder, other)	8	1.4 (0.6–2.8)	Fingerhut et al., 1991
≥ 1-year exposure, ≥ 20-year latency	2	1.1 (0.1–3.8)	
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, Michigan) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1937–2011 Potential dioxin exposure (n = 2,192), TCP production (n = 1,419), PCP production (n = 577), Both TCP and PCP (n = 196)			Collins et al., 2016
TCP or PCP, Kidney (ICD-10 C64–65)	8	0.93 (0.40–1.84)	
TCP, Bladder and other urinary (ICD-10 C64–C65)	4	0.63 (0.17–1.61)	
PCP, Bladder and other urinary (ICD-10 C64–C65)	4	1.37 (0.37–3.51)	
1942–2003 (n = 1,615)	2	0.4 (0.1–1.5)	Collins et al., 2009b
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, Washington, and Wichita, Kansas) and workers who made PCP and TCP at two additional plants (in Midland, Michigan, and Sauget, Illinois)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122) (kidney, ICD-9 189.0–189.2)	8	1.2 (0.5–2.4)	
PCP and TCP (n = 720)	4	1.8 (0.5–4.6)	
PCP (no TCP) (n = 1,402)	4	0.9 (0.3–2.3)	

TABLE 21 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3) (kidney, renal pelvis)	5	0.8 (0.3–1.8)	Burns CJ et al., 2011
Through 1994 (n = 1,517)	2	0.9 (0.1–3.3)	Burns et al., 2001
Through 1982 (n = 878)	0	nr (0.0–6.2)	Bond et al., 1988
Dow PCP Production Workers (1937–1989 in Midland, Michigan) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	4	1.7 (0.5–4.4)	Collins et al., 2009c
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	41	0.9 (0.7–1.3)	
Ever	18	0.5 (0.3–0.8)	
New Hampshire pulp and paper workers, 883 white men working ≥ 1 year, mortality through July 1985	3	1.5 (0.3–4.4)	Henneberger et al., 1989
Pulp and Paper cohorts independent of IARC cohort			
Northwestern US paper and pulp workers—5 mills in Washington, Oregon, and California, 3,523 worked ≥ 1 year 1945–1955, mortality through March 1977	6	90% CI 1.2 (0.5–3.0)	Robinson et al., 1986
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
DENMARK			
Danish farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	141	0.6 ($p < 0.05$)	
Employee	18	0.4 ($p < 0.05$)	
Women			
Self-employed	4	0.9 (nr)	
Employee	3	1.0 (nr)	
Family Worker	30	0.8 (nr)	
Danish gardeners—incidence from 3,156 male and 859 female gardeners (urinary system, ICD-7 180–181)			Hansen et al., 2007
25-year followup (1975–2001)		**Herbicides**	
Born before 1915 (high exposure)	25	1.1 (0.7–1.6)	
Born 1915–1934 (medium exposure)	23	0.5 (0.4–0.8)	
Born after 1934 (low exposure)	1	0.2 (0.0–1.1)	
10-year followup (1975–1984) of male gardeners (lymphohematopoietic, ICD-7 200–205)	18	0.9 (0.7–1.8)	Hansen et al., 1992
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	4	1.3 (0.4–3.4)	Swaen et al., 2004

continued

TABLE 21 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	16	0.6 (0.4–1.0)	Torchio et al., 1994
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of incident stomach cancer cases vs remainder of 19,904 men with any incident cancer			Reif et al., 1989
Forestry workers (n = 134)		**Herbicides**	
	2	0.6 (0.2–2.3)	
SWEDEN			
Incident cancer cases 1961–1973 with agriculture as economic activity in 1960 census (male, female)	775	99% CI 0.8 (0.7–0.9)	Wiklund, 1983
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	522	1.1 (1.0–1.2)	
Nonwhites (n = 11,446)	30	0.8 (0.5–1.1)	
Women			
Whites (n = 2,400)	6	0.8 (0.3–1.7)	
Nonwhites (n = 2,066)	6	1.4 (0.5–3.1)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	148	0.8 (0.7–1.0)	
Commercial applicators	2	nr	
Spouses	39	0.7 (0.5–1.0)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	71	0.9 (0.7–1.1)	
Spouses (n = 676)	12	0.6 (0.3–1.1)	
US Department of Agriculture Workers—nested case-control study of white men dying 1970–1979 of NHL		**Herbicides**	
Agricultural extension agents	nr	1.7 (0.9–3.3)	Alavanja et al., 1988
Forest conservationists	2.3	0.1	Alavanja et al., 1989
Soil conservationists	2.1	0.6	
Florida Licensed Pesticide Applicators (common phenoxy use assumed but not documented; had been listed by Blair et al., 1983)		**Herbicides**	
Pesticide applicators in Florida licensed 1965–1966 (n = 3,827)—mortality through 1976	1	0.5 (nr)	Blair et al., 1983
White Male Residents of Iowa—NHL cancer on death certificate, usual occupation: farmers vs not		**Herbicides** PMR	
> 20 years old when died 1971–1978	178	1.1 (ns)	Burmeister, 1981

TABLE 21 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Incidence			
20-year followup to 1996—men and women			Pesatori et al., 2009
Zone B	6	0.9 (0.4–2.0)	
Zone R	43	0.9 (0.7–1.2)	
10-year followup to 1991 (kidney, other urinary organs)			Bertazzi et al., 1993
Zone R—men	10	0.9 (0.4–1.7)	
Zone R—women	7	1.2 (0.5–2.7)	
10-year followup to 1991—men			Pesatori et al., 1992
Zone A, B	0	nr	
Zone R	11	0.9 (0.5–1.7)	
10-year followup to 1991—women			
Zone A, B	1	1.1 (0.2–8.1)	
Zone R	7	1.2 (0.5–2.6)	
Mortality			
25-year followup to 2001—men and women			Consonni et al., 2008
Zone A	0	nr	
Zone B	3	0.6 (0.2–2.0)	
Zone R	39	1.2 (0.8–1.6)	
20-year followup to 1996			Bertazzi et al., 2001
Zones A and B—men	3	0.8 (0.3–2.6)	
Zones A and B—women	3	1.8 (0.6–5.8)	
CASE-CONTROL STUDIES			
International Case-Control Studies			
Danish Cancer Registry patients (n = 365) and 396 referents, occupational herbicide exposure		**Herbicides**	Mellemgaard et al., 1994
Men	13	1.7 (0.7–4.3)	
Women	3	5.7 (0.6–58.0)	
UK men, 18–35 years of age from counties with particular chemical manufacturing—mortality		**Herbicides, Chlorophenols**	Magnani et al., 1987
Herbicides	nr	1.3 (0.6–3.1)	
Chlorophenols	nr	0.9 (0.4–1.9)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,5-DCP, 2,5-dichlorophenol; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job-exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; n, number; NHL, non-Hodgkin lymphoma; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; ns, not significant; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; PMR, proportional mortality ratio; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Subjects are male, and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

TABLE 22 Selected Epidemiologic Studies—Brain Tumors (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Incidence			
Through 1999—White subjects vs national rates (brain and nervous system)			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	5	1.8 (0.7–4.1)	
With tours between 1966–1970	5	2.2 (0.8–4.8)	
SEA comparison veterans (n = 1,776)	2	0.5 (0.1–1.8)	
With tours between 1966–1970	2	0.7 (0.1–2.3)	
Mortality			
Through 1999—White subjects vs national rates			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	3	1.3 (0.3–3.6)	
SEA comparison veterans (n = 1,776)	1	0.3 (nr)	
US VA Cohort of Army Chemical Corps—Expanded as of 1997 to include all Army men with chemical MOS (2,872 deployed vs 2,737 nondeployed) serving during Vietnam era (7/1/1965–3/28/1973)		**All COIs**	
Mortality—brain tumors			
Through 2005			Cypel and Kang, 2010
Deployed veterans (2,872) vs nondeployed (2,737)	4 vs 2	1.7 (0.3–10.2)	
ACC veterans vs US men			
Vietnam cohort	4	0.9 (0.2–2.2)	
Non-Vietnam cohort	2	0.5 (0.1–2.0)	
Through 1991	2	1.9 (nr)	Dalager and Kang, 1997
894 ACC members assigned to Vietnam in 1966–1971—Through 1987	2	nr	Thomas and Kang, 1990
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Mortality			
1965–2000 (meninges, brain, other CNS)	9	1.2 (0.4–3.2)	Boehmer et al., 2004
Post-service–1983	3	nr	Boyle et al., 1987
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1982			Breslin et al., 1988
Army, deployed (n = 19,708) vs nondeployed (n = 22,904)	116	1.0 (0.3–3.2)	
Marine Corps, deployed (n = 4,527) vs nondeployed (n = 3,781)	25	1.1 (0.2–7.1)	
US VA Cohort of Female Vietnam-era Veterans who served in Vietnam (n = 4,586; nurses only = 3,690); nondeployed (n = 5,325; nurses only 3,282)		**All COIs**	
Mortality—brain or other nervous system			
Through 2010	22	2.3 (0.9–5.7)	Kang et al., 2014
Vietnam nurses only	16	4.6 (1.3–16.8)	

TABLE 22 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Through 2004 (all female Vietnam veterans)	8	2.0 (0.7–5.9)	Cypel and Kang, 2008
Vietnam veteran nurses only	8	3.6 (0.9–14.5)	
Through 1991	4	1.4 (0.4–3.7)	Dalager et al., 1995a
State Studies of US Vietnam Veterans			
Michigan Vietnam-era veterans, PM study of deaths (1974–1989)—deployed vs nondeployed	36	1.1 (0.8–1.5)	Vistainer et al., 1995
New York			
—deployed vs nondeployed (brain, CNS)	4	0.5 (0.2–1.5)	Lawrence et al., 1985
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans	8	0.8 (0.3–1.5)	Anderson et al., 1986a,b
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000 (brain)	97	1.1 (0.9–1.2)	ADVA, 2005b
Navy	24	1.2 (0.7–1.7)	
Army	63	1.0 (0.8–1.3)	
Air Force	10	1.1 (0.6–2.1)	
Mortality			
All branches, return–2001 (brain, CNS)	99	1.0 (0.8–1.1)	ADVA, 2005a
Navy	23	1.0 (0.6–1.4)	
Army	66	0.9 (0.7–1.2)	
Air Force	9	0.9 (0.4–1.6)	
1980–1994	39	1.1 (0.7–1.4)	CDVA, 1997a
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Incidence (brain, CNS)			
1982–2000	23	1.4 (0.7–2.6)	ADVA, 2005c
Mortality (brain, CNS)			
1966–2001	27	1.6 (0.9–3.1)	ADVA, 2005c
1982–1994	13	1.4 (nr)	CDVA, 1997b
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores) (HRs)		**All COIs**	
Incidence (1992–2003)—brain cancer (C70–C72) categorized high (n =32) vs low (n = 30)		1.0 (0.6–1.7)	Yi and Ohrr, 2014
Mortality (1992–2005)—central nervous system cancer (C70–C72) categorized high (n = 36) vs low (n = 37)		0.9 (0.6–1.4)	Yi et al., 2014b
HR per unit of log EOI score (n = 180,639)	73	1.0 (0.9–1.1)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	22	0.7 (0.4–1.0)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	12	0.6 (0.3–1.1)	
7,553 not exposed to highly chlorinated PCDDs	10	0.8 (0.4–1.5)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	6	0.4 (0.1–0.8)	Saracci et al., 1991

continued

TABLE 22 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
British MCPA Plant—All manual employees employed January 1947–December 1975 (n = 1,146), ever potentially exposed to phenoxy herbicides (n = 1,544), potentially exposed to phenoxy herbicides ≥ 1 year (n = 848) (not included in IARC cohort)		**MCPA**	
Mortality through 2012, all workers			Coggon et al., 2015
Brain (ICD-10 C71–72)	33	1.15 (0.79–1.62)	
Mortality through 2012, workers ever exposed to phenoxy herbicides			
Brain (ICD-10 C71–72)	25	1.15 (0.74–1.70)	
Mortality through 2012, workers ever exposed to phenoxy herbicides ≥ 1 year			
Brain (ICD-10 C71–72)	10	1.04 (0.50–1.92)	
Mortality through 1983 (brain, CNS)	11	1.2 (0.6–2.2)	Coggon et al., 1986
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence 1943–1982	4	0.7 (nr)	Lynge, 1985
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 month in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992	0	—	Becher et al., 1996
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 month in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1965–1989	0	—	Becher et al., 1996
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 month in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1956–1989	0	—	Becher et al., 1996
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 month in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortalilty 1952–1989	3	2.3 (0.5–6.8)	Becher et al., 1996
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	4	2.0 (0.6–5.2)	
Never-exposed workers	0	0.0 (0.0–5.5)	
Production Workers (713 men and 100 women worked > 1 month in 1969–1984)			
Mortality 1969–2000	1	0.8 (0.0–4.6)	't Mannetje et al., 2005
Sprayers (697 men and 2 women on register of New Zealand applicators, 1973–1984)			
Mortality 1973–2000	1	0.6 (0.0–3.4)	't Mannetje et al., 2005

TABLE 22 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993 (brain, CNS)	8	0.8 (0.4–1.6)	Steenland et al., 1999
Through 1987 (brain, CNS)			Fingerhut et al., 1991
≥ 1-year exposure, ≥ 20-year latency	2	1.1 (0.1–3.8)	
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, Michigan) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)	3	0.6 (0.1–1.7)	Collins et al., 2009b
1940–1994 (n = 2,187 men)	nr	0.6 (0.1–1.8)	Bodner et al., 2003
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, Washington, and Wichita, Kansas) and workers who made PCP and TCP at two additional plants (in Midland, Michigan, and Sauget, Illinois)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122) (brain, other nervous system)	6	0.9 (0.3–1.9)	
PCP and TCP (n = 720)	1	0.4 (0.0–2.4)	
PCP (no TCP) (n = 1,402)	5	1.1 (0.4–2.6)	
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3) (brain, other CNS)	3	1.1 (0.2–3.2)	Burns CJ et al., 2011
Through 1994 (n = 1,517)	3	1.1 (0.1–3.2)	Burns et al., 2001
Through 1982 (n = 878) (brain, other system tissues)	0	nr (0.0–4.1)	Bond et al., 1988
Dow PCP Production Workers (1937–1989 in Midland, Michigan) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	1	0.4 (0.0–2.3)	Collins et al., 2009c
Mortality 1940–1989 (n = 770)			Ramlow et al., 1996
0-year latency	1	nr	
15-year latency	1	nr	
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	44	1.0 (0.7–1.4)	
Ever	28	0.8 (0.5–1.2)	
New Hampshire pulp and paper workers, 883 white men working ≥ 1 year, mortality through July 1985	2	1.2 (0.1–4.2)	Henneberger et al., 1989
Northwestern US paper and pulp workers—5 mills in Washington, Oregon, and California, 3,523 worked ≥ 1 year 1945–1955, mortality through March 1977	4	0.6 (0.2–2.1)	Robinson et al., 1986

continued

TABLE 22 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Canadian Farm Operator Study—156,242 men farming in Manitoba, Saskatchewan, and Alberta in 1971; mortality from brain cancer June 1971–December 1987			
210 histologically confirmed deaths attributed to brain cancer in farmers ≥ 35 years of age			Morrison et al., 1992
Herbicides sprayed on ≥ 250 acres vs 0 acres	24	0.8 (0.5–1.2)	
70,000 male Saskatchewan farmers identified in 1971 census data linked to mortality records (brain)	96	1.0 (0.8–1.3)	Wigle et al., 1990
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	194	1.1 (nr)	
Employee	39	0.9 (nr)	
Women			
Self-employed	5	1.0 (nr)	
Employee	2	0.5 (nr)	
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	4	1.6 (0.4–4.1)	Swaen et al., 2004
Through 1987	3	3.2 (0.6–9.3)	Swaen et al., 1992
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 weeks) not IARC (eye, brain)		**Phenoxy Herbicides**	
Incidence	3	0.7 (0.1–2.0)	Asp et al., 1994
Mortality 1972–1989	3	1.2 (0.3–3.6)	
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)			Torchio et al., 1994
Brain, nervous system	15	0.5 (0.3–0.9)	
Eye	4	2.4 (0.7–6.1)	
Italian rice growers with documented phenoxy use (n = 1,487) (brain, CNS)	4	**Phenoxy herbicides** 0.9 (0.2–2.3)	Gambini et al., 1997
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of incident brain cancer cases vs remainder of 19,904 men with any incident cancer		**Herbicides**	Reif et al., 1989
Forestry workers (n = 134) (brain, CNS)	4	1.2 (0.4–3.3)	
SWEDEN			
Swedish lumberjacks—Used phenoxys 1954–1967, Incidence 1958–1992			Thörn et al., 2000
Exposed (n = 154)	0	—	
Foremen (n = 15)	0	—	
Lumberjacks (n = 139)	0	—	
Unexposed lumberjacks (n = 241)	1	0.9 (0.0–5.1)	

TABLE 22 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)			
Brain	447	1.2 (1.1–1.3)	
Eye	17	1.6 (0.9–2.5)	
Nonwhites (n = 11,446) (brain)	16	1.0 (0.6–1.6)	
Women			
Whites (n = 2,400) (brain)	9	1.1 (0.5–2.1)	
Nonwhites (n = 2,066) (brain)	1	0.4 (0.0–2.1)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	51	0.8 (0.6–1.0)	
Commercial applicators	5	1.2 (0.4–2.8)	
Spouses	26	0.9 (0.6–1.4)	
Enrollment through 2002			Alavanja et al., 2005
Private applicators	33	0.8 (0.6–0.8)	
Spouses of private applicators (> 99% women)	15	0.9 (0.5–1.4)	
Commercial applicators	5	1.9 (0.6–4.3)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641) (brain, other nervous system)	59	0.8 (0.6–1.0)	
Spouses (n = 676)	25	0.8 (0.5–1.2)	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	19	0.7 (0.4–1.1)	
Years handled pesticides			
≤ 10 years	5	0.9 (ns)	
> 10 years	12	0.6 (ns)	
Spouses of private applicators (> 99% women)	11	1.1 (0.5–1.8)	
US Department of Agriculture Workers—nested case-control study of white men dying 1970–1979 of brain cancer		**Herbicides**	
Agricultural extension agents	nr	1.0 (0.4–2.4)	Alavanja et al., 1988
Forest conservationists	6	1.7 (0.6–3.7)	Alavanja et al., 1989
Pesticide applicators in Florida licensed 1965–1966 (n = 3,827)—mortality through 1976	5	**Herbicides** 2.0 (nr)	Blair et al., 1983
White Male Residents of Iowa—brain cancer on death certificate, usual occupation: farmers vs not		**Herbicides**	
> 20 years old when died 1971–1978—PMR	111	1.1 (nr)	Burmeister, 1981

continued

TABLE 22 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Incidence			
20-year followup to 1996—men and women			
Zone A	2	2.4 (0.6–9.8)	Pesatori et al., 2009
Zone B	4	0.8 (0.3–2.1)	
Zone R	37	1.0 (0.7–1.5)	
10-year followup to 1991—men			Bertazzi et al., 1993
Zone R	6	0.6 (0.3–1.4)	
10-year followup to 1991—women			Bertazzi et al., 1993
Zone R	6	1.4 (0.6–3.4)	
Mortality			
25-year followup to 2001—men and women			Consonni et al., 2008
Zone A	0	nr	
Zone B	3	0.7 (0.2–2.1)	
Zone R	34	1.1 (0.8–1.6)	
20-year followup to 1996			Bertazzi et al., 2001
Zones A, B—men	1	0.4 (0.1–3.0)	
Zones A, B—women	3	1.9 (0.6–6.0)	
15-year followup to 1991—men			Bertazzi et al., 1998
Zone B	1	0.8 (0.1–5.5)	
Zone R	12	1.3 (0.7–2.5)	
15-year followup to 1991—women			Bertazzi et al., 1998
Zone B	3	3.2 (1.0–10.3)	
Zone R	8	1.1 (0.5–2.4)	
10-year followup to 1986—men			Bertazzi et al., 1989a
Zone A, B, R	5	1.2 (0.4–3.1)	
10-year followup to 1986—women			Bertazzi et al., 1989a
Zone A, B, R	5	2.1 (0.8–5.9)	
Other International Environmental Studies			
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995
Incidence			
East coast	3	0.5 (0.1–1.5)	
West coast	24	0.9 (0.6–1.4)	
Mortality			
East coast	2	0.6 (0.1–2.1)	
West coast	15	1.1 (0.6–1.7)	

TABLE 22 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
CASE-CONTROL STUDIES			
US Case-Control Studies			
NIOSH UMHS—farm pesticide exposure and glioma risk in adults (18–80 years of age) living in Iowa, Michigan, Minnesota, Wisconsin (glioma cases diagnosed 1995–January 1997)		**Arsenicals, phenoxy herbicides, 2,4-D**	
798 glioma cases vs 1,175 population-based controls (excluding proxy, 438 vs 1,141)			Yiin et al., 2012
Herbicide use—including proxy (160 vs 265)		0.8 (0.6–1.0)	
Herbicide use—excluding proxy (90 vs 260)		0.8 (0.6–1.1)	
341 female glioma cases vs 528 population-based controls			Carreon et al., 2005
Arsenicals	13	1.0 (0.5–1.9)	
Phenoxy herbicides	25	0.9 (0.5–1.5)	
2,4-D	24	0.9 (0.5–1.6)	
457 male glioma cases vs 648 population-based controls			Ruder et al., 2004
Arsenicals	15	0.7 (0.4–1.4)	
Phenoxy herbicides	67	0.9 (0.6–1.2)	
2,4-D	nr	nr	
US hospital-based study of 462 glioma and 195 meningioma patients vs 765 patient controls; cumulative lifetime occupational exposure to herbicides vs unexposed		**Herbicides**	Samanic et al., 2008
Gliomas			
Men	65	0.9 (0.6–1.3)	
Low quartile	20	1.0 (0.5–1.9)	
Second quartile	16	1.0 (0.5–2.1)	
Third quartile	12	0.6 (0.3–1.3)	
Fourth quartile	17	0.8 (0.4–1.6)	
		p-trend = 0.50	
Women	35	1.3 (0.8–2.0)	
Below median	23	1.5 (0.8–2.7)	
Above median	12	1.0 (0.5–2.1)	
		p-trend = 0.91	
Meningiomas (women only)	33	2.4 (1.4–4.3)	
Below median	16	2.1 (1.0–4.4)	
Above median	17	2.9 (1.3–6.2)	
		p-trend = 0.01	
Nebraska men and women diagnosed with gliomas between 1988 and 1993; association between farming and pesticide use (251 cases vs 498 controls)			Lee et al., 2005
Phenoxy herbicides—combined reports (identical with results for 2,4-D specifically)	32	1.8 (1.0–3.3)	
By self	7	0.6 (0.2–1.6)	
By proxy	25	3.3 (1.5–7.2)	
2,4,5-T—combined reports	7	1.3 (0.5–3.6)	
By self	2	0.4 (0.1–2.3)	
By proxy	5	2.7 (0.7–9.8)	

continued

TABLE 22 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Missouri—Evaluation of occupational risks for brain cancer from the Missouri Cancer registry (312 cases, 1,248 cancer controls)			Brownson et al., 1990
Industry agricultural work	22	1.5 (1.0–2.4)	
Occupation farming	21	1.1 (0.6–1.7)	
International Case-Control Studies			
Irish farmers and farm workers		**Herbicides**	Dean, 1994
Men	195	nr	
Women	72	nr	
Italian hospital-based study of 240 brain glioma patients vs 742 controls		**Herbicides**	Musicco et al., 1988
Male, female farmers	61	1.6 (1.1–2.4)	
French hospital-based study of 125 brain glioma patients vs 238 controls		**Herbicides**	Cordier et al., 1988
Woodworkers		OR = 1.6 ($p > 0.05$)	
UK men, 18–35 years of age from counties with particular chemical manufacturing—mortality		**Herbicides, Chlorophenols**	Magnani et al., 1987
Herbicides	nr	1.2 (0.7–2.1)	
Chlorophenols	nr	1.1 (0.7–1.8)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; ACC, Army Chemical Corps; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; CNS, central nervous system; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job-exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; MOS, military occupation specialty; n, number; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; ns, not statistically significant; OR, odds ratio; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; PMR, proportional mortality ratio; SEA, Southeast Asia; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

TABLE 23 Selected Epidemiologic Studies—Endocrine Cancers (thyroid, thymus, and other) (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1982 (thyroid and other endocrine, ICD-9 193–194)			Breslin et al.,1986, 1988
Army, deployed (n = 19,708) vs nondeployed (n = 22,904)	15	0.6 (0.3–1.2)	
Marine Corps, deployed (n = 4,527) vs nondeployed (n = 3,781)	4	0.6 (0.1–3.4)	
US VA Corporate Data Warehouse—Incident cases of thyroid cancer from October 1, 1999 to December 21, 2013			Le et al., 2016
Proportion with Agent Orange exposure was significantly higher among thyroid cancer patients compared to the non-exposed Veterans Health Administration population	nr	10.0% versus 6.2%; p < 0.0001	
State Studies of US Vietnam Veterans			
Massachusetts Vietnam-era veterans			
Veterans aged 35–65 years in 1993—cases diagnosed 1988–1993 vs thyroid cancer	4	1.2 (0.3–4.5)	Clapp, 1997
International Vietnam-Veterans Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence—thyroid			
All branches, 1982–2000	17	0.6 (0.3–0.9)	ADVA, 2005b
Navy	3	0.5 (0.1–1.3)	
Army	11	0.5 (0.3–1.0)	
Air Force	3	1.2 (0.2–3.5)	
Mortality—thyroid			
All branches, return–2001	2	0.5 (0.0–1.8)	ADVA, 2005a
Navy	1	1.2 (0.0–6.5)	
Army	1	0.4 (0.0–2.0)	
Air Force	0	0.0 (0.0–7.8)	
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Incidence—thyroid			
1982–2000	4	0.6 (0.1–2.2)	ADVA, 2005c
Mortality—thyroid			
1966–2001	1	1.2 (0.0–91.7)	ADVA, 2005c
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores)		**All COIs**	
		HRs	
Incidence (1992–2003)—thyroid cancer (C73) categorized high (n = 41) vs low (n = 43)		1.1 (0.7–1.7)	Yi and Ohrr, 2014
Mortality (1992–2005)—thyroid cancer (C73) categorized high (n = 10) vs low (n = 1)		11.3 (1.3–96.6)	Yi et al., 2014b
HR per unit of log EOI scores (n = 180,639)	11	2.9 (1.1–7.4)	

continued

TABLE 23 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992			Kogevinas et al., 1997
Thyroid (ICD-9 193)	4	1.7 (0.5–4.3)	
13,831 exposed to highly chlorinated PCDDs	2	1.4 (0.2–4.9)	
7,553 not exposed to highly chlorinated PCDDs	2	2.2 (0.3–7.9)	
Other endocrine organs (ICD-9 194)	5	3.6 (1.2–8.4)	
13,831 exposed to highly chlorinated PCDDs	2	2.3 (0.3–8.1)	
7,553 not exposed to highly chlorinated PCDDs	3	6.4 (1.3–18.7)	
British MCPA Plant—All manual employees employed January 1947–December 1975 (n = 1,146), ever potentially exposed to phenoxy herbicides (n = 1,544), potentially exposed to phenoxy herbicides ≥ 1 year (n = 848) (not included in IARC cohort)		**MCPA**	
Mortality through 2012, all workers			Coggon et al., 2015
Thyroid (ICD-10 C73)	3	1.56 (0.32–4.57)	
Mortality through 2012, workers ever exposed to phenoxy herbicides			
Thyroid (ICD-10 C73)	3	2.15 (0.44–6.28)	
Mortality through 2012, workers ever exposed to phenoxy herbicides ≥ 1 year			
Thyroid (ICD-10 C73)	2	3.11 (0.38–11.22)	
Mortality through 1983 (thyroid)	1	1.8 (0.4–9.8)	Coggon et al., 1986
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004 (thyroid, other endocrine)			McBride et al., 2009a
Ever-exposed workers	0	0.0 (0.0–19.8)	
Production Workers (713 men and 100 women worked > 1 month in 1969–1984)			
Mortality 1969–2000	0	nr	't Mannetje et al., 2005
Sprayers (697 men and 2 women registered any time 1973–1984)			
Mortality 1973–2000	0	nr	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Through 1982 (n = 878)	0	nr	Bond et al., 1988
Dow PCP Production Workers (1937–1989 in Midland, Michigan) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–1989 (n = 770)	0	nr	Ramlow et al., 1996

TABLE 23 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Herbicide sprayers routinely exposed to herbicides for 6 months or more (1950–1982)	1	**Phenoxy herbicides** nr	Green, 1991
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	13	0.7 (nr)	
Employee	5	1.1 (nr)	
Women			
Self-employed	1	1.3 (nr)	
Employee	1	1.4 (nr)	
Family worker	15	1.7 ($p < 0.05$)	
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 weeks), not IARC		**Phenoxy herbicides**	
Incidence (thyroid, other endocrine)			Asp et al., 1994
No latency	2	1.9 (0.3–7.0)	
10-year latency	2	2.4 (0.3–8.6)	
15-year latency	2	3.4 (0.4–12.2)	
Mortality (thyroid)			
No latency	1	3.8 (0.1–21.3)	
10-year latency	1	4.7 (0.1–26.4)	
15-year latency	1	6.5 (0.2–36.2)	
ICELANDIC men (1,860), women (859) exposed to agricultural pesticides, primarily 2,4-D (other endocrine organs, ICD-9 194)—incidence	2	**2,4-D** 1.3 (0.1–4.7)	Zhong and Rafnsson, 1996
SWEDEN			
Swedish pesticide applicators—incidence	6	1.1 (0.4–2.4)	Wiklund et al., 1989a
Incident NHL cases 1961–1973 with agriculture as economic activity in 1960 census		99% CI	Wiklund, 1983
Thyroid	126	0.9 (0.7–1.1)	
Other endocrine gland	117	0.7 (0.5–0.9)	
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	39	1.3 (1.0–1.8)	
Nonwhites (n = 11,446)	1	0.6 (0.0–3.0)	
Women			
Whites (n = 2,400)	1	0.8 (0.0–4.4)	
Nonwhites (n = 2,066)	1	1.1 (0.0–6.4)	

continued

TABLE 23 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	39	1.0 (0.7–1.3)	
Commercial applicators	5	1.4 (0.5–3.3)	
Spous	49	0.9 (0.7–1.2)	
Enrollment through 2002 (thyroid, other endocrine)			Alavanja et al., 2005
Private applicators	29	1.3 (0.8–1.8)	
Spouses of private applicators (> 99% women)	24	0.9 (0.5–1.4)	
Commercial applicators	3	1.6 (0.3–5.0)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	8	1.5 (0.7–3.0)	
Spouses (n = 676)	1	nr	
Enrollment through 2000, vs state rates (thyroid)			Blair et al., 2005a
Private applicators (men and women)	3	1.8 (0.4–5.3)	
Spouses of private applicators (> 99% women)	0	0.0 (0.0–2.2)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Incidence			
20-year followup to 1996—men and women			
Zone A	1	2.6 (0.4–18.9)	Pesatori et al., 2009
Zone B	4	1.6 (0.6–4.4)	
Zone R	19	1.2 (0.7–1.9)	
Seveso population (1976–1996); incidence cases identified by hospital discharge records			
Zone A (prolactinoma)	1	6.2 (0.9–45.5)	Pesatori et al., 2008
Zone B (nonfunctioning pituitary tumors)	2	1.9 (0.5–7.7)	
Zone R (2 nonfunctioning pituitary adenomas and 3 prolactinomas)	5	0.7 (0.3–1.8)	
Mortality			
15-year followup to 1991—men			Bertazzi et al., 1997, 1998
Zone B	1	4.9 (0.6–39.0)	
Zone R	0	nr	
15-year followup to 1991—women			Bertazzi et al., 1997, 1998
Zone B	1	3.2 (0.4–24.5)	
Zone R	2	0.8 (0.2–3.6)	

TABLE 23 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
CASE-CONTROL STUDIES			
International Case-Control Studies			
Sweden—male, female thyroid cancers from Swedish Cancer Registry, 1980–1989		**Phenoxy herbicides, chlorophenols**	Hallquist et al., 1993
Phenoxy herbicide exposure	3	0.5 (0.0–2.0)	
Chlorophenols	4	2.8 (0.5–18.0)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; n, number; NHL, non-Hodgkin lymphoma; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

TABLE 24 Selected Epidemiologic Studies—Hodgkin Lymphoma (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Incidence			
Through 1999—white subjects vs national rates			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	10	0.9 (0.4–1.5)	
With tours between 1966–1970	7	0.7 (0.3–1.4)	
SEA comparison veterans (n = 1,776)	9	0.6 (0.3–1.0)	
With tours between 1966–1970	4	0.3 (0.1–0.8)	
Attended 1987 exam—Rand Hand personnel (n = 995) vs SEA veterans (n = 1,299)	0	nr	Wolfe et al., 1990
Mortality			
Through 1987—Ranch Hand personnel (n = 1,261) vs SEA veterans (n = 19,102)	0	nr	Michalek et al., 1990
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Mortality			
1965–2000	2	0.9 (nr)	Boehmer et al., 2004
Post-service–1983	0	nr	Boyle et al., 1987
US CDC Selected Cancers Study—case-control study of incidence (Dec 1, 1984–Nov 30, 1989) among US males born 1929–1953 (CDC, 1990a)		**All COIs**	CDC, 1990a
Vietnam veterans	28	1.2 (0.7–2.4)	
Army	12	1.0 (0.5–2.0)	
Marine Corps	4	1.7 (0.5–5.9)	
Air Force	5	1.7 (0.6–4.9)	
Navy	7	1.1 (0.4–2.6)	
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1988			Watanabe and Kang, 1996
Army, deployed (n = 27,596) vs nondeployed (n = 31,757)	125	1.0 (nr)	
Marine Corps, deployed (n = 6,237) vs nondeployed (n = 5,040)	25	1.9 (1.2–2.7)	
1965–1984			Watanabe et al., 1991
Army, deployed (n = 24,145) vs nondeployed (n = 27,917)			
vs Army non-Vietnam veterans	116	1.0 (nr)	
vs all non-Vietnam veterans	116	1.1 (nr)	
Marine Corps, deployed (n = 5,501) vs nondeployed (n = 4,505)			
vs Marine non-Vietnam veterans	25	1.9 (nr)	
vs all non-Vietnam veterans	25	1.0 (nr)	

TABLE 24 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
1965–1982			Breslin et al., 1988
Army, deployed (n = 19,708) vs nondeployed (n = 22,904)	92	1.2 (0.7–1.9)	
Marine Corps, deployed (n = 4,527) vs nondeployed (n = 3,781)	22	1.3 (0.7–2.6)	
US VA Cohort of Female Vietnam Veterans		**All COIs**	
Mortality			
Through 2004 (lymphopoietic cancers)[c]	18	0.7 (0.4–1.3)	Cypel and Kang, 2008
Vietnam-veteran nurses	14	0.7 (0.3–1.3)	
State Studies of US Vietnam Veterans			
Michigan Vietnam-era veterans, PM study of deaths (1974–1989)—deployed vs nondeployed	20	1.1 (0.7–1.8)	Vistainer et al., 1995
New York—deployed vs nondeployed (lymphoma, HD)		99% CI	Lawrence et al., 1985
	10	1.0 (0.4–2.2)	
West Virginia—deployed vs nondeployed	5	8.3 (2.7–19.5)	Holmes et al., 1986
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans	4	nr	Anderson et al., 1986a,b
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	51	2.1 (1.5–2.6)	ADVA, 2005b
Navy	7	1.3 (0.5–2.6)	
Army	40	2.3 (1.6–3.0)	
Air Force	4	2.1 (0.6–5.3)	
Mortality			
All branches, return–2001	13	0.9 (0.5–1.5)	ADVA, 2005a
Navy	2	0.6 (0.1–2.1)	
Army	11	1.1 (0.5–1.9)	
Air Force	0	0.0 (0.0–2.9)	
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Incidence			
1982–2000	12	0.9 (0.4–2.0)	ADVA, 2005c
Mortality			
1982–2000	12	0.9 (0.4–2.0)	ADVA, 2005c
1966–2001	4	1.7 (0.3–11.8)	ADVA, 2005c
1983–1985	0	nr	Fett et al., 1987b
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008)	3	2.1 (0.4–6.1)	
Mortality (1988–2008)	1	2.3 (0.0–12.8)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores)		**All COIs**	
		HRs	
Incidence (1992–2003)—Hodgkin lymphoma (C81) categorized high (n = 7) vs low (n = 6)		1.3 (0.4–3.9)	Yi and Ohrr, 2014

continued

TABLE 24 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	10	1.0 (0.5–1.8)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	8	1.3 (0.6–2.5)	
7,553 not exposed to highly chlorinated PCDDs	1	0.3 (0.0–1.5)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	2	0.4 (0.1–1.4)	Saracci et al., 1991
Mortality, incidence of women in production (n = 699) and spraying (n = 2) compared to national death rates and cancer incidence rates	1	**TCDD** nr	Kogevinas et al., 1993
Mortality—IARC cohort (16,863 men and 1,527 women) 10–19 years since first exposure	3	0.6 (0.1–1.7)	Kogevinas et al., 1992
British MCPA Plant—All manual employees employed January 1947–December 1975 (n = 1,146), ever potentially exposed to phenoxy herbicides (n = 1,544), potentially exposed to phenoxy herbicides ≥ 1 year (n = 848) (not included in IARC cohort)		**MCPA**	
Mortality through 2012, all workers			Coggon et al., 2015
Hodgkin's disease (ICD-10 C81)	3	0.53 (0.11–1.55)	
Mortality through 2012, workers ever exposed to phenoxy herbicides			
Hodgkin's disease (ICD-10 C81)	3	0.72 (0.15–2.11)	
Mortality through 2012, workers ever exposed to phenoxy herbicides ≥ 1 year			
Hodgkin's disease (ICD-10 C81)	3	1.71 (0.35–4.99)	
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–1991	1	3.2 (0.1–17.6)	Hooiveld et al., 1998
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 month in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992	0	nr	Becher et al., 1996
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 month in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4-DP; 2,4,5-T; MCPA; MCPP**	
Mortality 1965–1989	0	nr	Becher et al., 1996
German Production Workers at BASF Ludwigshafen Plant (680 men working >1 month in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4-DP; 2,4,5-T; MCPA; MCPP**	
Mortality 1956–1989	0	nr	Becher et al., 1996
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Mortality			
Through 1987 [Table 2]	0	nr	Zober et al., 1990

TABLE 24 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 month in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–1989	0	nr	Becher et al., 1996
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; 2,4,5-TCP; MCPA; MCPB; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	1	4.2 (0.1–23.3)	
Never-exposed workers	0	0.0 (0.0–47.1)	
Production Workers (713 men and 100 women worked > 1 month in 1969–1984)			
Mortality 1969–2000	1	5.6 (0.1–31.0)	't Mannetje et al., 2005
Sprayers (697 men and 2 women on register of New Zealand applicators, 1973–1984)			
Mortality 1973–2000	0	0.0 (0.0–16.1)	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993	3	1.1 (0.2–3.2)	Steenland et al., 1999
Chloracne subcohort (n = 608) (lymphatic, hematopoietic; ICD-9 200–208)	6	1.1 (0.4–2.5)	
Through 1987	3	1.2 (0.3–3.5)	Fingerhut et al., 1991
≥ 1-year exposure, ≥ 20-year latency	1	2.8 (0.1–15.3)	
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, Michigan) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1937–2011 Potential dioxin exposure (n = 2,192), TCP production (n = 1,419), PCP production (n = 577), Both TCP and PCP (n = 196)			Collins et al., 2016
TCP or PCP, Hodgkin's disease	2	1.17 (0.14–4.22)	
TCP, Hodgkin's disease	2	1.61 (0.20–5.85)	
PCP, Hodgkin's disease	0	0.00 (0.0–5.87)	
1942–2003 (n = 1,615)	0	0.0 (0.0–6.4)	Collins et al., 2009b
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, Washington and Wichita, Kansas) and workers who made PCP and TCP at two additional plants (in Midland, Michigan, and Sauget, Illinois)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122)	1	0.6 (0.0–3.6)	
PCP and TCP (n = 720)	0	nr (0.0–6.9)	
PCP (no TCP) (n = 1,402)	1	1.0 (0.0–5.4)	

continued

TABLE 24 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)	1	1.3 (0.0–7.2)	Burns CJ et al., 2011
Through 1994 (n = 1,517)	1	1.5 (0.0–8.6)	Burns et al., 2001
Through 1982 (n = 878)	1	2.7 (0.0–14.7)	Bond et al., 1988
Dow PCP Production Workers (1937–1989 in Midland, Michigan) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	2	1.8 (0.2–6.4)	Collins et al., 2009c
Mortality 1940–1989 (n = 770)			Ramlow et al., 1996
0-year latency	0	nr	
15-year latency	0	nr	
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	7	0.6 (0.2–1.2)	
Ever	17	1.8 (1.0–2.8)	
Danish paper workers			Rix et al., 1998
Men	18	2.0 (1.2–3.2)	
Women	2	1.1 (0.1–3.8)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Ontario Forestry Workers—1,222 men working ≥ 6 months 1950–1982			
80 deaths through 1982; 18 cancers (lung greatest with 5)	0	nr	Green, 1991
DENMARK			
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	27	0.6 ($p < 0.05$)	
Employee	13	1.0 (nr)	
Women			
Self-employed	1	1.1 (nr)	
Employee	1	1.2 (nr)	
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	0	nr	Swaen et al., 2004
Through 1987	1	3.3 (0.0–18.6)	Swaen et al., 1992
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 weeks) not IARC		**Phenoxy herbicides**	
Incidence	2	1.7 (0.2–6.0)	Asp et al., 1994
Mortality 1972–1989	0	0.0 (0.0–5.0)	
Except for lung cancer, numbers too small for reporting mortality 1972–1980	0	nr	Riihimaki et al., 1982

TABLE 24 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	11	1.0 (0.5–1.7)	Torchio et al., 1994
Italian rice growers with documented phenoxy use		**Phenoxy herbicides**	Gambini et al., 1997
(n = 1,487)	1	0.7 (0.0–3.6)	
SWEDEN			
Swedish Cancer-Environment Registry—National Cancer Registry linked to census		**Herbicides**	
Incidence data from Swedish Cancer Environment Register (1971–1984) linked to 1970 census			Eriksson et al., 1992a
Male sawmill workers	10	2.1 (1.0–4.0)	
Male farmers	97	1.2 (nr)	
Male forestry workers	35	1.2 (nr)	
Male horticulture workers	11	1.2 (nr)	
20,245 Swedish pesticide applicators with license issued between 1965 and 1976	15	1.5 (0.8–2.4)	Wiklund et al., 1989a
354,620 Swedish agriculture, forestry workers			Wiklund et al., 1988a
Workers in land or in animal husbandry	242	1.0 (0.9–1.2)	
Workers in silviculture	15	2.3 (1.3–3.7)	
Incident HD cases 1961–1973 with agriculture as economic		99% CI	Wiklund, 1983
activity in 1960 census	226	1.0 (0.9–1.2)	
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	56	1.0 (0.8–1.3)	
Nonwhites (n = 11,446)	2	0.7 (0.1–2.6)	
Women			
Whites (n = 2,400)	0	0.0 (0.0–3.4)	
Nonwhites (n = 2,066)	0	0.0 (0.0–7.2)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	18	1.0 (0.6–1.5)	
Commercial applicators	1	nr	
Spouses	7	0.9 (0.3–1.7)	
Enrollment through 2002			Alavanja et al., 2005
Private applicators	11	0.9 (0.4–1.6)	
Spouses of private applicators (> 99% women)	4	0.7 (0.2–1.9)	
Commercial applicators	1	0.8 (0.1–4.2)	

continued

TABLE 24 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	5	1.0 (0.3–2.4)	
Spouses (n = 676)			
Enrollment through 2000, vs state rates	3	1.1 (0.2–3.3)	Blair et al., 2005a
Private applicators (men and women)	3	1.7 (0.3–4.8)	
Spouses of private applicators (> 99% women)	0	0.0 (0.0–2.5)	
US Department of Agriculture Workers—nested case-control study of white men dying 1970–1979 of HD		**Herbicides**	
Agricultural extension agents			Alavanja et al., 1988
PM analysis	6	2.7 (1.2–6.3)	
Case-control analysis	6	1.1 (0.3–3.5)	
USDA forest, soil conservationists	4	2.2 (0.6–5.6)	Alavanja et al., 1989
White Male Residents of Iowa—HD on death certificate, usual occupation: farmers vs not		**Herbicides** PMR	
> 20 years old when died 1971–1978	47	1.2 (ns)	Burmeister, 1981
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Incidence			
20-year followup to 1996—men and women			
Zone A	0	nr	Pesatori et al., 2009
Zone B	3	1.2 (0.4–3.8)	
Zone R	23	1.5 (0.9–2.3)	
10-year followup to 1991—men			Bertazzi et al., 1993
Zone B	1	1.7 (0.2–12.8)	
Zone R	4	1.1 (0.4–3.1)	
10-year followup to 1991—women			Bertazzi et al., 1993
Zone B	1	2.1 (0.3–15.7)	
Zone R	3	1.0 (0.3–3.2)	
Mortality			
25-year followup to 2001—men and women			Consonni et al., 2008
Zone A	0	nr	
Zone B	3	2.2 (0.7–6.9)	
Zone R	9	0.9 (0.5–1.9)	
20-year followup to 1996			Bertazzi et al., 2001
Zones A, B—men	2	2.6 (0.6–10.9)	
Zones A, B—women	2	3.7 (0.9–16.0)	
15-year followup to 1991—men			Bertazzi et al., 1997
Zone B	2	3.3 (0.4–11.9)	
15-year followup to 1991—women			Bertazzi et al., 1997
Zone B	2	6.5 (0.7–23.5)	
Zone R	4	1.9 (0.5–4.9)	
Other International Environmental Studies			
FRANCE			
Residents near French solid-waste incinerator—incidence		**Dioxin**	Viel et al., 2000
1980–1995	9	1.5 (nr) (p = 0.89)	

TABLE 24 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
NEW ZEALAND			
Residents of New Plymouth Territorial Authority, New Zealand near plant manufacturing 2,4,5-T in 1962–1987		2,4,5-T	Read et al., 2007
Incidence	49	1.1 (0.8–1.5)[d]	
1970–1974	9	1.2 (0.6–2.3)	
1975–1979	9	1.1 (0.5–2.2)	
1980–1984	8	1.1 (0.5–2.1)	
1985–1989	9	1.3 (0.6–2.5)	
1990–1994	7	1.3 (0.5–2.7)	
1995–1999	4	0.7 (0.2–1.7)	
2000–2001	3	1.0 (0.2–3.1)	
Mortality	22	1.3 (0.8–2.0)[d]	
1970–1974	7	1.6 (0.7–3.3)	
1975–1979	4	1.2 (0.3–3.0)	
1980–1984	6	2.1 (0.8–4.5)	
1985–1989	3	1.2 (0.2–3.5)	
1990–1994	1	0.6 (0.0–3.5)	
1995–1999	1	0.6 (0.0–3.6)	
2000–2001	0	nr	
CASE-CONTROL STUDIES			
US Case-Control Studies			
Kansas residents–duration and frequency of herbicide use—incidence		**Phenoxy herbicides, 2,4-D**	Hoar et al., 1986
All farmers	71	0.8 (0.5–1.2)	
Farm-use of herbicides (phenoxy acids, others)	28	0.9 (0.5–1.5)	
Farmers using herbicides > 20 days/year	3	1.0 (0.2–4.1)	
Farmers using herbicides > 15 days/year	10	1.2 (0.5–2.6)	
Tecumseh, Michigan residents participating in longitudinal study (1959–1987)	13	**Herbicides** 2.0 (1.1–3.4)	Waterhouse et al., 1996
Hancock County, **Ohio**, residents—farmers	3	2.7 (nr)	Dubrow et al., 1988
International Case-Control Studies			
Cross-Canada Study of Pesticides and Health—men in one of 6 Canadian provinces (≥ 19 years of age) diagnosed September 1991–December 1994 (n = 316) vs matched population-based controls (n = 1,506)		**Phenoxy herbicides**	
Effect of multiple pesticide exposure on HL risk		**Phenoxy herbicides**	Navaranjan et al., 2013
Any 1 phenoxy herbicide	36	0.9 (0.6–1.4)	
Any 2 phenoxy herbicides	18	1.0 (0.6–1.8)	
3 or more phenoxy herbicides	10	1.0 (0.5–2.1)	
Association with specific herbicides and HL			Karunanayake et al., 2012; Pahwa et al., 2006
Any phenoxy herbicides	65	0.9 (0.7–1.3)	
2,4-D	57	0.9 (0.6–1.3)	
Mecoprop	20	1.4 (0.8–2.4)	
MCPA	11	1.0 (0.4–2.2)	
Diclofopmethyl	10	1.8 (0.7–4.5)	

continued

TABLE 24 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
France hospital-based case-control study		**Herbicides**	Orsi et al., 2009
Occupational use of herbicides	7	1.5 (0.6–4.1)	
Phenoxy herbicides	6	2.5 (0.8–7.7)	
Domestic use of herbicides	19	0.8 (0.4–1.6)	
Italian incident cases of malignancies of hematolymphopoietic system (HD = 258) in men and women (20–74 years of age) from agricultural and mixed use areas		**Herbicides**	Miligi et al., 2006
Men	5	0.4 (0.1–1.3)	
Women	1	0.5 (0.1–4.0)	
Italy—Residents of Milan area (men and women)—incidence		**Herbicides**	LaVecchia et al., 1989
Agricultural occupations	nr	2.1 (1.0–3.8)	
Chemical-industry occupations	nr	4.3 (1.4–10.2)	
New Zealand National Cancer Registry (1977–1981) (≥ 20 years of age) with agricultural occupations—incidence (ICD-9 200, 202)	107	**Herbicides** 1.1 (0.6–2.0)	Pearce et al., 1985
Swedish Regional Cancer Registry—HD patients		**Phenoxy herbicides**	Persson et al., 1993
Exposed to phenoxy herbicides	5	90% CI 7.4 (1.4–40.0)	
Örebro (**Sweden**) Hospital (men and women)—incidence		**Phenoxy herbicides, chlorophenols** 90% CI	Persson et al., 1989
Farming	6	1.2 (0.4–3.5)	
Exposed to phenoxy acids	4	3.8 (0.7–21.0)	
Sweden—Umea Hospital patients (men and women, 25–85 years of age) (1974–1978)		**Phenoxys, chlorophenols**	Hardell and Bengtsson, 1983
Exposed to phenoxy acids	14	5.0 (2.4–10.2)	
Exposed to high-grade chlorophenols	6	6.5 (2.2–19.0)	
Exposed to low-grade chlorophenols	5	2.4 (0.9–6.5)	
Swedish patients (1970–1977)		**Phenoxy acids, chlorophenols**	Hardell, 1981
Exposed to phenoxy herbicides	41	4.8 (2.9–8.1)	
Exposed to chlorophenols	50	4.3 (2.7–6.9)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HD, Hodgkin disease; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job-exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; n, number; NHL, non-Hodgkin lymphoma; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; PM, proportionate mortality; PMR, proportional mortality ratio; SEA, Southeast Asia; SIR, standardized incidence ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; USDA, US Department of Agriculture; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

[c]Lymphopoietic cancers comprise all of forms of lymphoma (including Hodgkin disease and non-Hodgkin lymphoma) and leukemia (ALL, AML, CLL, CML).

[d]Committee computed total SMR and SIR by dividing sum of observed values by sum of expected values over all years, 95% CIs on these total ratios were computed with exact methods.

TABLE 25 Selected Epidemiologic Studies—Non-Hodgkin's Lymphoma (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Incidence			
Through 1999—White subjects vs national rates (lymphopoietic cancer)[c]			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	10	0.9 (0.4–1.5)	
With tours between 1966–1970	7	0.7 (0.3–1.4)	
SEA comparison veterans (n = 1,776)	9	0.6 (0.3–1.0)	
With tours between 1966–1970	4	0.3 (0.1–0.8)	
Attended 1987 exam—Rand Hand personnel (n = 995) vs SEA veterans (n = 1,299)	1	nr	Wolfe et al., 1990
Mortality			
Through 1987—Ranch Hand personnel (n = 1,261) vs SEA veterans (n = 19,102)	0	nr	Michalek et al., 1990
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Army enlisted Vietnam veterans (all lymphomas) (1965–1983)	7	1.8 (nr)	O'Brien et al., 1991
Mortality			
1965–2000	6	0.9 (0.3–2.9)	Boehmer et al., 2004
US CDC Selected Cancers Study—case-control study of incidence (Dec 1, 1984–Nov 30, 1989) among US males born 1929–1953 (CDC, 1990a)	99	**All COIs** 1.5 (1.1–2.0)	CDC, 1990b
Army Vietnam veterans	45	1.2 (0.8–1.8)	
Marine Vietnam veterans	10	1.8 (0.8–4.3)	
Air Force Vietnam veterans	12	1.0 (0.5–2.2)	
Navy Vietnam veterans	32	1.9 (1.1–3.2)	
Blue Water Navy Vietnam veterans	28	2.2 (1.2–3.9)	
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1988			Watanabe and Kang, 1996
Army, deployed (n = 27,596) vs nondeployed (n = 31,757)	171	—	
Marine Corps, deployed (n = 6,237) vs nondeployed (n = 5,040)	46	1.7 (1.2–2.2)	
1965–1984—Army, deployed (n = 24,145) vs nondeployed (n = 27,917) (ICD-8 200, 202)	140	1.7 (1.2–2.2)	Watanabe et al., 1991
Army Vietnam veterans vs combined Army and Marine Vietnam-era veterans	140	0.9 (nr)	
Marine Vietnam veterans vs non-Vietnam veterans	42	1.8 (1.3–2.4)	
Marine Vietnam veterans vs combined Army and Marine Vietnam-era veterans	42	1.2 (nr)	

continued

TABLE 25 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
1965–1982 (ICDA-8 200, 202)			Breslin et al., 1986, 1988
Army, deployed (n = 19,708) vs nondeployed (n = 22,904)	108	0.8 (0.6–1.0)	
Marine Corps, deployed (n = 4,527) vs nondeployed (n = 3,781)	35	2.1 (1.2–3.8)	
Nested case-control study of NHL	39	1.1 (0.7–1.5)	Burt et al., 1987
Army combat Vietnam veterans	17	3.2 (1.4–7.4)	
Marine combat Vietnam veterans	64	0.9 (0.7–1.3)	
Army Vietnam veterans (service 1967–1969)	17	2.5 (1.1–5.8)	
Marine Vietnam veterans (service 1967–1969)	4	1.8 (0.4–8.0)	
US VA Cohort of Female Vietnam Veterans		**All COIs**	
Mortality			
Through 2004 (lymphopoietic cancers)[c]	18	0.7 (0.4–1.3)	Cypel and Kang, 2008
Vietnam–veteran nurses	14	0.7 (0.3–1.3)	
Through 1987 (ICD-8 200–203, 208)	3	1.3 (0.3–1.8)	Thomas et al., 1991
US Navy Enlisted Personnel (1974–1983)			
Active duty	68	0.7 (0.5–0.9)	Garland et al., 1988
VA Case-Control Studies			
US Vietnam veterans—incidence	100	1.0 (0.7–1.5)	Dalager et al., 1991b
State Studies of US Vietnam Veterans			
Massachusetts Vietnam-era veterans who served 1958–1973, cases diagnosed 1982–1988 (served in Vietnam)		1.2 (0.6–2.4)	Clapp et al., 1991
Michigan Vietnam-era veterans, PM study of deaths (1974–1989)—deployed vs nondeployed	32	1.5 (1.0–2.1)	Vistainer et al., 1995
New York—deployed vs nondeployed	10	1.0 (0.4–2.2)	Lawrence et al., 1985
West Virginia—deployed vs nondeployed	2	1.1 (nr)	Holmes et al., 1986
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans (includes lymphosarcoma, reticulosarcoma)	4	nr	Anderson et al., 1986a,b
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	126	0.7 (0.6–0.8)	ADVA, 2005b
Navy	31	0.8 (0.5–1.0)	
Army	86	0.7 (0.5–0.8)	
Air Force	9	0.5 (0.2–0.9)	
		Expected number of exposed cases	AIHW, 1999
Validation Study	62	48 (34–62)	
Men	137	48 (34–62)	CDVA, 1998a
Women	2	0 (0–4)	CDVA, 1998b
Mortality			
All branches, return–2001	70	0.8 (0.6–1.0)	ADVA, 2005a
Navy	10	0.5 (0.3–0.9)	
Army	52	0.9 (0.6–1.1)	
Air Force	8	0.9 (0.4–1.6)	
1980–1994	33	0.9 (0.6–1.2)	CDVA, 1997a

TABLE 25 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Incidence			
1982–2000	35	1.1 (0.7–1.9)	ADVA, 2005c
Mortality			
1966–2001	21	1.4 (0.7–2.8)	ADVA, 2005c
1983–1985 (ICD-8 200, 202)	4	1.8 (0.4–8.0)	Fett et al., 1987b
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008)	14	0.9 (0.5–1.4)	
Mortality (1988–2008)	3	0.4 (0.1–1.3)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores)		**All COIs**	
		HRs	
Incidence (1992–2003)—NHL (C82–C85) categorized high (n = 96) vs low (n = 89)		1.1 (0.8–1.5)	Yi and Ohrr, 2014
Mortality (1992–2005)—categorized high (n = 56) vs low (n = 47)		1.2 (0.8–1.8)	Yi et al., 2014b
HR per unit of log EOI scores (n = 180,639)	103	1.0 (1.0–1.2)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	34	1.3 (0.9–1.8)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	24	1.4 (0.9–2.1)	
7,553 not exposed to highly chlorinated PCDDs	9	1.0 (0.5–1.9)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort			Saracci et al., 1991
Nested case-control study			
IARC cohort (men and women)—incidence			Kogevinas et al., 1995
Exposed to 2,4,5-T	10	1.9 (0.7–4.8)	
Exposed to TCDD	11	1.9 (0.7–5.1)	
Mortality—IARC cohort (16,863 men and 1,527 women) 10–19 years since first exposure	11	1.0 (0.5–1.7)	Kogevinas et al., 1992
British MCPA Plant—All manual employees employed January 1947–December 1975 (n = 1,146), ever potentially exposed to phenoxy herbicides (n = 1,544), potentially exposed to phenoxy herbicides ≥ 1 year (n = 848) (not included in IARC cohort)		**MCPA**	
Mortality through 2012, all workers			Coggon et al., 2015
Non-Hodgkin's lymphoma (ICD-10 C82–C85)	29	0.96 (0.64–1.38)	
Mortality through 2012, workers ever exposed to phenoxy herbicides			
Non-Hodgkin's lymphoma (ICD-10 C82–C85)	26	1.15 (0.75–1.68)	
Mortality through 2012, workers ever exposed to phenoxy herbicides ≥ 1 year			
Non-Hodgkin's lymphoma (ICD-10 C82–C85)	19	1.85 (1.12–2.89)	

continued

TABLE 25 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Nested case control study by exposure level			
None	10	Referent	
< 1 year	16	0.65 (0.27–1.57)	
≥ 1 year	22	1.19 (0.51–2.77)	
None	8	Referent	
Low	13	1.47 (0.58–3.74)	
High	18	0.87 (0.33–2.26)	
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Mortality 1955–2006	7	1.4 (1.1–1.7)	Boers et al., 2012
TCDD plasma level (HRs, by tertile)			
Background (≤ 0.4)	1	nr	
Low (0.4–4.1)	3	3.8 (0.4–34.3)	
Medium (4.1–20.1)	2	7.8 (0.7–89.3)	
High (≥ 20.1)	1	8.1 (0.4–149.1)	
Incidence 1943–1987 (men only)	10	1.7 (0.5–4.5)	Lynge, 1993
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–2006 (HRs for lagged TCDD plasma levels)	6	1.3 (1.0–1.7)	Boers et al., 2012
Mortality 1955–2006	4 vs 3	0.9 (0.2–4.5)	Boers et al., 2010
Mortality 1955–1991	3	3.8 (0.8–11.0)	Hooiveld et al., 1998
Mortality 1955–1985	1	2.0 (0.1–11.4)	Bueno de Mesquita et al., 1993
Dutch production workers in Plant B (414 men exposed during production 1965–1986; 723 unexposed) (in IARC cohort)		**2,4-D; MCPA; MCPP; highly chlorinated dioxins unlikely**	
Mortality 1965–2006	1 vs 0	nr	Boers et al., 2010
Mortality 1965–1986	1	5.6 (0.1–31.0)	Bueno de Mesquita et al., 1993
German Production Workers—2,479 workers at 4 plants (in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
All for plants	6	3.3 (1.2–7.1)	Becher et al., 1996
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 month in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992	2	12.0 (1.5–43.5)	Becher et al., 1996
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 month in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4-DP; 2,4,5-T; MCPA; MCPP**	
Mortality 1965–1989	0	—	Becher et al., 1996
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 month in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4-DP; 2,4,5-T; MCPA; MCPP**	
Mortality 1956–1989	0	—	Becher et al., 1996

TABLE 25 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 month in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,5-DCP; 2,4,5-T; 2,4,5-TCP**	
Mortality 1952–2007	7	1.6 (0.6–3.3)	Manuwald et al., 2012
Men	5	1.6 (0.5–3.7)	
Women	2	1.7 (0.2–6.0)	
Mortalilty 1952–1989	4	3.8 (1.0–9.6)	Becher et al., 1996
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	3	1.6 (0.3–4.7)	
Never-exposed workers	1	1.6 (0.0–8.7)	
Production Workers (713 men and 100 women worked > 1 month in 1969–1984)			
Mortality 1969–2000	1	0.9 (0.0–4.9)	't Mannetje et al., 2005
Sprayers (697 men and 2 women registered any time 1973–1984)			
Mortality 1973–2000	1	0.7 (0.0–3.8)	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993	12	1.1 (0.6–1.9)	Steenland et al., 1999
Chloracne subcohort (n = 608) (Lymphatic and hematopoietic, ICD-9 200–208)	6	1.1 (0.4–2.5)	
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, Michigan) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1937–2011 Potential dioxin exposure (n = 2,192), TCP production (n = 1,419), PCP production (n = 577), Both TCP and PCP (n = 196)			Collins et al., 2016
TCP or PCP, Non-Hodgkin's lymphoma (ICD-10 = C82, C83.0–C83.8, C84, C85.1–C85.9)	17	1.38 (0.80–2.20)	
TCP, Non-Hodgkin's lymphoma (ICD-10 = C82, C83.0–C83.8, C84, C85.1–C85.9)	10	1.08 (0.52–1.99)	
PCP, Non-Hodgkin's lymphoma (ICD-10 = C82, C83.0–C83.8, C84, C85.1–C85.9)	8	1.92 (0.83–3.79)	
1942–2003 (n = 1,615)	9	1.3 (0.6–2.5)	Collins et al., 2009b
1940–1994 (n = 2,187 men)	nr	1.4 (0.6–2.7)	Bodner et al., 2003
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, Washington, and Wichita, Kansas) and workers who made PCP and TCP at two additional plants (in Midland, Michigan, and Sauget, Illinois)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122) (ICD-9 200, 202, 273.3)	17	1.8 (1.0–2.8)	
PCP and TCP (n = 720)	8	2.5 (1.1–4.9)	
PCP (no TCP) (n = 1,402)	9	1.4 (0.6–2.7)	

continued

TABLE 25 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)	14	1.7 (0.9–2.9)	Burns CJ et al., 2011
Through 1994 (n = 1,517)	3	1.0 (0.2–2.9)	Burns et al., 2001
Through 1986 (n = 878) vs national vs 36,804 "unexposed" workers at same location	2	2.0 (0.2–7.1)	Bloemen et al., 1993
Dow PCP Production Workers (1937–1989 in Midland, Michigan) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	8	2.4 (1.0–4.7)	Collins et al., 2009c
Mortality 1940–1989 (n = 770)			Ramlow et al., 1996
All lymphopoietic cancer (ICDA-8 200–209)			
0-year latency	7	1.4 (0.6–2.9)	
15-year latency	5	1.3 (0.4–3.1)	
Other, unspecified lymphopoietic cancer (ICDA-8 200, 202–203, 209)			
0-year latency	5	2.0 (0.7–4.7)	
15-year latency	4	2.0 (0.5–5.1)	
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	35	0.9 (0.7–1.3)	
Ever	25	0.9 (0.6–1.3)	
Exposure to chlorophenols	50	4.3 (2.7–6.9)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Canadian Farm Operator Study—156,242 men farming in Manitoba, Saskatchewan, and Alberta in 1971; mortality from NHL June 1971–December 1987			
Farm operators ≥ 35 years of age (June 1971–December 1987)			Morrison et al., 1994
All farm operators	nr	0.8 (0.7–0.9)	
Highest quartile of herbicides sprayed	19	2.1 (1.1–3.9)	
Highest quartile of herbicide sprayed relative to no spraying	6	3.0 (1.1–8.1)	
Farm operators ≥ 35 years of age during study period (June 1971–December 1985)			Wigle et al., 1990
All farmers	103	0.9 (0.8–1.1)	
Spraying herbicides on 250+ acres	10	2.2 (1.0–4.6)	

TABLE 25 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
DENMARK			
Danish gardeners—incidence from 3,156 male and 859 female gardeners			Hansen et al., 2007
25-year followup (1975–2001)		**Herbicides**	
Born before 1915 (high exposure)	16	1.4 (0.9–2.3)	
Born 1915–1934 (medium exposure)	25	1.2 (0.8–1.8)	
Born after 1934 (low exposure)	1	0.2 (0.0–1.0)	
10-year followup (1975–1984) of male gardeners (lymphohematopoietic, ICD-7 200–2005)	15	1.4 (0.8–2.4)	Hansen et al., 1992
NHL (ICD-7 200, 202, 205)	6	1.7 (0.6–3.8)	
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 1987	0	nr	Swaen et al., 1992
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 week) not IARC		**Phenoxy herbicides**	
Incidence			Asp et al., 1994
No latency	1	0.4 (0.0–2.0)	
10-year latency	1	0.4 (0.0–2.4)	
Except for lung cancer, numbers too small for reporting mortality 1972–1980	0	nr	Riihimaki et al., 1982, 1983
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401) (ICD-8 202.0–202.9)	15	0.9 (0.5–1.5)	Torchio et al., 1994
Incidence 1976–1983 (n = 25,945)			Corrao et al., 1989
Licensed pesticide users and nonusers	45	1.4 (1.0–1.9)	
Farmers in arable land areas	31	1.8 (1.2–2.5)	
Italian rice growers with documented phenoxy use (n = 1,487)	4	**Phenoxy herbicides** 1.3 (0.3–3.3)	Gambini et al., 1997
SWEDEN			
20,245 Swedish pesticide applicators with license issued between 1965 and 1976	27	1.1 (0.7–1.6)	Wiklund et al., 1989b
354,620 Swedish agriculture, forestry workers			Wiklund et al., 1988a
Workers in land, animal husbandry	670	1.0 (0.9–1.1)	
Timber cutters	111	0.9 (0.7–1.1)	
Incident NHL cases 1961–1973 with agriculture as economic activity in 1960 census	476	99% CI 1.1 (0.9–1.2)	Wiklund, 1983
Swedish lumberjacks—Used phenoxys 1954–1967, Incidence 1958–1992			Thörn et al., 2000
Exposed (n = 154)			
Foremen (n = 15)	0	—	
Lumberjacks (n = 139)	1	1.9 (0.0–10.7)	
Unexposed lumberjacks (n = 241)	1	0.8 (0.0–4.5)	
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	843	1.2 (1.1–1.3)	
Nonwhites (n = 11,446)	24	0.7 (0.5–1.1)	

continued

TABLE 25 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Women			
Whites (n = 2,400)	18	1.1 (0.6–1.7)	
Nonwhites (n = 2,066)	6	1.1 (0.4–2.3)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
NHL			
Private applicators	195	1.0 (0.9–1.1)	
Commercial applicators	9	0.8 (0.4–1.6)	
Spouses	86	1.0 (0.8–1.2)	
B-cell			
Private applicators	167	1.0 (0.9–1.2)	
Commercial applicators	8	0.9 (0.4–1.7)	
Spouses	78	1.1 (0.8–1.3)	
Enrollment through 2002			Samanic et al., 2006
Dicamba—lifetime days exposure			
None	39	1.0	
1– < 20	18	1.8 (1.0–3.2)	
20– < 56	14	1.3 (0.7–2.5)	
56– < 116	7	0.9 (0.4–2.2)	
≥ 116	7	1.2 (0.5–2.9)	
		p-trend = 0.92	
Enrollment through 2002			Alavanja et al., 2005
Private applicators	114	1.0 (0.8–1.2)	
Spouses of private applicators (> 99% women)	42	0.9 (0.6–1.2)	
Commercial applicators	6	1.0 (0.4–2.1)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	90	0.8 (0.7–1.0)	
Spouses (n = 676)	42	1.1 (0.8–1.5)	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	33	0.9 (0.6–1.2)	
Spouses of private applicators (> 99% women)	16	1.2 (0.7–2.0)	
California United Farm Workers of America			
Nested case-control analysis of Hispanic workers in cohort of 139,000 California United Farm Workers			Mills et al., 2005
Ever used 2,4-D	nr	3.8 (1.9–7.8)	
US Department of Agriculture Workers—nested case-control study of white men dying 1970–1979 of NHL		**Herbicides**	
Agricultural extension agents (from Table 3)	nr	1.2 (0.7–2.3)	Alavanja et al., 1988

TABLE 25 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
White Male Residents of Iowa—NHL cancer on death certificate, usual occupation: farmers vs not		**Herbicides**	
> 30 years old when died 1964–1978—case-control H_0: only for "modern methods" → born after 1900	1,101	1.3 (nr)	Burmeister et al., 1983
Born before 1880	154	2.9 (nr)	
Born 1980–1900	336	1.6 (nr)	
Born after 1900	611	0.9 (nr)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Incidence			
20-year followup to 1996—men and women			
Zone A	1	0.8 (0.1–5.7)	Pesatori et al., 2009
Zone B	12	1.5 (0.9–2.7)	
Zone R	49	0.9 (0.7–1.2)	
10-year followup to 1991—men			Bertazzi et al., 1993
Zone A	0	nr	
Zone B	3	2.3 (0.7–7.4)	
Zone R	12	1.3 (0.7–2.5)	
10-year followup to 1991—women			Bertazzi et al., 1993
Zone A	0	nr	
Zone B	1	0.9 (0.1–6.4)	
Zone R	10	1.2 (0.6–2.3)	
Mortality			
25-year followup to 2001—men and women			Consonni et al., 2008
Zone A	3	3.4 (1.1–10.5)	
Zone B	7	1.2 (0.6–2.6)	
Zone R	40	1.0 (0.7–1.4)	
20-year followup to 1996			Bertazzi et al., 2001
Zone A—men and women	2	3.3 (0.8–13.1)	
Zone B—men and women	5	1.2 (0.5–3.0)	
Zones A and B—men	3	1.2 (0.4–3.9)	
Zones A and B—women	4	1.8 (0.7–4.9)	
15-year followup to 1991—men			Bertazzi et al., 1997, 1998
Zone A	0	0.0 (0.0–18.1)	
Zone B	2	1.5 (0.2–5.3)	
Zone R	10	1.1 (0.5–2.0)	
15-year followup to 1991—women			Bertazzi et al., 1997, 1998
Zone A	0	0.0 (0.0–19.6)	
Zone B	0	0.0 (0.0–3.0)	
Zone R	8	0.9 (0.4–1.7)	
10-year followup to 1986—men			Bertazzi et al., 1989a,b
Zone B	nr	nr	
Zone R	3	1.0 (0.3–3.4)	

continued

TABLE 25 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
10-year followup to 1986—women			
Zone B	2	1.0 (0.3–4.2)	
Zone R	4	1.6 (0.5–4.7)	
Other International Environmental Studies			
FINLAND			
Finnish community exposed to chlorophenol contamination (men and women)—incidence	16	**Chlorophenol** 2.8 (1.4–5.6)	Lampi et al., 1992
FRANCE			
Residents near French solid-waste incinerator in Besancon. NHL cases diagnosed 2003–2005—incidence		**Dioxin, furans, PCBs**	Viel et al., 2011
pg WHO_{1998} TEQ/g lipid:			
Σ PCDD	13.4	1.1 (1.0–1.3) (p-trend < 0.01)	
Σ PCDF	9.4	1.2 (1.0–1.4) (p-trend = 0.01)	
Σ dioxin-like PCBs	33.1	1.0 (1.0–1.1) (p-trend = 0.01)	
Residents near French solid-waste incinerator—incidence		**Dioxin**	Viel et al., 2008a
Highly exposed census group vs slightly exposed	nr	1.1 (1.0–1.3)	
Residents near municipal solid-waste incinerator—incidence		**Dioxin**	Floret et al., 2003
High exposure category	31	2.3 (1.4–3.8)	
Residents near municipal solid-waste incinerator—incidence		**Dioxin**	Viel et al., 2000
Spatial cluster	286	1.3 (p = 0.00003)	
1994–1995	109	1.8 (p = 0.00003)	
NEW ZEALAND			
Residents of New Plymouth Territorial Authority, New Zealand near plant manufacturing 2,4,5-T in 1962–1987		2,4,5-T	Read et al., 2007
Incidence	223	1.0 (0.9–1.1)[d]	
1970–1974	33	1.8 (1.2–2.5)	
1975–1979	29	1.3 (0.9–1.9)	
1980–1984	22	0.8 (0.5–1.3)	
1985–1989	24	0.7 (0.5–1.1)	
1990–1994	35	0.8 (0.6–1.1)	
1995–1999	61	1.1 (0.8–1.4)	
2000–2001	19	0.8 (0.5–1.3)	
Mortality	138	1.1 (0.9–1.3)[d]	
1970–1974	19	1.6 (0.9–2.4)	
1975–1979	24	1.6 (1.0–2.4)	
1980–1984	14	1.0 (0.5–1.6)	
1985–1989	25	1.3 (0.9–2.0)	
1990–1994	23	0.9 (0.6–1.4)	
1995–1999	21	0.7 (0.4–1.1)	
2000–2001	12	1.0 (0.5–1.8)	

TABLE 25 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
CASE-CONTROL STUDIES			
US Case-Control Studies			
Central US—meta-analysis of NHL and farmers	nr	**Pesticides** 1.3 (1.2–1.6)	Keller-Byrne et al., 1997
Pooled incidence data on herbicide use from 3 case-control studies in **Iowa/Minnesota, Kansas,** and **Nebraska** (n = 973)		**Herbicides**	Chiu et al., 2004
Farmers (no herbicide use)	294	1.2 (1.0–1.5)	
Farmers (herbicide use)	273	1.0 (0.8–1.2)	
Pooled data from case-control studies in **Iowa, Minnesota,** and **Nebraska—**effect of asthma on NHL and pesticide use (n = 872)		**Pesticides**	Lee et al., 2004a
Asthmatics—incidence			
Herbicide exposure—phenoxy acid	17	1.3 (0.7–2.4)	
Exposure among farmers			
2,4-D	17	1.3 (0.7–2.5)	
2,4,5-T	7	2.2 (0.8–6.1)	
Nonasthmatics—incidence			
Herbicide exposure—phenoxy acid	176	1.0 (0.8–1.3)	
Exposure among farmers			
2,4-D	172	1.0 (0.8–1.3)	
2,4,5-T	36	1.1 (0.7–1.8)	
Kansas residents–duration and frequency of herbicide use—incidence		**Phenoxy herbicides, 2,4-D**	Hoar et al., 1986
All farmers	133	1.4 (0.9–2.1)	
Farm-use of herbicides	7	6.0 (1.9–19.5)	
NCI SEER study (Iowa, Los Angeles County, Detroit, Seattle), 1998–2000; *1,321 NHL patients and 1,057 controls—residential* exposures			Hartge et al., 2005
Cases first primary NHL, and uninfected with HIV between 1998 and June 2000 (n = 1,321) controls (n = 1,057)		**2,4-D/Dicamba/PCB 105**	Czarnota et al., 2015 (supplemental material Table S-1)
OR risk of NHL 4th quartile exposure compared to 1st quartile, adjusted for gender, race, education, age, and study site			
2,4-D	nr	0.70 (0.48–1.03)	
Dicamba	nr	0.74 (0.53–1.04)	
PCB 105	nr	1.20 (0.87–1.67)	
2,4-D exposure in carpet dust (ng/g)		**2,4-D**	
Under detection limit	147	1.0	
< 500	257	1.1 (0.8–1.6)	
500–999	86	0.9 (0.6–1.5)	
1,000–9,999	165	0.7 (0.5–1.0)	
> 10,000	24	0.8 (0.4–1.7)	

continued

TABLE 25 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Nebraska residents (men and women), NHL reclassified according to specific chromosomal translocation (t[14;18][q32;q21])—incidence		**Herbicides**	Chiu et al., 2006
Translocation present in cases			
Herbicides	25	2.9 (1.1–7.9)	
Translocation present in cases			
Herbicides	22	0.7 (0.3–1.2)	
		Herbicides	Zahm et al., 1993
Females on Eastern **Nebraska** farms	119	1.0 (0.7–1.4)	
Eastern **Nebraska** residents—incidence		**2,4-D**	Zahm et al., 1990
Ever done farm work	147	0.9 (0.6–1.4)	
Ever mixed or applied 2,4-D	43	1.5 (0.9–2.5)	
Upstate New York—population-based study, women (20–79 years old), 1995–1998 (376 cases vs 463 controls)		**Herbicides, pesticides**	Kato et al., 2004
Home use only of herbicides, pesticides (times)			
0	231	1.0	
1–4	33	0.9 (0.5–1.5)	
5–17	30	0.7 (0.4–1.3)	
18–39	27	1.0 (0.6–1.7)	
≥ 40	40	0.9 (0.5–1.5)	
Hancock County, **Ohio**, residents—farmers	15	1.6 (0.8–3.4)	Dubrow et al., 1988
Washington state residents—incidence (1983–1985)		**Phenoxy herbicides, chlorinated phenols**	Woods et al., 1987
Phenoxy herbicide use	nr	1.1 (0.8–1.4)	
Chlorophenol use	nr	1.0 (0.8–1.2)	
Farming occupations	nr	1.3 (1.0–1.7)	
Forestry herbicide appliers	nr	4.8 (1.2–19.4)	
Self-reported chloracne	nr	2.1 (0.6–7.0)	
Wisconsin residents—farmers (ICD-8 200.0, 200.1, 202.2)		**Herbicides**	Cantor, 1982
	175	1.2 (1.0–1.5)	
International Case-Control Studies			
Asian patients (≥ 20 years old) from China, Korea, and Japan diagnosed with NKTCL between March 2000 and March 2005—occupational exposures		**Herbicides, pesticides**	Xu et al., 2006
Pesticide use	23	4.0 (2.0–8.1)	
Herbicide	13	3.2 (1.4–7.4)	
Insecticide	20	3.5 (1.7–7.1)	
Fungicide	10	6.1 (2.0–18.5)	
Australian population-based study in New Wales (2000–2001)		**Phenoxy compounds**	Fritschi et al., 2005
Phenoxy herbicides			
Nonsubstantial exposures	10	0.7 0.3–1.7)	
Australian residents in Victorian Cancer Registry (1982–1987)		**Phenoxy compounds**	Smith and Christophers, 1992
Exposure > 1 day	15	1.5 (0.6–3.7)	
Exposure > 30 days	7	2.7 (0.7–9.6)	

TABLE 25 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Canadian population based study (March 2000–February 2004), men and women subjects and matched controls (20–79 years of age)—organochlorines and NHL		**dioxin-like PCBs**	Spinelli et al., 2007
Total dioxin-like PCBs			
Lowest quartile	82	1.0	
Second quartile	96	1.4 (0.9–2.2)	
Third quartile	82	1.6 (1.0–2.5)	
Highest quartile	143	2.4 (1.5–3.7)	
		p-trend < 0.001	
Cross-Canada Study of Pesticides and Health—men in one of 6 Canadian provinces (≥ 19 years of age) diagnosed (09/1991–12/1994) (n = 517) vs matched population-based controls (n = 1,506)		**Phenoxy herbicides, 2,4-D**	
Pesticide use, immunologic conditions, and NHL risk			Pahwa et al., 2012b
Phenoxy herbicides	44	1.5 (1.0–2.3)	
MCPA	7	2.7 (0.9–7.9)	
Mecoprop	16	1.7 (0.9–3.4)	
2,4-D	39	1.4 (0.9–2.2)	
Exposure to multiple pesticides			Hohenadel et al., 2011
0	369	1.0 (nr)	
1	45	1.2 (0.9–1.8)	
2–4	73	1.6 (1.2–2.2)	
5+	26	1.6 (1.0–2.6)	
Exposure to phenoxy herbicides			
0	384	1.0 (nr)	
1	66	1.3 (1.0–1.8)	
2+	63	1.8 (1.3–2.5)	
Exposure to Mecoprop	23	2.1 (1.2–5.4)	
Exposure to 2,4-D	49	0.9 (0.7–1.3)	
Pesticide exposure of ≥ 10 h/year	131	1.4 (1.1–1.8)	McDuffie et al., 2001
2,4-D	111	1.3 (1.0–1.7)	
Mecoprop	53	2.3 (1.6–3.4)	
Italy and Northern Sweden EnviroGen markers study case control study nested within the EPIC-Italy and the Northern Sweden Health and Disease Study		**dioxin-like PCBs**	Kelly et al., 2017
OR for risk of B-cell NHL Q4 exposure compared to Q1, adjusted for BMI, age, education level, vegetables, dairy, protein, total fat, and alcohol consumption			
PCB 118 Q4 to Q1	77	0.67 (0.3–1.49)	
PCB 156 Q4 to Q1	70	0.69 (0.33–1.45)	

continued

TABLE 25 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Danish residents (Copenhagen and Aarhus) in the Diet, Cancer and Health prospective study diagnosed with NHL from enrollment (1994–May 1977) through 2008		**Organochlorines**	Bräuner et al., 2012
Organochlorines in adipose tissue (ug/kg lipids)			
dioxin-like PCB 118			
10–25	53	1.0 (nr)	
25–34	63	0.9 (0.5–1.6)	
34–48	58	1.0 (0.6–1.7)	
48–62	34	0.7 (0.3–1.3)	
62–150	25	0.7 (0.4–1.4)	
dioxin-like PCB 156			
13–28	62	1.0 (nr)	
28–34	51	0.6 (0.3–1.0)	
34–41	54	0.7 (0.4–1.2)	
41–50	45	0.9 (0.5–1.8)	
50–88	23	0.7 (0.3–1.4)	
Denmark—Danish farm workers—incidence		**Phenoxy herbicides**	Ronco et al., 1992
	147	1.0 (nr)	
Italian farm workers—mortality	14	1.3 (nr)	
France hospital-based case-control study		**Herbicides**	Orsi et al., 2009
Occupational use of herbicides	25	1.3 (0.7–2.2)	
Phenoxy herbicides	11	0.9 (0.4–1.9)	
Domestic use of herbicides	86	1.0 (0.7–1.5)	
German population-based study (1986–1998), men and women, 15–75 years of age—occupational factors associated with NHL		**TCDD, Herbicides**	Richardson et al., 2008
Chlorophenols			
NHL—high-grade malignancy	61	2.0 (1.3–2.9)	
NHL—low-grade malignancy	77	1.3 (1.0–1.8)	
CLL	44	0.9 (0.6–1.3)	
Herbicides			
NHL—high-grade malignancy	56	2.2 (1.4–3.3)	
NHL—low-grade malignancy	79	1.4 (1.0–1.9)	
CLL	43	1.2 (0.8–1.7)	
Irish farmers and farm workers		**Herbicides**	Dean, 1994
Other malignant neoplasms of lymphoid and histiocytic tissue (including some types of NHL) (ICD-9 202)	164	1.8 (1.2–2.6)	
Italian incident cases of malignancies of the hematolymphopoietic system in men and women (20–74 years of age) from agricultural and mixed use areas (HD cases = 258)		**Herbicides**	Miligi et al., 2006
Men, women	73	1.0 (0.7–1.4)	
Men	49	0.8 (0.5–1.3)	
Women	24	1.3 (0.7–2.5)	

TABLE 25 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
NHL (men, women)			
Phenoxy herbicides—ever	32	1.1 (0.6–1.8)	
Probability of use more than "low," lack of protective equipment	13	2.4 (0.9–7.6)	
2,4-D—ever	17	0.9 (0.5–1.8)	
Probability of use more than "low," lack of protective equipment	9	4.4 (1.1–29.1)	
MCPA—ever	18	0.9 (0.4–1.8)	
Probability of use more than "low," lack of protective equipment	7	3.4 (0.8–23.2)	
Italian residents of 11 areas (NHL other than lymphosarcoma and reticulosarcoma)—incidence		**Herbicides**	Miligi et al., 2003
Phenoxy acid herbicides exposure			
Men	18	1.0 (0.5–2.0)	
Women	11	1.3 (0.5–3.7)	
2,4-D exposure			
Men	6	0.7 (0.3–1.9)	
Women	7	1.5 (0.4–5.7)	
Italian farming and animal-breeding workers (men and women) (NHL other than lymphosarcoma and reticulosarcoma)—incidence		**Herbicides**	Nanni et al., 1996
Exposure to herbicides	3	1.4 (0.4–5.7)	
Italian farming, animal-breeding workers (men and women)—incidence		**Herbicides**	Amadori et al., 1995
NHL, CLL combined	164	1.8 (1.2–2.6)	
Residents of selected **Italian** provinces		**Herbicides**	Vineis et al., 1991
Male residents of contaminated areas	nr	2.2 (1.4–3.5)	
Residents of Milan, **Italy**, area (men and women)—incidence		**Herbicides**	LaVecchia et al., 1989
Agricultural occupations	nr	2.1 (1.3–3.4)	
New Zealand National Cancer Registry (1980–1984)—case-control study of 652 incident NHL cases vs remainder of 19,904 men with any incident cancer		**Herbicides**	Reif et al., 1989
Forestry workers (n = 134)			
Aged 20–59 years	4	2.0 (0.7–5.6)	
Aged ≥ 60 years	3	1.7 (0.5–5.4)	
		Herbicides, Chlorophenols	
Sawmill workers (n = 139)	4	1.2 (0.4–3.2)	
New Zealand National Cancer Registry (1977–1981) (< 70 years of age)—incidence (1977–1981) (ICD-9 200 and 202)		**Herbicides**	Pearce et al., 1987
Farming occupations	33	1.0 (0.7–1.5)	
Fencing work	68	1.4 (1.0–2.0)	
New Zealand National Cancer Registry (1977–1981) (< 70 years of age)—incidence (1977–1981) (ICD-9 202 only)		**Phenoxy herbicides**	Pearce et al., 1986b
Agricultural sprayers	19	1.5 (0.7–3.3)	
New Zealand National Cancer Registry (1977–1981) (≥ 20 years of age) with agricultural occupations—incidence (ICD-9 200 and 202)	nr	**Herbicides** 1.4 (0.9–2.0)	Pearce et al., 1985

continued

TABLE 25 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Sweden—male, female subjects (18–74 years of age) with NHL living in Sweden between December 1, 1999, and April 30, 2002, vs controls from national population registry		**Pesticides, herbicides**	Eriksson et al., 2008
Herbicides, total	74	1.7 (1.2–2.5)	
≤ 20 days	36	1.6 (1.0–2.7)	
> 20 days	38	1.9 (1.1–3.2)	
Phenoxyacetic acids	47	2.0 (1.2–3.4)	
≤ 45 days	32	2.8 (1.5–5.5)	
> 45 days	15	1.3 (0.6–2.7)	
MCPA	21	2.8 (1.3–6.2)	
≤ 32 days	15	3.8 (1.4–10.5)	
> 32 days	6	1.7 (0.5–6.0)	
2,4,5-T, 2,4-D	33	1.6 (0.9–3.0)	
≤ 29 days	21	2.1 (1.0–4.4)	
> 29 days	12	1.3 (0.6–3.1)	
Sweden—male and female patients (18–74 years of age) diagnosed December 1999–April 2002		**Pesticides, herbicides**	Hardell et al., 2002
Chlorophenols			
NHL—high grade malignancy	61	2.0 (1.3–2.9)	
Sweden—pooled analysis of case-control NHL, hairy-cell leukemia studies		**Herbicides**	Hardell et al., 2002
Herbicide exposure	77	1.8 (1.3–2.4)	
Phenoxyacetic acids	64	1.7 (1.2–2.3)	
MCPA	21	2.6 (1.4–4.9)	
2,4-D, 2,4,5-T	48	1.5 (1.0–2.2)	
Other	15	2.9 (1.3–6.4)	
Substantial exposure	5	1.8 (0.4–7.4)	
Sweden—adipose tissue from 33 NHL patients and 39 surgical controls from Örebro-Uppsala medical region (1994–1997)		**Dioxin, dibenzofurans**	Hardell et al., 2001
TEQ > 27.8, EA > 80	8	2.8 (0.5–18.0)	
Umea (**Sweden**) Hospital patients—incidence		**Phenoxy herbicides, chlorophenols**	Hardell et al., 1994
Exposed to phenoxy herbicides	25	5.5 (2.7–11.0)	
Exposed to chlorophenols	35	4.8 (2.7–8.8)	
Swedish Regional Cancer Registry—NHL patients		**Phenoxy herbicides**	Persson et al., 1993
Exposed to phenoxy herbicides	10	2.3 (0.7–7.2)	
Exposed to chlorophenols	9	6.0 (1.1–31.0)	
Örebro (**Sweden**) Hospital (men and women)—incidence		**Phenoxy herbicides, chlorophenols**	Persson et al., 1989
Exposed to phenoxy acids	6	4.9 (1.0–27.0)	
Lund (**Sweden**) Hospital patients—incidence		**Herbicides**	Olsson and Brandt, 1988
Exposed to herbicides	nr	1.3 (0.8–2.1)	
Exposed to chlorophenols	nr	1.2 (0.7–2.0)	
Swedish patients (1970–1977)		**Phenoxy acids, chlorophenols**	Hardell, 1981
Exposed to phenoxy herbicides	41	4.8 (2.9–8.1)	
Exposed to chlorophenols	50	4.3 (2.7–6.9)	

TABLE 25 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
CASE-CONTROL STUDIES			
Participants in the EPILYMPH study in six European countries (1998–2003)		**Pesticides**	Cocco et al., 2012
Exposure to phenoxy herbicides and CLL	2	0.9 (0.2–4.1)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,5-DCP, 2,5-dichlorophenol; ACC, Army Chemical Corps; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; ; CLL, chronic lymphocytic leukemia; COI, chemical of interest; EOI, Exposure Opportunity Index; HD, Hodgkin disease; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; ICDA, *International Classification of Diseases, Adapted for Use in the United States*; JEM, job-exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; MOS, military occupation specialty; n, number; NCI, National Cancer Institute; NHL, non-Hodgkin lymphoma; NIOSH, National Institute for Occupational Safety and Health; NKTCL, NK/T-cell lymphoma; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; PM, proportionate mortality; SEA, Southeast Asia; SEER, Surveillance, Epidemiology, and End Results; SIR, standardized incidence ratio; SMR, standardized mortality rate; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; TEQ, toxicity equivalent; USDA, US Department of Agriculture; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

[c]Lymphopoietic cancers comprise all of forms of lymphoma (including Hodgkin disease and non-Hodgkin lymphoma) and leukemia (ALL, AML, CLL, CML).

[d]Committee computed total SMR and SIR by dividing sum of observed values by sum of expected values over all years; 95% CIs on these total ratios were computed with exact methods.

TABLE 26 Selected Epidemiologic Studies—Chronic Lymphocytic Leukemia (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
United States, Minnesota—195 patients who attended Minneapolis between 2001 and 2010, with CLL diagnosis in VA tumor registry			Baumann Kreuziger et al., 2014
Hazard ratio of death AO exposed vs unexposed, adjusted for age	33	1.8 (0.7–4.5)	
United States—Patients diagnosed with CLL between 2009 and 2013 in National VA Tumor Registry			Mescher et al., 2017
Median survival AO exposed vs unexposed	418	Median not reached vs 91.2 months, $p < 0.0001$	
International Vietnam-Veteran Study			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	58	1.2 (0.7–1.7)	ADVA, 2005b
Navy	12	1.5 (0.8–2.6)	
Army	42	1.7 (1.2–2.2)	
Air Force	4	0.9 (0.2–2.2)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Sawmill Workers in British Columbia—23,829 workers for ≥ 1 year at 11 mills using chlorophenates 1940–1985		**Chlorophenates, not TCDD**	
Incidence—all leukemias (1969–1989)	47	1.2 (0.9–1.5)	Hertzman et al., 1997
ALL	2	1.0 (0.2–3.1)	
CLL	24	1.7 (1.2–2.4)	
AML	5	0.8 (0.3–1.7)	
CML	7	1.1 (0.5–2.0)	
Other, unspecified	5	0.5 (0.2–1.0)	
DENMARK			
Danish gardeners—incidence from 3,156 male and 859 female gardeners		**Herbicides**	Hansen et al., 1992, 2007
10-year followup (1975–1984) of Danish gardeners			
All gardeners	6	2.5 (0.9–5.5)	
Male gardeners	6	2.8 (1.0–6.0)	
UNITED STATES			
White Male Residents of Iowa—chronic lymphocytic leukemia on death certificate, usual occupation: farmers vs not > 30 years old when died 1964–1978—case-control (1,675 leukemia deaths, 1968–1978)		**Herbicides**	Burmeister et al., 1982
Farmer usual occupation on death certificate		1.2 ($p < 0.05$)	
CLL	132	1.7 (1.2–2.4)	
Lived in counties with highest herbicide use	nr	1.9 (1.2–3.1)	

TABLE 26 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
White Male Residents of Iowa and Minnesota— > 30 years old diagnosed 1981–1983 in Iowa or 1980–1982 in Minnesota—case-control		**Herbicides**	
> 30 years old diagnosed 1981–1983 in Iowa or 1980–1982 in Minnesota—case-control (ever farmer)			Brown et al., 1990
Ever farmed	156	1.4 (1.1–1.9)	
Any herbicide used	74	1.4 (1.0–2.0)	
Ever used 2,4,5-T	10	1.6 (0.7–3.4)	
Use at least 20 years before interview	7	3.3 (1.2–8.7)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Incidence			
20-year followup to 1996—men and women (lymphatic leukemia, ICD-9 204)			
Zone A	1	2.8 (0.4–19.9)	Pesatori et al., 2009
Zone B	0	nr	
Zone R	13	0.8 (0.5–1.5)	
Mortality			
25-year followup to 2001—men and women (lymphatic leukemia, ICD-9 204)			Consonni et al., 2008
Zone A	0	nr	
Zone B	3	1.3 (0.4–4.1)	
Zone R	23	1.4 (0.9–2.2)	
20-year followup to 1996 (lymphatic leukemia)			Bertazzi et al., 2001
Zones A, B—men	2	1.6 (0.4–6.8)	
Zones A, B—women	0	nr	
Other International Environmental Studies			
NEW ZEALAND			
Residents of New Plymouth Territorial Authority, New Zealand near plant manufacturing 2,4,5-T in 1962–1987		**2,4,5-T**	Read et al., 2007
Incidence	104	1.3 (1.1–1.6)[c]	
1970–1974	16	2.5 (1.4–4.1)	
1975–1979	7	0.9 (0.4–1.8)	
1980–1984	21	2.6 (1.6–3.9)	
1985–1989	16	1.4 (0.8–2.3)	
1990–1994	13	0.9 (0.5–1.6)	
1995–1999	19	0.9 (0.5–1.4)	
2000–2001	12	1.1 (0.6–1.9)	
Mortality	40	1.3 (0.9–1.8)[c]	
1970–1974	7	1.7 (0.7–3.5)	
1975–1979	7	1.8 (0.7–3.6)	
1980–1984	6	1.4 (0.5–3.0)	
1985–1989	4	0.8 (0.2–2.2)	
1990–1994	6	1.1 (0.4–2.5)	
1995–1999	8	1.3 (0.6–2.6)	
2000–2001	2	0.8 (0.1–2.8)	

continued

TABLE 26 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
CASE-CONTROL STUDIES			
US Case-Control Studies			
Tecumseh, Michigan residents participating in longitudinal study (1959–1987)	10	**Herbicides** 1.8 (0.8–3.2)	Waterhouse et al., 1996
Nebraska—1,084 leukemia deaths in 1957–1974; farmers–usual occupation on death certificate	nr	**Herbicides, pesticides** 1.3 ($p < 0.05$)	Blair and White, 1985
248 CLL cases	nr	1.7 ($p < 0.05$)	
International Case-Control Studies			
Europe—Participants in the EPILYMPH study in six European countries (1998–2003)		**Pesticides**	Cocco et al., 2012
Exposure to phenoxy herbicides and CLL	2	0.9 (0.2–4.1)	
France hospital-based case-control study		**Herbicides**	Orsi et al., 2009
Occupational use of herbicides	5	0.5 (0.2–1.3)	
Phenoxy herbicides	3	0.4 (0.1–1.7)	
German population-based study (1986–1998), men and women, 15–75 years of age—occupational factors associated with CLL		**TCDD, Herbicides**	Richardson et al., 2008
Chlorophenols	44	0.9 (0.6–1.3)	
Lowest tertile cumulative exposure	12	0.9 (0.4–1.8)	
Middle tertile	15	0.9 (0.5–1.8)	
Highest tertile	17	0.9 (0.5–1.6) p-trend = 0.770	
Herbicides	43	1.2 (0.8–1.7)	
Lowest tertile cumulative exposure	13	1.3 (0.7–2.7)	
Middle tertile	15	1.3 (0.7–2.5)	
Highest tertile	15	1.0 (0.5–1.9) p-trend = 0.755	
Italian farming, animal-breeding workers (men and women)—incidence	15	**Herbicides** 2.3 (0.9–5.8)	Amadori et al., 1995
Farming workers only	5	1.6 (0.5–5.2)	
Breeding workers only	10	3.1 (1.1–8.3)	

NOTE: 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; CI, confidence interval; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; COI, chemical of interest; ICD, *International Classification of Diseases*; n, number; nr, not reported; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

[c]The total SMR/SIR were computed by dividing sum of observed values by sum of expected values over all years; 95% CIs on these total ratios were computed with exact methods.

TABLE 27 Selected Epidemiologic Studies—Plasma Cell Dyscrasias (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)			
Incidence of MGUS 479 Ranch Hand Veterans, 479 comparison veterans		**TCDD**	Landgren et al., 2015
Adjusted OR for MGUS association wth lipid adjusted TCDD ppt, adjusted for age, race, BMI change between 2002 and blood draw for TCDD measurement			
Ranch Hand vs Comparison	477	2.37 (1.28–4.42)	
< 3.65	241	1.0 (referent)	
3.66–5.80	237	2.09 (0.77–5.66)	
5.81–10.92	239	2.62 (1.00–6.88)	
≥ 10.92	239	2.81 (1.08–7.31)	
Adjusted ORs estimated for cohort status (Ranch Hand vs Comparison)			
Ranch Hand vs Comparison	477	2.37 (1.27–4.44)	
< 3.65	241	1.0 (referent)	
3.66–5.80	237	1.78 (0.65–4.89)	
5.81–10.92	239	2.10 (0.79–5.59)	
≥ 10.92	239	2.43 (0.92–6.44)	
Incidence		**All COIs**	
Through 1999—White subjects vs national rates			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	10	0.9 (0.4–1.5)	
With tours between 1966–1970	7	0.7 (0.3–1.4)	
SEA comparison veterans (n = 1,776)	9	0.6 (0.3–1.0)	
With tours between 1966–1970	4	0.3 (0.1–0.8)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Mortality			Boehmer et al., 2004
1965–2000	1	0.4 (nr)	
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1988			Watanabe and Kang, 1996
Army, deployed (n = 27,596) vs nondeployed (n = 31,757)	36	0.9 (nr)	
Marine Corps, deployed (n = 6,237) vs nondeployed (n = 5,040)	4	0.6 (nr)	
1965–1982			Breslin et al., 1988
Army, deployed (n = 19,708) vs nondeployed (n = 22,904)	18	0.8 (0.2–2.5)	
Marine Corps, deployed (n = 4,527) vs nondeployed (n = 3,781)	2	0.5 (0.0–17.1)	
US VA Cohort of Female Vietnam Veterans		**All COIs**	
Mortality, through 2004	18	0.7 (0.4–1.3)	Cypel and Kang, 2008
Vietnam-veteran nurses only	14	0.7 (0.3–1.3)	

continued

TABLE 27 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	31	0.7 (0.4–0.9)	ADVA, 2005b
Navy	4	0.4 (0.1–1.0)	
Army	21	0.7 (0.4–1.0)	
Air Force	6	1.1 (0.4–2.4)	
Mortality			
All branches, return–2001	24	0.9 (0.5–1.2)	ADVA, 2005a
Navy	3	0.5 (0.1–1.5)	
Army	15	0.8 (0.4–1.3)	
Air Force	6	1.7 (0.6–3.6)	
1980–1994	6	0.6 (0.2–1.3)	CDVA, 1997a
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Incidence			
1982–2000	8	2.1 (0.7–6.0)	ADVA, 2005c
Mortality			
1966–2001	5	0.9 (0.2–3.4)	ADVA, 2005c
1982–1994	0	nr	CDVA, 1997b
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008)	9	1.5 (0.7–2.9)	
Mortality (1988–2008)	5	1.6 (0.5–3.7)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores)		**All COIs**	
		HRs	
Incidence (1992–2003)—MM (90) categorized high (n = 28) vs low (n = 23)	28	1.1 (0.7–2.0)	Yi and Ohrr, 2014
Mortality (1992–2005)—MM (90) categorized high (n = 19) vs low (n = 20)		0.8 (0.4–1.5)	Yi et al., 2014b
HR per unit of log EOI scores (n = 180,639)	39	1.0 (0.9–1.1)	
OCCUPATIONAL—Industrial			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	17	1.3 (0.8–2.1)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	9	1.2 (0.6–2.3)	
7,553 not exposed to highly chlorinated PCDDs	8	1.6 (0.7–3.1)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	4	0.7 (0.2–1.8)	Saracci et al., 1991

TABLE 27 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
British MCPA Plant—All manual employees employed January 1947–December 1975 (n = 1,146), ever potentially exposed to phenoxy herbicides (n = 1,544), potentially exposed to phenoxy herbicides ≥ 1 year (n = 848) (not included in IARC cohort)		**MCPA**	
Mortality through 2012, all workers			Coggon et al., 2015
Multiple myeloma (ICD-10 C90)	18	1.04 (0.62–1.64)	
Mortality through 2012, workers ever exposed to phenoxy herbicides			
Multiple myeloma (ICD-10 C90)	15	1.18 (0.66–1.94)	
Mortality through 2012, workers ever exposed to phenoxy herbicides ≥ 1 year			
Multiple myeloma (ICD-10 C90)	6	1.01 (0.37–2.20)	
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence 1943–1987 (men only)	0	nr	Lynge, 1993
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–1991	0	0.0 (nr)	Hooiveld et al., 1998
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 month in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992	0	nr	Becher et al., 1996
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 month in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4-DP; 2,4,5-T; MCPA; MCPP**	
Mortality 1965–1989	0	nr	Becher et al., 1996
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 month in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4-DP; 2,4,5-T; MCPA; MCPP**	
Mortality 1956–1989	0	nr	Becher et al., 1996
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 month in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,5-DCP; 2,4,5-T; 2,4,5-TCP**	
Mortality 1952–1989	3	5.4 (1.1–15.9)	Becher et al., 1996
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	2	2.2 (0.2–8.1)	
Never-exposed workers	0	0.0 (0.0–12.2)	
Production Workers (713 men and 100 women worked > 1 month in 1969–1984)			't Mannetje et al., 2005
Mortality 1969–2000	3	5.5 (1.1–16.1)	
Sprayers (697 men and 2 women on register of New Zealand applicators, 1973–1984)			
Mortality 1973–2000	0	0.0 (0.0–5.3)	‘

continued

TABLE 27 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993	10	2.1 (1.0–3.8)	Steenland et al., 1999
Through 1987	5	1.6 (0.5–3.9)	Fingerhut et al., 1991
≥ 1-year exposure, ≥ 20-year latency	3	2.6 (0.5–7.7)	
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, Washington, and Wichita, Kansas) and workers who made PCP and TCP at two additional plants (in Midland, Michigan, and Sauget, Illinois)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122)	7	1.5 (0.6–3.1)	
PCP and TCP (n = 720)	1	0.7 (0.0–4.0)	
PCP (no TCP) (n = 1,402)	6	1.8 (0.7–4.0)	
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)	2	0.8 (0.1–2.9)	Burns CJ et al., 2011
Through 1994 (n = 1,517)	1	0.8 (0.0–4.5)	Burns et al., 2001
OCCUPATIONAL—Paper And Pulp Workers		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	21	0.8 (0.5–1.3)	
Ever	20	1.1 (0.7–1.7)	
OCCUPATIONAL—Herbicide-Using Workers (not related to IARC sprayer cohorts)			
CANADA			
Canadian Farm Operator Study—156,242 men farming in Manitoba, Saskatchewan, and Alberta in 1971; mortality from MM June 1971–December 1987			
Farmers from Canadian prairie provinces	160	0.8 (0.7–1.0)	Semenciw et al., 1994
DENMARK			
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	3	2.1 (0.4–6.1)	Swaen et al., 2004
Through 1987	3	8.2 (1.6–23.8)	Swaen et al., 1992
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 weeks) not IARC		**Phenoxy herbicides**	
Incidence	2	1.5 (0.2–5.2)	Asp et al., 1994
Mortality 1972–1989	3	2.6 (0.5–7.7)	
Except for lung cancer, numbers too small for reporting mortality 1972–1980		*Expected number of exposed cases*	Riihimaki et al., 1982
	1	0.2 (nr)	
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401)	5	0.4 (0.1–1.0)	Torchio et al., 1994
Italian rice growers with documented phenoxy use (n = 1,487)	0	**Phenoxy herbicides** nr	Gambini et al., 1997

TABLE 27 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of incident multiple myeloma cancer cases vs remainder of 19,904 men with any incident cancer		**Herbicides**	Reif et al., 1989
Forestry workers (n = 134)	1	0.5 (0.1–3.7)	
SWEDISH lumberjacks—Used phenoxys 1954–1967, incidence (1958–1992)			Thörn et al., 2000
Exposed (n = 154)			
Foremen (n = 15)	0		
Lumberjacks (n = 139)	0		
Unexposed lumberjacks (n = 241)	1	1.5 (0.0–8.6)	
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	413	1.2 (1.0–1.3)	
Nonwhites (n = 11,446)	51	0.9 (0.7–1.2)	
Women			
Whites (n = 2,400)	14	1.8 (0.97–3.0)	
Nonwhites (n = 2,066)	11	1.1 (0.6–2.0)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	71	1.2 (0.9–1.5)	
Commercial applicators	1	nr	
Spouses	21	0.9 (0.6–1.4)	
Nested case-control study of MGUS among male private and commercial applicators			Landgren et al., 2009
2,4-D	33	1.8 (0.7–4.8)	
Dicamba	17	0.9 (0.5–1.8)	
Enrollment through 2002			Alavanja et al., 2005
Private applicators	43	1.3 (1.0–1.8)	
Spouses of private applicators (> 99% women)	13	1.1 (0.6–1.9)	
Commercial applicators	0	0.0 (0.0–2.7)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	52	1.0 (0.8–1.3)	
Spouses (n = 676)	10	0.6 (0.3–1.0)	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	11	0.6 (0.3–1.2)	
Spouses of private applicators (> 99% women)	5	0.9 (0.3–2.1)	

continued

TABLE 27 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
US Department of Agriculture Workers—nested case-control study of white men dying 1970–1979 of MM		**Herbicides**	
Forest conservationists	1.3	nr (p-trend = 0.35)	Alavanja et al., 1989
Soil conservationists	1.3	nr (p-trend = 0.32)	
White Male Residents of Iowa—MM on death certificate, usual occupation: farmers vs not		**Herbicides**	
> 30 years old diagnosed 1981–1984—case-control (ever farmer)	111	1.2 (0.8–1.7)	Brown et al., 1993
> 30 years old when died 1964–1978—case-control			Burmeister et al., 1983
H_0: only for "modern methods" → born after 1900			
Born 1980–1900	nr	2.7 ($p < 0.05$)	
Born after 1900	nr	2.4 ($p < 0.05$)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Incidence			
20-year followup to 1996—men and women			
Zone A	1	2.9 (0.4–20.7)	Pesatori et al., 2009
Zone B	6	2.8 (1.2–6.3)	
Zone R	18	1.2 (0.7–1.9)	
10-year followup to 1991—men			Bertazzi et al., 1993
Zone B	2	3.2 (0.8–13.3)	
Zone R	1	0.2 (0.0–1.6)	
10-year followup to 1991—women			Bertazzi et al., 1993
Zone B	2	5.3 (1.2–22.6)	
Zone R	2	0.6 (0.2–2.8)	
Mortality			
25-year followup to 2001—men and women			Consonni et al., 2008
Zone A	2	4.3 (1.1–17.5)	
Zone B	5	1.7 (0.7–4.1)	
Zone R	24	1.1 (0.7–1.7)	
20-year followup to 1996			Bertazzi et al., 2001
Zones A, B—men	1	0.6 (0.1–4.3)	
Zones A, B—women	4	3.2 (1.2–8.8)	
15-year followup to 1991—men			Bertazzi et al., 1997
Zone B	1	1.1 (0.0–6.2)	
Zone R	5	0.8 (0.3–1.9)	
15-year followup to 1991—women			Bertazzi et al., 1997
Zone B	4	6.6 (1.8–16.8)	
Zone R	5	1.0 (0.3–2.3)	

TABLE 27 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
CASE-CONTROL STUDIES			
US Case-Control Studies			
ACS Prevention Study II subjects, MM on death certificate (128 MM cases vs 154 controls)		**Herbicides, pesticides**	Boffetta et al., 1989
	12	2.1 (1.0–4.2)	
Farmers using herbicides, pesticides	8	4.3 (1.7–10.9)	
Residents of four SEER program areas, 698 cases (< 80 years of age) vs 1,683 controls (July 1977–June 1981)		**Pesticides**	Morris et al., 1986
	nr	2.9 (1.5–5.5)	
Nebraska herbicide and pesticide use by Nebraska residents		**Herbicides**	Zahm et al., 1992
Eastern Nebraska users of herbicides			
Men	8	0.6 (0.2–1.7)	
Women	10	2.3 (0.8–7.0)	
Eastern Nebraska users of insecticides			
Men	11	0.6 (0.2–1.4)	
Women	21	2.8 (1.1–7.3)	
Wisconsin mortality listings (1968–1976)—farmers (30–39 years of age) in counties with highest herbicide use		**Herbicides**	Cantor and Blair, 1984
	nr	1.4 (0.8–2.3)	
International Case-Control Studies			
Cross-Canada Study of Pesticides and Health—men in one of 6 Canadian provinces (> 19 years of age) diagnosed 9/1991–12/1994 (n = 342) vs population-based matched controls (n = 1,506)		**Phenoxy herbicides**	Kachuri et al., 2013; Pahwa et al., 2006, 2012a,b
Expose to any phenoxy herbicide	87	1.3 (1.0–1.8)	
2,4-D	80	1.3 (1.0–1.8)	
Mecoprop	27	1.9 (1.2–3.2)	
MCPA	8	0.7 (0.3–1.5)	
Days/year of mixing or applying phenoxy herbicides			
> 0 and ≤ 2	35	1.5 (1.0–2.3)	
> 2 and ≤ 5	23	1.3 (0.8–2.8)	
> 5	26	1.1 (0.7–1.9)	
France hospital-based case-control study		**Herbicides**	Orsi et al., 2009
Occupational use of herbicides	12	2.9 (1.3–6.5)	
Phenoxy herbicides	7	2.6 (0.9–7.0)	
Domestic use of herbicides	22	1.0 (0.6–2.0)	
Irish farmers and farm workers		**Herbicides**	Dean, 1994
Other malignant neoplasms of lymphoid and histiocytic tissue (including some types of NHL) (ICD-9 202)	171	1.0 (nr)	
Italian residents of 11 areas (NHL other than lymphosarcoma and reticulosarcoma)—incidence		**Herbicides**	Miligi et al., 2003
Herbicide exposure	11	1.6 (0.8–3.5)	
Men	8	1.4 (0.6–3.5)	
Women	3	3.2 (0.7–14.7)	
Residents of Milan, **Italy**, area (men and women)—incidence		**Herbicides**	LaVecchia et al., 1989
Agricultural occupations	nr	2.0 (1.1–3.5)	
New Zealand National Cancer Registry (1977–1981)—agricultural workers (< 70 years of age) (76 MM cases vs 315 controls)—incidence		**Phenoxy herbicides, chlorophenols**	Pearce et al., 1986a
Use of agricultural spray	16	1.3 (0.7–2.5)	
Likely sprayed 2,4,5-T	14	1.6 (0.8–3.1)	

continued

TABLE 27 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Swedish residents from 4 counties diagnosed with MM (n = 275) vs 275 controls from population registry (July 1982–June 1986)		**Phenoxy herbicides** 90% CI	Eriksson and Karlsson, 1992
Exposed to phenoxy herbicides	20	2.2 (1.2–4.7)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,5-DCP, 2,5-dichlorophenol; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job-exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; n, number; NHL, non-Hodgkin lymphoma; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chlorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; SEA, Southeast Asia; SEER, Surveillance, Epidemiology, and End Results; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; TEQ, toxicity equivalent; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

TABLE 28 Selected Epidemiologic Studies—Leukemia (shaded entries are new information for Update 11 [2018])

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Incidence			
Through 1999—White subjects vs national rates (lymphopoietic cancer)[c]			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	10	0.9 (0.4–1.5)	
With tours between 1966–1970	7	0.7 (0.3–1.4)	
SEA comparison veterans (n = 1,776)	9	0.6 (0.3–1.0)	
With tours between 1966–1970	4	0.3 (0.1–0.8)	
Mortality			
Through 1999—White subjects vs national rates (lymphopoietic cancer)[c]			Akhtar et al., 2004
Ranch Hand veterans (n = 1,189)	6	1.0 (0.4–2.0)	
SEA comparison veterans (n = 1,776)	5	0.6 (0.2–1.2)	
US VA Cohort of Army Chemical Corps—Expanded as of 1997 to include all Army men with chemical MOS (2,872 deployed vs 2,737 nondeployed) serving during Vietnam era (7/1/1965–3/28/1973)		**All COIs**	
Mortality—Through 2005			Cypel and Kang, 2010
All lymphopoietic			
Deployed vs nondeployed	6 vs 6	1.1 (0.4–2.5)	
ACC veterans vs US men			
Vietnam cohort	6	0.5 (0.2–1.0)	
Non-Vietnam cohort	6	0.6 (0.2–1.4)	
Leukemia			
Deployed vs nondeployed	2 vs 4	0.6 (0.1–3.2)	
ACC veterans vs US men			
Vietnam cohort	2	0.4 (0.1–1.5)	
Non-Vietnam cohort	4	1.2 (0.3–3.0)	
Mortality—Through 2001		1.0 (0.1–3.8)	Dalager and Kang, 1997
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Mortality			
1965–2000	8	1.0 (0.4–2.5)	Boehmer et al., 2004
US VA Cohort of Female Vietnam Veterans		**All COIs**	
Mortality			
Through 2004 (lymphopoietic cancers)[c]	18	0.7 (0.4–1.3)	Cypel and Kang, 2008
Vietnam–veteran nurses	14	0.7 (0.3–1.3)	
State Studies of US Vietnam Veterans			
Michigan Vietnam-era veterans, PM study of deaths (1974–1989)—deployed vs nondeployed	30	1.0 (0.7–1.5)	Vistainer et al., 1995

continued

TABLE 28 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
All branches, 1982–2000	130	1.1 (1.0–1.4)	ADVA, 2005b
Lymphocytic leukemia	72	1.4 (1.1–1.7)	
Myeloid leukemia	54	1.0 (0.8–1.3)	
Navy	35	1.5 (1.0–2.0)	
Lymphocytic leukemia	14	1.3 (0.7–2.1)	
Myeloid leukemia	19	1.7 (1.0–2.6)	
Army	80	1.1 (0.8–1.3)	
Lymphocytic leukemia	50	1.4 (1.0–1.8)	
Myeloid leukemia	28	0.8 (0.5–1.1)	
Air Force	15	1.2 (0.7–2.0)	
Lymphocytic leukemia	8	1.4 (0.6–2.7)	
Myeloid leukemia	7	1.3 (0.5–2.6)	
		Expected number of exposed cases	AIHW, 1999
Validation Study	27	26 (16–36)	
Men	64	26 (16–36	CDVA, 1998a
Women	1	0 (0–4)	CDVA, 1998b
Mortality			
All branches, return–2001	84	1.0 (0.8–1.3)	ADVA, 2005c
Lymphocytic leukemia	24	1.2 (0.7–1.7)	
Myeloid leukemia	55	1.1 (0.8–1.3)	
Army	48	0.1 (0.7–1.2)	
Lymphocytic leukemia	17	1.3 (0.7–2.0)	
Myeloid leukemia	30	0.8 (0.5–1.1)	
Air Force	14	1.6 (0.8–2.6)	
Lymphocytic leukemia	6	2.7 (1.0–5.8)	
Myeloid leukemia	8	1.3 (0.5–2.5)	
1980–1994	33	1.3 (0.8–1.7)	CDVA, 1997a
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Incidence—1982–2000	16	0.6 (0.3–1.1)	ADVA, 2005c
Lymphocytic leukemia	9	0.8 (0.3–2.0)	
Myeloid leukemia	7	0.5 (0.2–1.3)	
Mortality—1966–2001	11	0.6 (0.3–1.3)	ADVA, 2005c
Lymphocytic leukemia	2	0.4 (0.0–2.4)	
Myeloid leukemia	8	0.7 (0.3–1.7)	
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	McBride et al., 2013
Incidence (1988–2008)			
All leukemia	21	1.6 (1.0–2.5)	
Non-lymphoid leukemia	7	1.3 (0.5–2.7)	
Lymphoid leukemia	14	1.9 (1.0–3.2)	

TABLE 28 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Mortality (1988–2008)			
All leukemia	4	0.7 (0.2–1.8)	
Non-lymphoid leukemia	3	0.8 (0.2–2.3)	
Lymphoid leukemia	1	0.6 (0.0–3.2)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores)		**All COIs**	
		HRs	
Incidence (1992–2003)			Yi and Ohrr, 2014
Lymphoid leukemia (C91)	5 vs 9	0.5 (0.2–1.4)	
ALL (C91)	3 vs 5	0.5 (0.1–2.2)	
Myeloid leukemia (C92–C94)	45 vs 38	1.1 (0.7–1.8)	
AML (C92)	20 vs 25	0.8 (0.5–1.6)	
CML (C92.1)	17 vs 6	2.4 (0.9–6.2)	
Mortality (1992–2005)			Yi et al., 2014b
HR per unit of log EOI (n = 180,639)			
Leukemia (C91–C95)	107	1.0 (1.0–1.1)	
ALL (C91)	5	0.9 (0.6–1.3)	
AML (C92)	46	1.0 (0.9–1.2)	
CML (C92.1)	15	1.6 (1.1–2.3)	
High exposure vs low exposure			
Leukemia (C91–C95)	58 vs 49	1.2 (0.8–1.8)	
ALL (C91)	2 vs 3	0.7 (0.1–4.1)	
AML (C92)	24 vs 22	1.2 (0.6–2.2)	
CML (C92.1)	13 vs 2	7.9 (1.7–37.5)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992	34	1.0 (0.7–1.4)	Kogevinas et al., 1997
13,831 exposed to highly chlorinated PCDDs	16	0.7 (0.4–1.2)	
7,553 not exposed to highly chlorinated PCDDs	17	1.4 (0.8–2.3)	
Mortality 1955–1988 of 12,492 production workers and 5,898 sprayers exposed—13,482 in exposed subcohort	18	1.2 (0.7–1.9)	Saracci et al., 1991
Mortality, incidence of women in production (n = 699) and spraying (n = 2) compared to national death rates and cancer incidence rates (myeloid leukemia)	1	**TCDD** 2.0 (0.2–7.1)	Kogevinas et al., 1993
British MCPA Plant—All manual employees employed January 1947–December 1975 (n = 1,146), ever potentially exposed to phenoxy herbicides (n = 1,544), potentially exposed to phenoxy herbicides ≥ 1 year (n = 848) (not included in IARC cohort)		**MCPA**	
Mortality through 2012, all workers			Coggon et al., 2015
Leukaemia (ICD-10 C91–C95)	40	1.27 (0.91–1.73)	
Myloid leukaemia (ICD-10 C92)	22	1.21 (0.76–1.84)	
Mortality through 2012, workers ever exposed to phenoxy herbicides			
Leukaemia (ICD-10 C91–C95)	30	1.29 (0.87–1.84)	
Myloid leukaemia (ICD-10 C92)	15	1.11 (0.62–1.83)	

continued

TABLE 28 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Mortality through 2012, workers ever exposed to phenoxy herbicides ≥ 1 year			
Leukaemia (ICD-10 C91–C95)	11	1.04 (0.52–1.86)	
Myloid leukaemia (ICD-10 C92)	6	0.98 (0.36–2.13)	
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Mortality 1955–2006	9	0.9 (0.6–1.4)	Boers et al., 2012
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–2006 (hazard ratios for lagged TCDD plasma levels)	5	0.7 (0.4–1.4)	Boers et al., 2012
Mortality 1955–2006			Boers et al., 2010
LHC	11 vs 7	0.9 (0.3–2.6)	
Leukemia	2 vs 3	0.3 (0.0–2.6)	
Mortality 1955–1991	1	1.0 (0.0–5.7)	Hooiveld et al., 1998
Mortality 1955–1985			Bueno de Mesquita et al., 1993
Leukemia, aleukemia (ICD-9 204–207)	1	1.5 (0.0–8.2)	
Myeloid leukemia (ICD-8 205)	1	2.9 (0.0–15.9)	
Dutch production workers in Plant B (414 men exposed during production 1965–1986; 723 unexposed) (in IARC cohort)		**2,4-D; MCPA; MCPP; highly chlorinated dioxins unlikely**	
Mortality 1965–2006			Boers et al., 2010
LHC	3 vs 3	1.5 (0.3–7.5)	
Leukemia	2 vs 2	1.5 (0.2–10.8)	
Mortality 1965–1986			Bueno de Mesquita et al., 1993
Leukemia, aleukemia (ICD-9 204–207)	1	4.4 (0.1–24.2)	
Myeloid leukemia (ICD-8 205)	1	7.7 (0.2–42.9)	
German Production Workers—2,479 workers at 4 plants (in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Mortality			
Through 1987		90% CI	Zober et al., 1990
All cohorts (n = 247)	1	1.7 (nr)	
Cohort 3	1	5.2 (0.4–63.1)	
German Production Workers at Bayer Plant in Uerdingen (135 men working >1 month in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992	0	—	Becher et al., 1996
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 month in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1965–1989	0	—	Becher et al., 1996
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 month in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1956–1989	0	—	Becher et al., 1996

TABLE 28 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 month in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortalilty 1952–1989	4	1.8 (0.5–4.7)	Becher et al., 1996
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Mortality 1969–2004 (leukemia, aleukemia)			McBride et al., 2009a
Ever-exposed workers	1	0.6 (0.0–3.1)	
Never-exposed workers	0	0.0 (0.0–6.0)	
Production Workers (713 men and 100 women worked > 1 month in 1969–1984)			
Mortality 1969–2000	0	0.0 (0.0–5.3)	't Mannetje et al., 2005
Sprayers (697 men and 2 women registered any time 1973–1984)			
Mortality 1973–2000	1	1.2 (0.0–6.4)	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993	10	0.8 (0.4–1.5)	Steenland et al., 1999
Through 1987	6	0.7 (0.2–1.5)	Fingerhut et al., 1991
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, Michigan) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1937–2011 Potential dioxin exposure (n = 2,192), TCP production (n = 1,419), PCP production (n = 577), Both TCP and PCP (n = 196)			Collins et al., 2016
TCP or PCP, Leukaemia and leukaemia (ICD-10 C91–C95)	18	1.39 (0.82–2.19)	
TCP or PCP, Total lymphoid leukaemia (ICD-10 C91–C95)	5	1.48 (0.48–3.45)	
TCP or PCP, Total myeloid leukaemia (ICD-10 C92)	11	2.02 (1.01–3.61)	
TCP or PCP, Acute non-lymphatic leukaemia (ICD-10 92.0, 93.0, 94.0)	10	2.43 (1.16–4.47)	
TCP or PCP, All other non lymphatic leukaemia (ICD-10 C93–C95)	2	0.70 (0.90–2.54)	
TCP, Leukaemia and leukaemia (ICD-10 C91–C95)	17	1.78 (1.04–2.85)	
TCP, Total lymphoid leukaemia (ICD-10 C91–C95)	5	1.99 (0.64–4.64)	
TCP, Total myeloid leukaemia (ICD-10 C92)	10	2.42 (1.16–4.46)	
TCP, Acute non-lymphatic leukaemia (92.0, 93.0, 94.0)	9	2.88 (1.32–5.47)	
TCP, All other non lymphatic leukaemia (ICD-10 C92)	2	0.94 (0.11–3.39)	
PCP, Leukaemia and leukaemia (ICD-10 C91–C95)	3	0.67 (0.14–1.96)	
PCP, Total lymphoid leukaemia (ICD-10 C91–C95)	1	0.87 (0.02–4.87)	
PCP, Total myeloid leukaemia (ICD-10 C92)	2	1.12 (0.14–4.03)	
PCP, Acute non-lymphatic leukaemia (92.0, 93.0, 94.0)	2	1.49 (0.18–5.38)	
PCP, All other non lymphatic leukaemia (ICD-10 C92)	0	0.00 (0.00–3.89)	

continued

TABLE 28 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
1942–2003 (n = 1,615) (leukemia, aleukemia)	13	1.9 (1.0–3.2)	Collins et al., 2009b
Excluding subset with PCP exposure	2	1.9 (1.0–3.4)	
1942–2003 (n = 1,615) (other lymphopoietic)	2	0.6 (0.1–2.3)	
Excluding subset with PCP exposure	2	0.7 (0.1–2.6)	
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, Washington, and Wichita, Kansas) and workers who made PCP and TCP at two additional plants (in Midland, Michigan, and Sauget, Illinois)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122)	9	0.9 (0.4–1.7)	
PCP and TCP (n = 720)	2	0.6 (0.1–2.2)	
PCP (no TCP) (n = 1,402)	7	1.0 (0.4–2.1)	
Dow PCP Production Workers (1937–1989 in Midland, Michigan) (not in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)			Collins et al., 2009c
1942–2003 (n = 773) (leukemia, aleukemia)	2	0.6 (0.1–2.0)	
Excluding subset with TCP exposure	1	0.4 (0.0–2.0)	
1942–2003 (n = 773) (other lymphopoietic)	2	1.3 (0.2–4.6)	
Excluding subset with TCP exposure	2	1.7 (0.2–6.0)	
Mortality 1940–1989 (n = 770)			Ramlow et al., 1996
0-year latency	2	1.0 (0.1–3.6)	
15-year latency	1	nr	
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan)		**2,4-D, lower chlorinated dioxins**	
Cancer incidence through 2007 in Dow workers (n = 1,256) vs comparisons from state cancer registries (n = 23,354) (Cohort 3)	5	0.9 (0.3–2.0)	Burns CJ et al., 2011
Through 1994 (n = 1,517)—lymphopoietic mortality in workers with high 2,4-D exposure	4	1.3 (0.4–3.3)	Burns et al., 2001
Through 1982 (n = 878)	2	3.6 (0.4–13.2)	Bond et al., 1988
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			McLean et al., 2006
Exposure to nonvolatile organochlorine compounds			
Never	49	1.0 (0.7–1.3)	
Ever	35	0.9 (0.6–1.2)	
Danish paper workers			Rix et al., 1998
Men	20	0.8 (0.5–1.2)	
Women	7	1.3 (0.5–2.7)	
OCCUPATIONAL—Herbicide-Using Workers (not related to IARC sprayer cohorts)			
CANADA			
Canadian Farm Operator Study—156,242 men farming in Manitoba, Saskatchewan, and Alberta in 1971; mortality from leukemia June 1971–December 1987		**Herbicides**	
Farm operators ≥ 35 years of age (June 1971–December 1987)	357	0.9 (0.8–1.0)	Semenciw et al., 1994
Lymphatic	132	0.9 (0.8–1.1)	
Myeloid	127	0.8 (0.7–0.9)	

TABLE 28 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Farm operators ≥ 35 years of age during study period (June 1971–December 1985)	138	0.9 (0.7–1.0)	Wigle et al., 1990
Sawmill workers in British Columbia—23,829 workers for ≥ 1 year at 11 mills using chlorophenates 1940–1985		**Chlorophenates, not TCDD**	Hertzman et al., 1997
All leukemias—incidence	47	1.2 (0.9–1.5)	
ALL	2	1.0 (0.2–3.1)	
CLL	24	1.7 (1.2–2.4)	
AML	5	0.8 (0.3–1.7)	
CML	7	1.1 (0.5–2.0)	
Other, unspecified	5	0.5 (0.2–1.0)	
DENMARK			
Danish gardeners—incidence from 3,156 male and 859 female gardeners		**Herbicides**	Hansen et al., 2007
25-year followup (1975–2001)	42	1.1 (0.8–1.4)	
Leukemia (ICD-7 204)	22	1.4 (0.9–2.1)	
Born before 1915 (high exposure)	16	1.4 (0.9–2.3)	
Leukemia (ICD-7 204)	12	2.3 (1.3–4.1)	
Born 1915–1934 (medium exposure)	25	1.2 (0.8–1.8)	
Leukemia (ICD-7 204)	9	1.0 (0.5–2.0)	
Born after 1934 (low exposure)	1	0.2 (0.0–1.0)	
Leukemia (ICD-7 204)	1	0.5 (0.0–3.4)	
10-year followup (1975–1984) reported in Hansen et al. (1992)	15	1.4 (0.8–2.4)	
NHL (ICD-7 200, 202, 205)	6	1.7 (0.6–3.8)	
HD (ICD-7 201)	0	nr	
Multiple myeloma (ICD-7 203)	0	nr	
CLL (ICD-7 204.0)	6	2.8 (1.0–6.0)	
Other leukemia (ICD-7 204.1–204.4)	3	1.4 (0.3–4.2)	
10-year followup (1975–1984) of male gardeners			Hansen et al., 1992
All gardeners—CLL	6	2.5 (0.9–5.5)	
Men	6	2.8 (1.0–6.0)	
All gardeners—all other types of leukemia	3	1.2 (0.3–3.6)	
Men	3	1.4 (0.3–4.2)	
Danish Farmers—incidence from linking farmers on 1970 census with national cancer registry (1970–1980)		**Herbicides**	Ronco et al., 1992
Men			
Self-employed	145	0.9 (nr)	
Employee	33	1.0 (nr)	
Women			
Self-employed	8	2.2 ($p < 0.05$)	
Employee	3	1.3 (nr)	
Family worker	27	0.9 (nr)	
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980			
Through 2000	3	1.3 (0.3–3.7)	Swaen et al., 2004
FINNISH Phenoxy Herbicide Sprayers (1,909 men working 1955–1971 ≥ 2 weeks) not IARC		**Phenoxy herbicides**	
Incidence			Asp et al., 1994
Lymphatic	3	1.0 (0.2–3.0)	

continued

TABLE 28 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Mortality	2	nr	
Lymphatic	1	0.9 (0.0–5.1)	
Myeloid	1	0.7 (0.0–3.7)	
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Mortality 1970–1986 (n = 23,401) (ICD-8 202.0–202.9)	27	0.8 (0.5–1.1)	Torchio et al., 1994
Italian rice growers with documented phenoxy use		**Phenoxy herbicides**	Gambini et al., 1997
(n = 1,487)	4	0.6 (0.2–1.6)	
NEW ZEALAND National Cancer Registry (1980–1984)—case-control study of 571 incident pancreatic cancer cases vs remainder of 19,904 men with any incident cancer		**Herbicides**	Reif et al., 1989
Forestry workers (n = 134) (leukemia)	4	1.0 (0.4–2.6)	
Aged 20–59 (AML)	2	2.8 (0.7–11.0)	
Aged ≥ 60 (AML)	1	1.6 (0.2–11.5)	
Sawmill workers (n = 139)		**Herbicides, chlorophenols**	
Leukemia (ICD-7 204–248)	2	0.5 (0.1–2.1)	
AML (ICD-7 205.0)	1	0.9 (0.1–6.4)	
SWEDEN			
Swedish lumberjacks—Used phenoxys 1954–1967, Incidence 1958–1992	0	nr	Thörn et al., 2000
UNITED STATES			
US farmers—usual occupation of farmer and industry of agriculture on death certificates 1984–1988 from 23 states		**Herbicides** PCMRs	Blair et al., 1993
Men			
Whites (n = 119,648)	1,072	1.3 (1.2–1.4)	
Nonwhites (n = 11,446)	55	0.9 (0.7–1.3)	
Women			
Whites (n = 2,400)	24	1.5 (0.9–2.2)	
Nonwhites (n = 2,066)	8	0.9 (0.4–1.9)	
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Enrollment through 2006—SIRs for participants			Koutros et al., 2010a
Private applicators	133	1.0 (0.8–1.1)	
Commercial applicators	7	0.9 (0.4–1.9)	
Spouses	37	0.8 (0.6–1.1)	
Enrollment through 2002			Alavanja et al., 2005
Private applicators	70	0.9 (0.7–1.2)	
Spouses of private applicators (> 99% women)	17	0.7 (0.4–1.2)	
Commercial applicators	4	0.9 (0.3–2.4)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	91	0.9 (0.7–1.0)	
Spouses (n = 676)	33	1.1 (0.8–1.5)	

TABLE 28 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	27	0.8 (0.5–1.1)	
Spouses of private applicators (> 99% women)	14	1.4 (0.8–2.4)	
California United Farm Workers of America			
Nested case-control analysis of Hispanic workers in cohort of 139,000 California United Farm Workers			Mills et al., 2005
Ever used 2,4-D—total leukemia	nr	1.0 (0.4–2.6)	
Lymphocytic leukemia	nr	1.5 (0.3–6.6)	
Granulocytic (myeloid) leukemia	nr	1.3 (0.3–5.4)	
US Department of Agriculture Workers—nested case-control study of white men dying 1970–1979 of NHL		**Herbicides**	
Agricultural extension agents	23	1.9 (1.0–3.5)	Alavanja et al., 1988
Lymphatic	nr	2.1 (0.7–6.4)	
Trend over years worked		($p < 0.01$)	
Myeloid	nr	2.8 (1.1–7.2)	
Trend over years worked		($p < 0.01$)	
White Male Residents of Iowa—leukemia cancer on death certificate, usual occupation: farmers vs not		**Herbicides**	
> 30 years old when died 1964–1978—case-control		1.2 ($p < 0.05$)	Burmeister et al., 1983
ALL	28	0.7 (0.4–1.2)	
CLL	132	1.7 (1.2–2.4)	
Lived in one of 33 counties with highest herbicide use	nr	1.9 (1.2–3.1)	
Unspecified lymphatic	64	1.7 (1.0–2.7)	
AML	86	1.0 (0.8–1.5)	
CML	46	1.0 (0.7–1.7)	
Unspecified myeloid	36	0.8 (0.5–1.4)	
Acute monocytic	10	1.1 (0.4–2.6)	
Unspecified leukemia	31	1.1 (0.6–2.0)	
White Male Residents of Iowa and Minnesota— > 30 years old diagnosed 1981–1983 in Iowa or 1980–1982 in Minnesota (ever farmer, used herbicides)	578	**Herbicides**	Brown et al., 1990
Ever farmed	335	1.2 (1.0–1.5)	
AML	81	1.2 (0.8–1.8)	
CML	27	1.1 (0.6–2.0)	
CLL	156	1.4 (1.1–1.9)	
ALL	7	0.9 (0.3–2.5)	
Myelodysplasias	32	0.8 (0.5–1.4)	
Any herbicide use	157	1.2 (0.9–1.6)	
AML	39	1.3 (0.8–2.0)	
CML	16	1.3 (0.7–2.6)	
CLL	74	1.4 (1.0–2.0)	
ALL	2	0.5 (0.1–2.2)	
Myelodysplasias	10	0.7 (0.3–1.5)	
Phenoxy acid use	120	1.2 (0.9–1.6)	
2,4-D use	98	1.2 (0.9–1.6)	
2,4,5-T use	22	1.3 (0.7–2.2)	
First use > 20 years before	11	1.8 (0.8–4.0)	
MCPA	11	1.9 (0.8–4.3)	
First use > 20 years before	5	2.4 (0.7–8.2)	

continued

TABLE 28 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Incidence—20-year followup to 1996—men and women			
Leukemia (ICD-9 204–208)			Pesatori et al., 2009
Zone A	2	2.2 (0.5–8.8)	
Zone B	8	1.4 (0.7–2.7)	
Zone R	31	0.8 (0.5–2.1)	
Lymphatic leukemia (ICD-9 204)			
Zone A	1	2.8 (0.4–19.9)	
Zone B	0	nr	
Zone R	13	0.8 (0.5–1.5)	
Myeloid leukemia (ICD-9 205)			
Zone A	1	2.2 (0.3–16.0)	
Zone B	7	2.4 (1.1–5.2)	
Zone R	15	0.8 (0.4–1.3)	
Leukemia, unspecified (ICD-9 208)			
Zone A	0	nr	
Zone B	1	2.2 (0.3–16.1)	
Zone R	2	0.6 (0.1–2.6)	
10-year followup to 1991—men			Bertazzi et al., 1993
Zone B	2	1.6 (0.4–6.5)	
Myeloid leukemia (ICD-9 205)	1	2.0 (0.3–14.6)	
Zone R	8	0.9 (0.4–1.9)	
Myeloid leukemia (ICD-9 205)	5	1.4 (0.5–3.8)	
10-year followup to 1991—women			Bertazzi et al., 1993
Zone B	2	1.8 (0.4–7.3)	
Myeloid leukemia (ICD-9 205)	2	3.7 (0.9–15.7)	
Zone R	3	0.4 (0.1–1.2)	
Myeloid leukemia (ICD-9 205)	2	0.5 (0.1–2.1)	
Mortality—25-year followup to 2001 (men and women)			
Leukemia (ICD-9 204–208)			Consonni et al., 2008
Zone A	1	0.9 (0.1–6.3)	
Zone B	13	1.7 (1.0–3.0)	
Zone R	51	1.0 (0.7–1.3)	
Lymphatic leukemia (ICD-9 204)			
Zone A	0	nr	
Zone B	3	1.3 (0.4–4.1)	
Zone R	23	1.4 (0.9–2.2)	
Myeloid leukemia (ICD-9 205)			
Zone A	1	2.1 (0.3–15.2)	
Zone B	6	2.0 (0.9–4.5)	
Zone R	16	0.7 (0.4–1.2)	
Monocytic leukemia (ICD-9 206)	0	nr	
Leukemia, unspecified (ICD-9 208)			
Zone A	0	nr	
Zone B	4	2.4 (0.9–6.5)	
Zone R	10	0.8 (0.4–1.6)	

TABLE 28 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
20-year followup to 1996			Bertazzi et al., 2001
Zones A, B—men	9	2.1 (1.1–4.1)	
Zones A, B—women	3	1.0 (0.3–3.0)	
15-year followup to 1991—men			Bertazzi et al., 1998
Zone B	7	3.1 (1.4–6.7)	
Zone R	12	0.8 (0.4–1.5)	
15-year followup to 1991—women			Bertazzi et al., 1998
Zone B	1	0.6 (0.1–4.0)	
Zone R	12	0.9 (0.5–1.6)	
Chapaevsk, Russia Residential Cohort		**Dioxin**	Revich et al., 2001
Incidence—Crude incidence rate in 1998 vs			
Men			
Regional (Samara)	nr	14.6 (nr)	
National (Russia)	nr	15.2 (nr)	
Women			
Regional (Samara)	nr	13.9 (nr)	
National (Russia)	nr	10.7 (nr)	
Mortality—1995–1998 (SMR vs regional rates)			
Men	11	1.5 (0.8–2.7)	
Women	15	1.5 (0.8–2.4)	
Other International Environmental Studies			
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995a
Incidence			
Lymphocytic			
East coast (higher serum TEQs)	4	1.2 (0.3–3.3)	
West coast (lower serum TEQs)	16	1.3 (0.8–2.2)	
Myeloid			
East coast (higher serum TEQs)	2	0.9 (0.1–3.1)	
West coast (lower serum TEQs)	6	0.5 (0.2–1.1)	
Mortality—all leukemias			
East coast (higher serum TEQs)	5	1.4 (0.5–3.2)	
West coast (lower serum TEQs)	24	1.0 (0.6–1.5)	
CASE-CONTROL STUDIES			
US Case-Control Studies			
1,084 leukemia deaths in Nebraska in 1957–1974; farmers–usual occupation on death certificate		**Herbicides, pesticides** 1.3 ($p < 0.05$)	Blair and White, 1985
99 ALL cases	nr	1.3 (nr)	
248 CLL cases	nr	1.7 ($p < 0.05$)	
105 unspecified lymphatic cases	nr	0.9 (nr)	
235 AML cases	nr	1.2 (nr)	
96 CML cases	nr	1.1 (nr)	
39 unspecified myeloid cases	nr	1.0 (nr)	
39 acute monocytic cases	nr	1.9 (nr)	
52 acute unspecified leukemia cases	nr	2.4 (nr)	
65 unspecified leukemia cases	nr	1.2 (nr)	

continued

TABLE 28 Continued

Study Population[a]	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Tecumseh, Michigan, residents participating in longitudinal study (1959–1987)		**Herbicides**	Waterhouse et al., 1996
All leukemias			
Men	42	1.4 (1.0–1.9)	
Women	32	1.2 (0.9–1.8)	
CLL	10	1.4 (1.0–1.9)	
International Case-Control Studies			
Italian residents of 11 areas (incidence of leukemia excluding CLL)		**Herbicides**	Miligi et al., 2003
Exposure to phenoxy herbicides	6	2.1 (0.7–6.2)	
Italian farming, animal-breeding workers (men and women)—incidence (CLL)	15	**Herbicides** 2.3 (0.9–5.8)	Amadori et al., 1995
Farmers	5	1.6 (0.5–5.2)	
Breeders	10	3.1 (1.1–8.3)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,5-DCP, 2,5-dichlorophenol; ACC, Army Chemical Corps; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; COI, chemical of interest; EOI, Exposure Opportunity Index; HD, Hodgkin disease; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job-exposure matrix; LHC, lymphohematopoietic cancers; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; MOS, military occupation specialty; n, number; NHL, non-Hodgkin lymphoma; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; PCDD, polychlorinated dibenzo-*p*-dioxin (highly chllorinated, if four or more chlorines); PCMR, proportionate cancer mortality ratios; PCP, pentachlorophenol; PM, proportionate mortality; SEA, Southeast Asia; SIR, standardized incidence ratio; SMR, standardized mortality rate; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; TEQ, toxicity equivalent; VA, US Department of Veterans Affairs.

[a]Subjects are male and outcome is mortality unless otherwise noted.

[b]Given when available; results other than estimated risk explained individually.

[c]Lymphopoietic cancers comprise all forms of lymphoma (including Hodgkin lymphoma and non-Hodgkin lymphoma) and leukemia (ALL, AML, CLL, CML).

TABLE 29 Selected Epidemiologic Studies—Male Reproductive Health Outcomes (Altered Hormone Concentrations, Decreased Sperm Counts or Quality, Subfertility, or Infertility) (shaded entries are new to Update 11 [2018])

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
VIETNAM VETERANS			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
AFHS (964 Ranch Hands, 1,259 comparisons)		Coefficient (p-value) for ln(Testosterone) vs ln(TCDD) in 1987	Gupta et al., 2006b
Comparison TCDD quartile I (mean, 2.14 ppt)	nr	0 (referent)	
Comparison TCDD quartile II (mean, 3.54 ppt)	nr	–0.063 (0.004)	
Ranch Hand TCDD quartile I (mean, 4.14 ppt)	nr	0.002 (0.94)	
Comparison TCDD quartile III (mean, 4.74 ppt)	nr	–0.048 (0.03)	
Comparison TCDD quartile IV (mean, 7.87 ppt)	nr	–0.079 (< 0.001)	
Ranch Hand TCDD quartile II (mean, 8.95 ppt)	nr	–0.052 (0.03)	
Ranch Hand TCDD quartile III (mean, 18.40 ppt)	nr	–0.029 (0.22)	
Ranch Hand TCDD quartile IV (mean, 76.16 ppt)	nr	–0.056 (0.02)	
Effects on specific hormone concentrations or sperm count in Ranch Hands			Henriksen et al., 1996
Low testosterone			
High dioxin (1992)	18	1.6 (0.9–2.7)	
High dioxin (1987)	3	0.7 (0.2–2.3)	
Low dioxin (1992)	10	0.9 (0.5–1.8)	
Low dioxin (1987)	10	2.3 (1.1–4.9)	
Background (1992)	9	0.5 (0.3–1.1)	
High FSH			
High dioxin (1992)	8	1.0 (0.5–2.1)	
Low dioxin (1992)	12	1.6 (0.8–3.0)	
Background (1992)	16	1.3 (0.7–2.4)	
High LH			
High dioxin (1992)	5	0.8 (0.3–1.9)	
Low dioxin (1992)	5	0.8 (0.5–3.3)	
Background (1992)	8	0.8 (0.4–1.8)	
Low sperm count			
High dioxin	49	0.9 (0.7–1.2)	
Low dioxin	43	0.8 (0.6–1.0)	
Background	66	0.9 (0.7–1.2)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Detailed description of cohort			CDC, 1989c
Lower sperm concentration	42	2.3 (1.2–4.3)	
Proportion of abnormal sperm	51	1.6 (0.9–2.8)	
Reduced sperm motility	83	1.2 (0.8–1.8)	
US American Legion Cohort		**All COIs**	
American Legionnaires who served in SEA			Stellman SD et al., 1988b
Difficulty in having children	349	1.3 (p < 0.01)	

continued

TABLE 29 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
NIOSH Cross-sectional Medical Study—248 Chemical workers employed at plants in Newark, New Jersey (1951–1969) and Verona, Michigan (1968–1972) vs 231 nonexposed neighborhood referents, measured in 1987		**Dioxins, phenoxy herbicides**	
Testosterone (< 10.4 nmol/L)			Egeland et al., 1994
Referents (TCDD < 20 ppt)	11	1.0	
Workers	25	2.1 (1.0–4.6)	
Quartile I (TCDD < 20 ppt)	2	0.9 (0.2–4.5)	
Quartile II (TCDD 20–75 ppt)	7	3.9 (1.3–11.3)	
Quartile III (TCDD 76–240 ppt)	6	2.7 (0.9–8.2)	
Quartile IV (TCDD 241–3,400 ppt)	10	2.1 (0.8–5.8)	
FSH (> 31 IU/L)	20	1.5 (0.7–3.3)	
LH (> 28 IU/L)	23	1.6 (0.8–3.3)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
Canada—Sawmill Workers in British Columbia; 26,487 workers for ≥ 1 year at 14 mills using chlorophenates 1950–1985		**Chlorophenates, not TCDD**	
Workers having a live-birth within 1 year after the initiation of employment			Heacock et al., 1998
Standard fertility ratio	18,016 (births)	0.7 (0.7–0.8)[c]	
Mantel-Haenszel rate-ratio estimator	18,016 (births)	0.9 (0.8–0.9)[c]	
Cumulative exposure (hours)			
120–1,999	7,139	0.8 (0.8–0.9)[c]	
2,000–3,999	4,582	0.9 (0.8–1.0)[c]	
4,000–9,999	4,145	1.0 (0.9–1.1)[c]	
≥ 10,000	1,300	1.1 (1.0–1.2)[c]	
		($p < 0.01$ overall)	
Denmark—Danish farmers (n = 1,146), 18–50 years of age, who used any potentially spermatotoxic pesticides, including 2,4-D		**Herbicides**	Larsen et al., 1998
Farmers using pesticides vs organic farmers	523	1.0 (0.8–1.4)[b]	
Used three or more pesticides	nr	0.9 (0.7–1.2)[b]	
Used manual sprayer for pesticides	nr	0.8 (0.6–1.1)[b]	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Men exposed in Seveso, Zone A vs age-matched men residing outside the contamination zone, measured semen characteristics, estradiol, FSH, testosterone, LH, inhibin B		Author's evaluation	Mocarelli et al., 2008
Age at 1976 exposure:		(data not shown)	
Infant/prepuberty (1–9 years), n = 71 vs 176		Sensitive	
Puberty (10–17 years), n = 44 vs 136		Intermediate response	
Adult (18–26 years), n = 20 vs 60		No associations	

TABLE 29 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
Other International Environmental Studies			
Spain (Alicante)—Case-control study of adult males at an IVF clinic, cases (n = 56) were men whose semen had at least one alteration in at least one semen quality parameter, controls (n = 26) had semen quality above all WHO, 2010, cut points		Dioxin-like PCBs	Paul et al., 2017
Regression coefficients for statistically significant relationships between COIs and sperm quality		β (p-value)	
mono-ortho PCBs Semen volume (mL)		3566.400 (0.029)	
∑ dioxin-like PCBs		4221.700 (0.025)	
Belgium		**PCBs, dioxin**	
163 men, age < 50 years, BMI ≤ 35, no known congenital, genetic or acquired cause of infertility, recruited through academic fertility clinics			
OR risk of subfertility (total sperm motility counts of < 20 million) for an interquartile range (IQR) increase in exposure or for exposure above LOQ vs exposure below LOQ, adjusted for age, BMI, smoking, ETS exposure and educational level; urinary analyses (urinary phthalate metabolites, BPA and TCS) are additionally adjusted for urinary creatinine; persistent components in serum (chlorinated and brominated compounds) are additionally adjusted for serum lipids			Den Hond et al., 2015
dioxin-like PCBs (pg BEQ/g)		0.45 (0.17–1.22)	
PCDD/F (pg BEQ/g)		1.59 (0.96–2.65)	
Men in general population			
Association with 2-fold increase in CALUX-TEQ		Change (p-value)	Dhooge et al., 2006
Sperm concentration		25.2% (p = 0.07)	
Semen volume		–16.0% (p = 0.03)	
Total testosterone		–7.1% (p = 0.04)	
Free testosterone		–6.8% (p = 0.04)	
Adolescents (17 years of age; males and females) in communities close to sources of heavy metals, PCBs, VOCs, and PAHs—delays in sexual maturity vs peer controls	200	**PCBs, dioxin-like chemicals**	Staessen et al., 2001
In Hoboken, Belgium	8	(p = 0.01)	
In Wilrijk, Belgium	15	(p < 0.0001)	
Russia			
Ufa—PCDD/PCDF levels in the semen of 168 infertile and 49 fertile men living in a city close to a 2,4,5-T manufacturing plant		**PCDD/PCDF**	Galimova et al., 2015
PCDD/PCDF concentration (TEQ, pg/g lipids)		2.2–2.3 increase in infertile donors compared to non-infertile donors	

continued

TABLE 29 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
Russian Children's Study—prospective study of 516 males enrolled at ages 8–9 with annual followups; analyses conducted with specimens collected at ages 18–19 [n = 133]		**PCDD/PCDF** p-trend by quartile of pg TEQ/g lipid	Mínguez-Alarcón et al., 2017
TCDD Volume (mL)		0.55	
TCDD Sperm concentration (million/mL)		0.005	
TCDD Total sperm count (million)		0.05	
TCDD Motile sperm (%)		0.17	
TCDD Total motile sperm count (million)		0.05	
PCDD Volume (mL)		0.89	
PCDD Sperm concentration (million/mL)		0.02	
PCDD Total sperm count (million)		0.04	
PCDD Motile sperm (%)		0.55	
PCDD Total motile sperm count (million)		0.05	
PCDF Volume (mL)		0.48	
PCDF Sperm concentration (million/mL)		0.78	
PCDF Total sperm count (million)		0.82	
PCDF Motile sperm (%)		0.90	
PCDF Total motile sperm count (million)		0.82	
Co-PCB TEQ Volume (mL)		0.89	
Co-PCB TEQ Sperm concentration (million/mL)		0.73	
Co-PCB TEQ Total sperm count (million)		0.88	
Co-PCB TEQ Motile sperm (%)		0.47	
Co-PCB TEQ Total motile sperm count (million)		0.77	
Total TEQ Volume (mL)		0.84	
Total TEQ Sperm concentration (million/mL)		0.61	
Total TEQ Total sperm count (million)		0.68	
Total TEQ Motile sperm (%)		0.99	
Total TEQ Total motile sperm count (million)		0.68	
Poland, Greenland, Ukraine, Sweden men in general population; AHR binding measured with CALUX assay		**dioxin-like activity**	Toft et al., 2007
Measurement of semen quality (concentration, motility, percentage normal)		No consistent associations	
United States			
Male partners (aged 18–51) in subfertile couples seeking infertility evaluations and treatment in Massachusetts General Hospital (01/2000–05/2003)		dioxin-like PCBs	Ferguson et al., 2012
PCB 118 with steroid hormone binding globulin		$\beta = -0.13$, $p < 0.01$	
LIFE Study a prospective cohort study of 501 males, age 18+ years, in a committed relationship, able to communicate in English or Spanish, not medically sterile, and were discontinuing contraception for the purposes of becoming pregnant recruited from 16 counties in Michigan and Texas from 2005–2009			Mumford et al., 2015
Regression coefficients for statistically significant relationships between COIs and sperm quality		β (SE)	
β-HCH Amplitude of lateral head displacement (μm)		0.52 (0.19)	
β-HCH Avg. path velocity (μm s^{-1})		6.19 (1.81)	
β-HCH Curvilinear velocity (μm s^{-1})		9.93 (3.1)	

TABLE 29 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
β-HCH Linearity (%)		6.16 (1.82)	
β-HCH Straightness (%)		9.05 (2.82)	
β-HCH Straight-line velocity (μm s^{-1})		4.98 (1.48)	
β-HCH Cytoplasmic droplet (%)		2.22 (0.85)	
β-HCH High DNA stainability (%)		–2.20 (0.77)	
PCB 118 Sperm head with acrosome (%)		2.33 (0.75)	
PCB 157 Linearity (%)		6.41 (1.91)	
PCB 189b Hypo-osmotic swollen (%)		3.1 (1.19)	
PCB 189b Percent motility (%)		4.82 (1.48)	
CASE-CONTROL STUDIES			
US Case-Control Studies			
Missouri—men with or without low sperm quality (21–40 years of age)		**2,4-D**	Swan et al., 2003
Increased urinary metabolite markers for 2,4-D	5	0.8 (0.2–3.0)	
International Case-Control Studies.			
Argentinean farmers exposed to 2,4-D (n = 32) vs 25 non-exposed controls, March–July 1989		**2,4-D**	Lerda and Rizzi, 1991
Sperm count (millions/mL)	exposed: 49.0 vs control: 101.6		
Motility (%)	exposed: 24.8 vs control: 70.4		
Sperm death (%)	exposed: 82.9 vs control: 37.1[d]		
Anomalies (%)	exposed: 72.9 vs control: 33.4		
Canada—study of erectile dysfunction in urology patients in Ontario		**PCBs/**Highest vs lowest PCB groups	Polsky et al., 2007
PCB-118 (TEF = 0.0001)		1.0 (0.5–2.1)	
PCB-118 (TEF = 0.0001)		0.9 (0.5–1.6)	
PCB-170		0.6 (0.3–1.2)	
PCB-180		0.7 (0.4–1.4)	
Greenland Inuit men (n = 53) and European men (n = 247), DNA sperm integrity among Inuit men.		**persistent organic pollutants**	Krüger et al., 2008
Median % DNA fragmentation index			
Inuits		6.8	
Europeans		12	
Median % DNA stainability			
Inuits		11	
Europeans		8.9	
Korean male waste incinerator workers (n = 6) vs controls (n = 8), dioxin measured by air monitoring		**Phenoxy herbicides**	Oh et al., 2005
Reduced number of sperm (10^6/ml)		(p = 0.050)	
Workers		42.9 ± 18.0	
Controls		56.1 ± 44.5	
DNA damaged sperm (%)		(p = 0.001)	
Workers		1.40 ± 0.08	
Controls		1.26 ± 0.03	
Turkey (Ankara)—Adipose-tissue samples from fertile and infertile men (21–46 years of age) assayed for PCB-118, April 2002–June 2007	21 fertile 25 infertile	**dioxin-like chemicals** 68.8 ng/g lipid 21.7 ng/g lipid (p = 0.003)	Cok et al., 2010

continued

TABLE 29 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
Turkey (Ankara)—Adipose-tissue samples from fertile and infertile men (21–45 years of age) assayed for dioxin, furans, dioxin-like PCBs, June 2003–September 2005		**dioxin-like chemicals**	Cok et al., 2008
	22 fertile	9.4 TEQ pg/g lipid (p = 0.003)	
	23 infertile	12.5 TEQ pg/g lipid (p = 0.065)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; AFHS, Air Force Health Study; AHR, aryl hydrocarbon receptor; β-HCH, β-hexochlorobenzene; BEQ, biologic equivalent; CALUX, assay for determination of dioxin-like activity; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemicals of interest; DNA, deoxyribonucleic acid; ETS, environmental tobacco smoke; FSH, follicle-stimulating hormone; ICD, *International Classification of Diseases*; IU, international unit; IVF, in vitro fertilization; LH, luteinizing hormone; ln, natural logarithm; LOQ, limit of quantification; nr, not reported; PAH, polycyclic aromatic hydrocarbon; PCB, polychlorinated biphenyl; SE, standard error; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEF, toxicity equivalency factor; TEQ, (total) toxic equivalent; VOC, volatile organic compound.

[a]Given when available; results other than estimated risk explained individually.

[b]For this study, relative risk has been replaced with fecundability ratio, for which value less than 1.0 indicates adverse effect.

[c]For this study, relative risk has been replaced with standardized fertility ratio, for which value less than 1.0 indicates adverse effect.

[d]Table 1 in reference reverses these figures—control, 82.9%; exposed, 37.1%—but text ("The percentages of asthenospermia, mobility, necrosperma and teratospermia were greater in the exposed group than in controls. . .") suggests that this is a typographical error.

TABLE 30 Selected Epidemiologic Studies—Endometriosis (shaded entries are new to Update 11 [2018])

Study Population	Study Results	Reference
ENVIRONMENTAL		
United States		
Case-control study of women in Atlanta, Georgia, with endometriosis; 60 cases and 64 controls	Results for cases vs controls: Total TEQ (determined by GC/MS): OR = 01.0 (95% CI 0.9–1.1)	Niskar et al., 2009
International		
Belgium		
88 matched triads (264 total); patients with deep endometriotic nodules, pelvic endometriosis, controls matched for age, gynecologic practice in Belgium; routes of exposure to DLCs examined	Results for pelvic endometriosis vs controls: Dietary fat: OR = 1.0 (95% CI 1.0–1.0) BMI: OR = 1.0 (95% CI 0.9–1.0) Occupation: OR = 0.5 (95% CI 0.2–1.1) Traffic: OR = 1.0 (95% CI 0.3–2.8) Incinerator: OR = 1.0 (95% CI 1.0–1.1)	Heilier et al., 2007
Serum dioxin-like compound and aromatase activity in endometriotic tissue from 47 patients in Belgium	No association between TEQs (determined by GC/MS) of DLCs in serum and aromatase activity by regression analyses p-values = 0.37–0.90 for different endometriosis subgroups	Heilier et al., 2006
Endometriosis in Belgian women with overnight fasting serum levels of PCDD, PCDF, PCB	50 exposed cases, risk of increase of 10 pg/g lipid of TEQ compounds (determined by GC/MS); OR = 2.6 (95% CI 1.3–5.3)	Heilier et al., 2005
Belgian women with environmental exposure to PCDDs, PCDFs; compared analyte concentrations in cases vs controls	Mean concentration of TEQ (determined by GC/MS) Cases (n = 10), 26.2 (95% CI 18.2–37.7) Controls (n = 132), 25.6 (95% CI 24.3–28.9) No significant difference	Fierens et al., 2003a
Patients undergoing infertility treatment in Belgium; compared number of women with, without endometriosis who had serum dioxin levels up to 100 pg TEQ/g of serum lipid (determined by CALUX bioassay)	Six exposed cases: OR = 4.6 (95% CI 0.5–43.6)	Pauwels et al., 2001
France		
Case-control of internal exposure to persistent organic pollutants and deep infiltrating endometriosis; adipose tissue and serum samples were collected from surgically confirmed cases (n = 55) and controls (n = 44) enrolled during 2013 and 2015 in Pays de la Loire, France	Statistically significant associations between deep infiltrating endometriosis and adipose tissue levels of four mono-ortho dioxin-like PCBs were observed: • PCB 105 (aOR 2.09 [1.24–3.77]) • PCB 114 (1.89 [1.04–3.69]) • PCB 118 (2.30 [1.31–4.36]) • PCB 123 (2.47 [1.42–4.66])	Ploteau et al., 2017
Italy		
Case-control study of Italian women with endometriosis; 80 cases and 78 controls (TEQs determined by CALUX bioassay)	Results for endometriosis vs controls: dioxin-like PCB 118 compared to ≤ 13.2 ng/g: 13.3–24.2 ng/g; OR = 3.17 (95% CI 1.36–7.37) ≥ 24.3 ng/g; OR = 3.79 (95% CI 1.61–8.91) Total TEQ compared to ≤ 15.6 pgC-TEQ/g fat: 15.7–29.5 pgC-TEQs/g fat; OR = 0.52 (95% CI 0.18–1.48) ≥ 29.6 pgC-TEQ/g fat; OR = 0.73 (95% CI 0.26–2.01)	Porpora et al., 2009
Case-control study of Italian women with endometriosis, measured serum PCBs	Mean total PCBs (ng/g) Cases, 410 ng/g Control, 250 ng/g All PCB congeners: OR = 4.0 (95% CI 1.3–13)	Porpora et al., 2006

continued

TABLE 30 Continued

Study Population	Study Results	Reference
Pilot study of Italian and Belgian women of reproductive age; compared concentrations of TCDD, total TEQ (determined by GC/MS) in pooled blood samples from women who had diagnosis endometriosis with controls	Mean concentration of TCDD (ppt of lipid): Italy: Controls (10 pooled samples), 1.6 Cases (two sets of 6 pooled samples), 2.1, 1.3 Belgium: Controls (7 pooled samples), 2.5 Cases (Set I, 5 pooled samples; Set II, 6 pooled samples), 2.3, 2.3 Mean concentration of TEQ (ppt of lipid): Italy: Controls (10 pooled samples), 8.9 ± 1.3 (99% CI 7.2–11.0) Cases (two sets of 6 pooled samples), 10.7 ± 1.6; 10.1 ± 1.5 Belgium: Controls (7 pooled samples), 24.7 ± 3.7 (99% CI 20–29) Cases (Set I, 5 pooled samples; Set II, 6 pooled samples), 18.1 ± 2.7; 27.1 ± 4.0	De Felip et al., 2004
Residents of Seveso Zones A and B up to 30 years old in 1976; population-based historical cohort comparing incidence of endometriosis across serum TCDD concentrations	Serum TCDD (ppt): ≤ 20 (n = 2 cases), RR = 1.0 (reference) 20.1–100, (n = 8), RR = 1.2 (90% CI 0.3–4.5) > 100, (n = 9), RR = 2.1 (90% CI 0.5–8.0)	Eskenazi et al., 2002b
Spain		
Case control study of deep infiltrating endometriosis (n = 30) compared to controls undergoing laparoscopic surgery for benign adnexal gynecological diseases.	2,3,7,8-TCDD TEQ pg/g lipid OR = 1.41 (95% CI 1.12–2.10) p < 0.01 1,2,3,7,8-PeCDD TEQ pg/g lipid OR = 1.82 (1.36–7.14) p < 0.01	Martínez-Zamora et al., 2015
Israel		
Residents of Jerusalem being evaluated for infertility; compared number of women with high TCDD who had (n = 44), did not have (n = 35) diagnosis of endometriosis	8 exposed cases: OR = 7.6 (95% CI 0.9–169.7)	Mayani et al., 1997
Japan		
17 women undergoing diagnostic laparoscopy for infertility, 10 were found to have endometriosis and 7 did not	TEQ calculated for each person based on PCDDs, PCDFs, and 12 dioxin-like PCBs; no difference in lipid-adjusted exposure levels between those with and without endometriosis. Association was seen with endometriosis and women with high PCDD and PCDF (OR = 2.5, 95% CI 1.2–5.3)	Cai et al., 2011
138 infertility patients in Japan; laparoscopically confirmed case-control status, serum dioxin, PCB TEQ (determined by GC/MS); P450 genetic polymorphism	Results for advanced endometriosis: Total TEQ: OR = 0.5 (95% CI 0.2–1.7) Genotype-specific: ORs = 0.3–0.6 No significant interaction between genotype, dioxin TEQ	Tsuchiya et al., 2007

NOTE: BMI, body mass index; CALUX, chemical activated luciferase gene expression; CI, confidence interval; GC/MS, gas chromatography/mass spectrometry; OR, odds ratio; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDF, polychlorinated dibenzofuran; RR, relative risk or risk ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEQ, (total) toxic equivalent.

TABLE 31 Other Female Reproductive Outcomes (Altered Hormone Concentrations, Subfertility, or Infertility) (shaded entries are new to Update 11 [2018])

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
UNITED STATES			
US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395; 97.4% men), and spouses of private sprayers (n = 32,347; 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
8,038 premenopausal women aged 30–55 at enrollment			Farr et al., 2006
Pesticide exposure	5,013	0.9 (0.8–1.0)	
Herbicide exposure	3,725	0.9 (0.7–1.1)	
Phenoxy herbicide exposure	1,379	0.9 (0.7–1.1)	
Menstrual-cycle characteristics of 3,103 premenopausal women aged 21–40			Farr et al., 2004
Reported at enrollment had used herbicides	1,291		
Short menstrual cycle		0.6 (0.4–1.0)	
Long menstrual cycle		1.0 (0.5–2.0)	
Irregular		0.6 (0.3–0.9)	
Missed period		1.4 (1.0–2.0)	
Intermenstrual bleeding		1.1 (0.8–1.7)	
ENVIRONMENTAL			
Vietnam—Exposed group (n = 37) mother-child pairs from near the former US air base at Bien Hoa, where known accidental releases of Agent Orange took place; Control group (n = 47 control pairs) from a rural community in northern Vietnam—where no US spraying took place		**TCDD**	Anh et al., 2017
		Hot spot vs Control	
Maternal serum androstenedione (ng/ml)	37	1.91 ± 1.00 vs 0.61 ± 0.27 $p < 0.001$	
Child saliva dehydroepiandrosterone (DHEA) (ng/ml)	37	0.13 ± 0.08 vs 0.04 ± 0.02 $p < 0.001$	
Seveso (Italy) Women's Health Study—Industrial accident July 10, 1976; 981 women between infancy and 40 years of age at the time of the accident, who resided in Zones A and B		**TCDD**	
Time to pregnancy and infertility in women from Zones A and B who attempted pregnancy after 1976			Eskenazi et al., 2010
20-year followup to 1996—men and women			
Time to pregnancy (adjusted fecundability OR)			
Log_{10} TCDD	278	0.8 (0.6–1.0)	
Categorical TCDD (ppt)			
≤ 20	52	1.0 (reference)	
20.1–44.4	76	0.8 (0.5–1.3)	
44.5–100	75	0.7 (0.5–1.1)	
> 100	75	0.6 (0.4–1.0)	

continued

TABLE 31 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
Infertility (adjusted OR)			
Log_{10} TCDD	49	1.9 (1.1–3.2)	
Categorical TCDD (ppt)			
≤ 20	6	1.0 (reference)	
20.1–44.4	9	1.1 (0.4–3.6)	
44.5–100	16	2.5 (0.8–7.3)	
> 100	18	2.8 (1.0–8.1)	
Fibroids among women from Zones A and B who were newborn to age 40 in 1976			Eskenazi et al., 2007
Uterine fibroids (age-adjusted HR)			
Log_{10} TCDD (ppt)	251	0.8 (0.7–1.1)	
Categorical TCDD (ppt)			
≤ 20	62	1.0 (reference)	
20.1–75.0	110	0.6 (0.4–0.8)	
> 75	79	0.6 (0.4–0.9)	
Ovarian function in women from Zones A and B who were newborn to age 40 in 1976; results are for a 10-fold increase in serum TCDD			Warner at al., 2007
Ovarian follicles (age-adjusted OR):			
in follicular phase	65	1.0 (0.4–2.2)	
Ovulation (age-adjusted OR):			
in luteal phase	87	1.0 (0.5–1.9)	
in midluteal phase	55	1.0 (0.4–2.7)	
Estradiol (age-adjusted ß):		slopes for log TCDD	
in luteal phase	87	–1.8 (–10.4–6.8)	
in midluteal phase	55	–3.1 (–14.1–7.8)	
Progesterone (age-adjusted ß):			
in luteal phase	87	–0.7 (–2.4–1.0)	
in midluteal phase	55	–0.8 (–3.7–2.0)	
Age at menopause in women from Zones A and B who were newborn to age 40 in 1976			Eskenazi et al., 2005
Onset of natural menopause (unadjusted HR)			
Log_{10} TCDD	169	1.0 (0.8–1.3)	
Menopause Category		Serum TCDD median (IQR)	
Premenopause	260	43.6 (0.2–0.9)	
Natural menopause	169	45.8 (0.3–1.0)	
Surgical menopause	83	43.4 (0.3–1.0)	
Impending menopause	13	43.8 (0.2–1.1)	
Perimenopause	33	36.5 (0.2–0.9)	
Other	58	39.6 (0.2–0.9)	
Age at menarche in women from Zones A and B who were premenarcheal in 1976	282	1.0 (0.8–1.1)	Warner et al., 2004
All premenarcheal women in 1976 (unadjusted HR)			
Log_{10} TCDD	282	1.0 (0.8–1.1)	
Women < 8 years in 1976 (unadjusted HR)			
Log_{10} TCDD	158	1.1 (0.9–1.3)	

TABLE 31 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
Menstrual cycle characteristics in women from Zones A and B who were premenopausal, less than age 44, and not recently pregnant, breastfeeding, or using hormonal medications			Eskenazi et al., 2002a
Menstrual cycle length (adjusted ß)			
Log_{10} TCDD	277	0.4 (–0.1–0.9)	
Premenarcheal at explosion		0.9 (0.0–1.9)	
Postmenarcheal at explosion		0.0 (–0.6–0.5)	
Days of menstrual flow (adjusted ß)			
Log_{10} TCDD	301	0.2 (–0.1–0.4)	
Premenarcheal at explosion		0.2 (–0.2–0.5)	
Postmenarcheal at explosion		0.2 (–0.2–0.5)	
Heaviness of flow (scanty vs moderate/heavy; adjusted OR)			
Log_{10} TCDD	30	0.8 (0.4–1.6)	
Premenarcheal at explosion		0.3 (0.1–1.1)	
Postmenarcheal at explosion		1.4 (0.7–2.6)	
Irregular cycle (vs regular; adjusted OR)			
Log_{10} TCDD	24	0.5 (0.2–1.0)	
Premenarcheal at explosion		0.5 (0.2–1.4)	
Postmenarcheal at explosion		0.4 (0.2–1.2)	
Other International Environmental Studies			
Sweden (Uppsala County) POPUP study cross sectional study of randomly selected pregnant women. 1996–1999 325 pregnant women non-fasting blood samples in early (first trimester, week 6–12) and late (third trimester, week 32–34) pregnancy		**Dioxin-like PCBs**	Lignell et al., 2016
di-ortho PCB	219	β, mean ± standard error	
Total triiodo-thyronine (T3)		–0.15 ± 0.06	
Free thyroxine (T4)		0.04 ± 0.25	
Thyroid stimulating hormone (TSH)		0.08 ± 0.15	
Antibodies to thyroid peroxidase (anti-TPO)		0.013 ± 0.063	
mono-ortho PCB TEQ	219	β, mean ± standard error	
Total T3		–0.15 ± 0.06	
Free T4		0.16 ± 0.22	
TSH		0.07 ± 0.14	
anti-TPO		–0.0096 ± 0.055	
Greece (Crete) gestational diabetes mellitus (GDM) in 1st trimester (24–28 weeks) pregnancies; maternal serum levels of ∑ dioxin-like PCBs measured (n = 939; 63 with GDM)		**Dioxin-like PCBs**	Vafeiadi et al., 2017
aOR GDM "medium" (middle) tertile of dioxin-like PCBs		5.63 (1.81–17.51)	
aOR GDM high tertile dioxin-like PCBs		4.71 (1.38–16.01)	
Taiwanese pregnant women (18–40 years of age); placental TEQ concentrations of TCDDs, TCDFs, PCBs		**Dioxin**/Regression adjusted for maternal age, BMI, parity	Chao et al., 2007
Older of "regular menstrual cycle"			
Dioxin TEQ		p = 0.032	
PCB TEQ		p = 0.077	

continued

TABLE 31 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
Longer "longest menstrual cycle"			
Dioxin TEQ		p = 0.269	
PCB TEQ		p = 0.006	
CASE-CONTROL STUDIES			
US Case-Control Studies			
Cedars Sinai Medical Center, Los Angeles, California, PCOS case-patients (diagnosed using the National Institutes of Health 1990 definition, n = 52) and 50 controls were recruited in 2007–2008		**PCBs**	Vagi et al., 2014
		Geo Mean pg/g serum Cases vs Controls	
Serum PCBs			
PCB 105		3.8 vs 3.8	
PCB 118		15.6 vs 15.6	
PCB 156		4.3 vs 5.4	
Women in Wisconsin with or without infertility (maternal exposure)—incidence		**Phenoxy herbicides**	Greenlee et al., 2003
Mixed or applied herbicides	21	2.3 (0.9–6.1)	
Used 2,4,5-T	9	9 cases (2.7%) 11 controls (3.4%)	
Used 2,4-D	4	4 cases (1.2%) 4 controls (1.2%)	
Chinese Case-Control Studies			
PCOS cases (n = 169) and controls (n = 338) were recruited from Chengdu, China		**Pesticides**	Zhang et al., 2014
OR reported exposure and PCOS			
Pesticide		1.76 (1.09–2.87)	
Eating fruit with pericarp		5.00 (2.67–9.48)	
PCOS cases (n = 50) and controls (n = 30) were recruited in 2012 from a hospital in Northern China. All participants were ethnic Han		**PCBs**	Yang et al., 2015
OR serum PCBs above median associated with PCOS, wet-weight data adjusted for triglycerides and total cholesterol levels, age, education, and occupation			
PCB 105		4.79 (1.33–17.3)	
PCB 118		5.97 (1.62–22.1)	
PCB 156		2.93 (0.85–10.1)	
PCB 157		2.01 (0.66–6.11)	
PCB 167		2.00 (0.63–6.33)	
∑dioxin-like PCBs		5.52 (1.51–20.2)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; AFHS, Air Force Health Study; BMI, body mass index; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; HR, hazard ratio; IARC, International Agency for Research on Cancer; IQR, inter-quartile range; OR, odds ratio; PCB, polychlorinated biphenyl; PCOS, polycystic ovary syndrome; ppt, parts per trillion; TCDD, 2,3,7,8–tetrachlorodibenzo-*p*-dioxin; TCDF, tetrachlorodibenzofuran; TEQ, (total) toxic equivalent.

[a]Given when available; results other than estimated risk explained individually.

TABLE 32 Selected Epidemiologic Studies—Spontaneous Abortion[a]

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs Southeast Asia veterans (unless otherwise noted)		**All COIs**	
Air Force Ranch Hand veterans	157		Wolfe et al., 1995
Background	57	1.1 (0.8–1.5)	
Low exposure	56	1.3 (1.0–1.7)	
High exposure	44	1.0 (0.7–1.3)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Overall	1,566	1.3 (1.2–1.4)	CDC, 1989c
Self-reported low exposure	489	1.2 (1.0–1.4)	
Self-reported medium exposure	406	1.4 (1.2–1.6)	
Self-reported high exposure	113	1.7 (1.3–2.1)	
US VA Cohort of Female Vietnam Veterans		**All COIs**	
Female Vietnam-era veterans (maternal exposure)		1.0 (0.82–1.21)	Kang et al., 2000a
Vietnam veterans (1,665 pregnancies)	278	nr	
Vietnam-era veterans who did not serve in Vietnam (1,912 pregnancies)	317	nr	
US National Vietnam Veterans		**All COIs**	
Female Vietnam veterans (maternal exposure)			Schwartz, 1998
Women who served in Vietnam	113	nr	
Women who did not serve in the war zone	124	nr	
Civilian women	86	nr	
US American Legion Cohort		**All COIs**	
American Legionnaires with service 1961–1975			Stellman SD et al., 1988b
Vietnam veterans vs Vietnam-era veterans			
All Vietnam veterans	231	1.4 (1.1–1.6)	
Low exposure	72	1.3 (1.0–1.7)	
Medium exposure	53	1.5 (1.1–2.1)	
High exposure	58	1.7 (1.2–2.4)	
Vietnam-era veterans vs herbicide handlers	9	1.6 (0.7–3.3)	
Vietnam veterans			
Low exposure	72	1.0	
Medium exposure	53	1.2 (0.8–1.7)	
High exposure	58	1.4 (0.9–1.9)	
State Studies of US Vietnam Veterans			
Massachusetts—Wives of Vietnam veterans presenting at Boston Hospital for Women			Aschengrau and Monson, 1989
27 weeks of gestation	10	0.9 (0.4–1.9)	
13 weeks of gestation	nr	1.2 (0.6–2.8)	
International Vietnam Veterans Studies			
Tasmanian Veterans with Service in Vietnam		**All COIs**	
Followup of Australian Vietnam veterans	199	1.6 (1.3–2.0)	Field and Kerr, 1988

continued

TABLE 32 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates		**Dioxins, phenoxy herbicides**	
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Wives and partners of men in NIOSH cohort			Schnorr et al., 2001
Estimated paternal TCDD serum at time of conception			
< 20 ppt	29	0.8 (0.5–1.2)	
20 to < 255 ppt	11	0.8 (0.4–1.6)	
255 to < 1,120 ppt	11	0.7 (0.3–1.6)	
≥ 1,120 ppt	8	1.0 (0.4–2.2)	
Dow Workers with Potential TCDD Exposure and reproductive outcomes studied in offspring of 930 men working with chlorophenol, 1939–1975		**Dioxins, phenoxy herbicides**	Townsend et al., 1982
Wives of men employed involved in chlorophenol processing at Dow Chemical Co.	85	1.0 (0.8–1.4)	
Monsanto workers in Nitro, West Virginia occupationally exposed and potentially exposed after 1949 explosion (1948–1969)		**Dioxins, phenoxy herbicides**	
Followup of current and retired 2,4,5-T production workers (n = 235; 117 with chloracne exposure), 1948–1969	14	0.9 (0.4–1.8)	Moses et al., 1984
Followup of 2,4,5-T production workers (204 exposed, 163 unexposed), 1948–1969	69	0.9 (0.6–1.2)	Suskind and Hertzberg, 1984
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
New Zealand—Followup of 2,4,5-T sprayers vs nonsprayers (n = 989)	43	**Herbicides** 90% CI 0.9 (0.6–1.3)	Smith et al., 1982
US Forest Service		**Herbicides**	
Women employed by US Forest Service—miscarriages (maternal exposure)	141	2.0 (1.1–3.5)	Driscoll et al., 1998
ENVIRONMENTAL			
Seveso (Italy) Women's Health Study—Industrial accident July 10, 1976; 981 women between infancy and 40 years of age at the time of the accident, who resided in Zones A, B)		**TCDD**	
SWHS—30 year updated analysis of pregnancy outcomes			Wesselink et al., 2014
10-fold increase in TCDD level at time of accident	160	0.8 (0.6–1.0)	
Effects on first birth after explosion	75	0.8 (0.6–1.2)	
SWHS participants living in zones A, B in 1976 (maternal exposure)			Eskenazi et al., 2003a
Pregnancies 1976–1998	97	0.8 (0.6–1.2)	
Pregnancies 1976–1984	44	1.0 (0.6–1.6)	

TABLE 32 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Ecological Study of Residents of Chapaevsk, Russia		**TCDD**	
Residents of Samara Region, Russia (maternal and paternal exposure)			Revich et al., 2001
Chapaevsk	nr	24.4% (20.0–29.5%)[c]	
Samara	nr	15.2% (14.3–16.1%)[c]	
Toliatti	nr	10.6% (9.8–11.5%)[c]	
Syzran	nr	15.6% (13.4–18.1%)[c]	
Novokuibyshevsk	nr	16.9% (14.0–20.3%)[c]	
Other small towns	nr	11.3% (9.4–13.8%)[c]	
Ontario Farm Family Health Study		**Phenoxy herbicides**	
Ontario farm families (maternal, paternal exposures)			Arbuckle et al., 2001
Phenoxyacetic acid herbicide exposure in preconception period, spontaneous-abortion risk	48	1.5 (1.1–2.1)	
Other International Environmental Studies			
Japan—Spontaneous abortions among pregnancies (excluding induced abortions) of women in 1968 Yusho incident (maternal exposure)		**PCBs, PCDFs**	Tsukimori et al., 2008
10 years after vs 10 years before	nr	2.1 (0.8–5.2)	
10-fold increase in maternal blood concentration (drawn 2001–2005) of:			
PeCDF	nr	1.6 (1.1–2.3)	
PCB 126 (TEF = 0.1)	nr	2.5 (0.9–6.9)	
PCB 169 (TEF = 0.01)	nr	2.3 (1.1–4.8)	
Taiwanese pregnant women (18–40 years of age); placental TEQ concentrations of PCDDs, PCDFs, PCBs		**PCDD, PCBs** nr, but reported ns	Chao et al., 2007
Vietnamese women who were or whose husbands were exposed to herbicides sprayed during Vietnam War	nr	**COIs**/nr, anecdotal reports of miscarriage in pilot study	Tuyet and Johansson, 2001
CASE-CONTROL STUDIES			
US Case-Control Studies			
Washington, Oregon—wives of men occupationally exposed to 2,4-D; all reported work exposure to herbicides (high and medium)	63	**2,4-D** 90% CI 0.8 (0.6–1.1)	Carmelli et al., 1981
Farm exposure	32	0.7 (0.4–1.5)	
Forest and commercial exposure	31	0.9 (0.6–1.4)	
Exposure during conception period			
Farm exposure	15	1.0 (0.5–1.8)	
Forest and commercial exposure	16	1.6 (0.9–1.8)	
Fathers 18–25 years old			
Farm exposure	1	0.7 (nr)	
Forest and commercial exposure	3	4.3 (nr)	

continued

TABLE 32 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Fathers 26–30 years old			
Farm exposure	4	0.4 (nr)	
Forest and commercial exposure	8	1.6 (nr)	
Fathers 31–35 years old			
Farm exposure	10	2.9 (nr)	
Forest and commercial exposure	5	1.0 (nr)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; IARC, International Agency for Research on Cancer; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; ns, not significant (usually refers to $p < 0.05$); PCB, polychlorinated biphenyl; PCDF, polychlorinated dibenzofuran; PeCDF, 2,3,4,7,8-pentachlorodibenzofuran; SWHS, Seveso Women's Health Study; TCDD, 2,3,7,8–tetrachlorodibenzo-*p*-dioxin; TEF, toxic equivalency factor; TEQ, (total) toxic equivalent; VA, US Department of Veterans Affairs.

[a]Unless otherwise indicated, results are for paternal exposure.

[b]Given when available; results other than estimated risk explained individually.

[c]Spontaneous abortion rate per 100 full-term pregnancies for 1991–1997.

TABLE 33 Selected Epidemiologic Studies—Sex Ratio[a] (shaded entry is new to Update 11 [2018])

Study Population	Sex Ratio of Offspring (boys/total)[b]	Comments	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)			
Births from service through 1993 in AFHS			Michalek et al., 1998a
Comparison group	0.504	Not formally analyzed	
Dioxin level in Ranch Hand personnel			
Background	0.502		
Low	0.487		
High	0.535		
OCCUPATIONAL—INDUSTRIAL			
NIOSH Cross-Sectional Study			
Workers producing trichlorophenol and derivatives, including 2,4,5-T		No difference on basis of age at first exposure	Schnorr et al., 2001
Serum TCDD in fathers			
Neighborhood controls (< 20 ppt)	0.544	Referent	
Working fathers			
< 20 ppt	0.507	None significantly decreased (or increased)	
20–255 ppt	0.567		
255– < 1,120 ppt	0.568		
≥ 1,120 ppt	0.550		
Other Studies of Industrial Workers (not related to NIOSH phenoxy cohort)			
Austrian chloracne cohort—157 men, 2 women; exposed to TCDD during 2,4,5-T production			Moshammer and Neuberger, 2000
Children born after starting TCDD exposure in 1971	0.464 (26 boys: 30 girls)	Fewer sons, especially if father was under 20 years old when exposed: SR = 0.20 (1 boy: 4 girls)	
Children born before 1971	0.613 (19 boys: 12 girls)		
Russian workers manufacturing 2,4,5-trichlorophenol (1961–1988) or 2,4,5-T (1964–1967)			Ryan et al., 2002
Either parent exposed	0.401 (91 boys: 136 girls)	$p < 0.001$	
Only father exposed	0.378 (71 boys: 117 girls)	$p < 0.001$	
Only mother exposed	0.513 (20 boys: 19 girls)	ns	
New Zealand—Phenoxy herbicide producers exposed to 2,3,7,8 TCDD. 127 men and 21 women reported that 355 children were conceived after starting employment at the plant	0.55 (197 boys, 158 girls)	OR (95% CI)	't Mannetje et al., 2017
Fathers with serum TCDD concentrations ≥ 20 pg/g lipid at time of birth	0.47	0.49 (0.30–0.79)	
< 4 pg/g lipid	0.60	1.00 (referent)	
4–20 pg/g lipid	0.62	1.00 (0.50–2.02)	
20–100 pg/g lipid	0.47	0.52 (0.29–0.92)	
≥ 100 pg/g lipid	0.46	0.45 (0.23–0.89)	

continued

TABLE 33 Continued

Study Population	Sex Ratio of Offspring (boys/total)[b]	Comments	Reference
OCCUPATIONAL—PAPER AND PULP WORKERS			
Canada—British Columbian sawmill workers (n = 26,487)			Heacock et al., 1998
Chlorophenate-exposed workers	0.515		
Nonexposed workers	0.519		
Province overall	0.512		
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
Canadian OFFHS fathers' exposure during 3 months before conception:			Savitz et al., 1997
No chemical activity	0.503	referent	
Crop herbicides (some phenoxy herbicides)	0.500	ns	
Protective equipment used not used	0.510	ns	
No protective equipment	0.450	ns	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group)			
Births 1994–2005 in women 0–28 years old at time of Seveso accident			Baccarelli et al., 2008
Zone A	0.571		
Zone B	0.508		
Zone R	0.495		
Births 1977–1996 in people from Zones A, B, R, 3–45 years old at time of 1976 Seveso accident	0.514	referent	Mocarelli et al., 2000
Neither parent exposed	0.608	ns	
Father exposed (whether or not mother exposed)	0.440	p = 0.03	
Father under 19 years old in 1976	0.382	p = 0.002	
Father at least 19 years old in 1976	0.469	ns	
Only mother exposed	0.545	ns	
Parent (either sex) from Seveso Zone A			Mocarelli et al., 1996
Births 1977–1984	0.351 (26 boys: 48 girls)	p < 0.001, related to parental TCDD serum	
Births 1985–1994	0.484 (60 boys: 64 girls)	ns	
Ecological Study of Residents of Chapaevsk, Russia			
Residents near chemical plant in operation 1967–1987 in Chapaevsk, Russia			Revich et al., 2001
1983–1997	0.507	No clear pattern	
Minimum in 1989	0.401		
Maximum in 1987	0.564		
Maximum in 1995	0.559		
Other International Environmental Studies			
JAPAN—Yusho incident			
Parents (one or both) exposed to PCBs, PCDFs (not TCDD) in 1968			Yoshimura et al., 2001
All Japan in 1967	0.513	referent	
Births 1967 (before poisoning incident)	0.516	ns	
Births 1968–1971 (after incident)	0.574	ns	

TABLE 33 Continued

Study Population	Sex Ratio of Offspring (boys/total)[b]	Comments	Reference
Births 1968–2009			Tsukimori et al., 2012b
Father exposed (whether or not mother exposed)	0.505	p = 0.74	
Father under 20 years old in 1967	0.465	p = 0.15	
Mother exposed (whether or not father exposed)	0.501	p = 0.62	
Mother under 20 years old in 1967	0.450	p = 0.06	
TAIWAN			
Taiwanese pregnant women (18–40 years of age); placental TEQ concentrations of TCDDs, TCDFs, PCBs	nr	No association	Chao et al., 2007
Births in individuals exposed to PCBs, PCDFs, PCDDs in 1979 **Yucheng incident**		vs unexposed with same demographics	del Rio Gomez et al., 2002
Father exposed (whether or not mother exposed)	0.490	p = 0.037	
Father under 20 years old in 1979	0.458	p = 0.020	
Father at least 20 years old in 1979	0.541	p = 0.60	
Mother exposed (whether or not father exposed)	0.504	p = 0.45	
Mother under 20 years old in 1979	0.501	p = 0.16	
Mother at least 20 years old in 1979	0.500	p = 0.40	
UNITED STATES			
San Francisco Bay area—serum concentrations in pregnant women during 1960s	OR for male birth (not SR)		Hertz-Picciotto et al., 2008
90th percentile vs 10th percentile		SRs all < 0.5	
Total PCBs	0.4 (0.3–0.8)	p = 0.007	
dioxin-like PCBs			
PCB 105	0.6 (0.4–0.9)	p = 0.02	
PCB 118	0.7 (0.5–1.2)	p = 0.17	
PCB 170	0.6 (0.4–0.9)	p = 0.02	
PCB 180	0.8 (0.5–1.2)	p = 0.32	
Births after 1963 to Michigan fish-eaters with serum PCBs in both parents			Karmaus et al., 2002
Paternal PCBs > 8.1 μg/L	0.571	p < 0.05 (but for *more* sons)	
Maternal PCBs > 8.1 μg/L	0.494	ns	

NOTE: 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; AFHS, Air Force Health Study; IARC, International Agency for Research on Cancer; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; ns, not significant; OFFHS, Ontario Farm Family Health Study; OR, odds ratio; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzodioxin; PCDF, polychlorinated dibenzofurans; ppt, parts per trillion; SR, sex ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCDF, tetrachlorodibenzofuran; TEQ, (total) toxic equivalent.

[a]*VAO* reports before *Update 1998* did not address association between perturbations in sex ratio of offspring and exposure to chemicals of interest.

[b]Given when available.

TABLE 34 Selected Epidemiologic Studies—Birth Weight Following Paternal Exposure (shaded entry is new to Update 11 [2018])

Primary Exposure	Sample Size	Outcome/Main Findings	Adjustment Covariates	Reference
VIETNAM VETERANS				
US Air Force Health Study—Ranch Hand veterans vs SEA veterans; births from service through 1993 in AFHS				
Ranch Hands	2,082 births	No association with IUGR	Adjusted by stratification for father's race, mother smoking during pregnancy, mother's alcohol use, mother's age, father's age, father's military occupation	Michalek et al., 1998d
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed				
Military service in VA	1,771 Vietnam; 1,561 non-Vietnam	LBW/RR 1.1 (0.8–1.4)	Maternal age and gravidity. Also model with smoking history, alcohol use, educational attainment, marital status, illicit drug use in military	CDC, 1989b,c
US American Legion Cohort—American Legionnaires with service 1961–1975				
US men deployed to SEA during Vietnam War, and other deployed men during same time period	2,858 in SEA 3,933 deployed elsewhere (n = 6,081)	"no difference between the birth weight of boys born to servicemen stationed in SEA compared to those born to controls, nor did girls' birth weight differ between two groups"	Sex, age of father at time of child's birth, age of mother, mother smoking during pregnancy, military service in SEA and exposure to combat and AO—these were not multivariate adjusted models, so strong smoking effect might have had an influence. These appear to have all been independent models	Stellman SD et al., 1988b
Tasmanian Veterans with Service in Vietnam—Followup of Australian Vietnam veterans				
Military service in Vietnam	~550	LBW/RR 1.6 (1.0–2.5)	RR calculated by committee member	Field and Kerr, 1988
OCCUPATIONAL—INDUSTRIAL				
Wives of chemical workers highly exposed to TCDD- contaminated chemicals	~500 exposed 600 referents	No association with birth weight overall	Adjusted for sex, education, parity, smoking, length of gestation, no stratification by sex	Lawson et al., 2004
OCCUPATIONAL—HERBICIDE-USING WORKERS				
Chlorophenate, wood preservative in sawmill industry	19,675 births	No association (ORs for SGA ~1)	Sex, maternal and paternal age, birth year, matching	Dimich-Ward et al., 1996

TABLE 34 Continued

Primary Exposure	Sample Size	Outcome/Main Findings	Adjustment Covariates	Reference
ENVIRONMENTAL—UNITED STATES				
Paternal serum concentrations of PCBs measured before conception for 234 couples living in Michigan and Texas (LIFE cohort)	Girls (n = 117) Boys (n = 113)	β-change per 1 SD increase in paternal serum concentration of PCB-167– Girls: –97.49g (–187.45, –7.54) Boys: –38.24g (–139.86, 63.37)	Maternal and paternal serum lipids, serum cotinine, maternal prepregnancy BMI (kg/m^2), maternal age, difference in parental age, infant sex, and the individual and partner sum of remaining chemical concentrations in each chemical's respective class	Robledo et al., 2015

NOTE: AFHS, Air Force Health Study; AO, Agent Orange; BMI, body mass index; CDC, Centers for Disease Control and Prevention; IUGR, intrauterine growth restriction; LBW, low birth weight; OR, odds ratio; RR, relative risk; SD, standard deviation; SEA, Southeast Asia; SGA, small for gestational age; TCDD, 2,3,7,8-trichlorodibenzo-*p*-dioxin; VA, US Department of Veterans Affairs; VES, Vietnam Experience Study.

TABLE 35 Selected Epidemiologic Studies—Birth Weight Following Maternal Exposure (shaded entries are new information for Update 11 [2018])

Primary Exposure	Sample Size	Outcome/Main Findings	Adjustment Covariates	Reference
VIETNAM VETERANS				
US VA Cohort of Female Vietnam Veterans				
Military Service	2,689	BW girls = +0.5 oz BW boys = –0.8 oz (Difference in boys comes to –22.7 g)	Unadjusted differences and major uncontrolled confounders (smoking, parity, race)	H. Kang, personal correspondence, February 27, 2013
Military Service	4,140	LBW (OR = 1.06, 95% CI 0.8–1.5)	Maternal age, education, race, marital status, military characteristics, smoking, drinking, average number of hours worked during pregnancy, complications during pregnancy	Kang et al., 2000a
ENVIRONMENTAL				
International Studies				
Mother–child pairs from four European cohorts	967	BW decreased with increased dioxin measured in cord blood	Country, gestational age, gestational age squared, parity, maternal prepregnancy BMI, gender	Vafeiadi et al., 2014a
Japan				
Yusho, Japan—population exposed to PCDDs, PCDFs, and PCBs in contaminated cooking oil	190	~ –200g birth weight reduction with PCDD TEQ (p = 0.003) in males, also overall effect but driven by effect in boys	Gestational age, maternal age, parity, smoking, duration breastfeeding, seafood consumption	Kuratsune et al., 1972; Tsukimori et al., 2012a
Hokkaido Study on Environment and Children's Health, Sapporo, Japan; contemporary cohort	514	BW (–220.5 g per 10-fold increase in TEQ, 95% CI –399.2 to –41.9); effect driven by males	Gestational age, maternal age, maternal height, maternal weight before pregnancy, parity, smoking, inshore fish intake, blood sampling period, infant sex	Konishi et al., 2009
Hokkaido Study on Environment and Children's Health, Sapporo, Japan	421	Mothers with a glutathione S-transferase mu 1 (*GSTM1*) null genotype –345g (95% CI: –584, –105) BW for each 10-fold increase in total dioxin TEQ	Maternal age, height, and weight before pregnancy, caffeine intake, alcohol consumption during pregnancy, smoking status during pregnancy, parity, educational level, annual household income, inshore fish intake during pregnancy, deep-sea fish intake during pregnancy, and blood sampling period	Kobayashi et al., 2017
Hokkaido Study on Environment and Children's Health	367 women-child pairs	Prenatal exposure to PCBs measured in blood collected during third trimester of pregnancy was not associated with anthropometric measurements at birth	Hair Hg, demographic characteristics, socioeconomic status, and maternal level of long-chain polyunsaturated fatty acids	Miyashita et al., 2015
Coastal Japan; contemporary cohort	75	Some weak negative correlations	Unadjusted; Spearman correlations	Tawara et al., 2009

TABLE 35 Continued

Primary Exposure	Sample Size	Outcome/Main Findings	Adjustment Covariates	Reference
Breast milk dioxin levels	42	Negative correlation for TEQ-PCDD and TEQ, PCDF, but not "significant"	Spearman correlations	Nishijo et al., 2008
Finland				
Random sampling of mother–infant pairs from urban/rural Finland	167	BW decreased with increasing concentrations of I-TEQ, especially among boys	Unadjusted; effect goes away when restricted to primiparas	Vartiainin et al., 1998
Italy				
Seveso Women's Health Study—30-year updated analysis	807	Small inverse relationship with LBW	Gestational age, maternal height, pre-explosion history of LBW, year of pregnancy, parity, maternal age	Eskenazi et al., 2003a; Wesselink et al., 2014
Seveso Residential Cohort	51	No association with LBW	None	Baccarelli et al., 2008
Netherlands				
Dutch children—PCB 118 exposure (only total)	207	BW = –119 (53.7); p = 0.03	Smoking, alcohol, gestational age, target height, parity	Patandin et al., 1998
Norway				
NewGeneris cohort—Maternal dietary intake of dioxins and PCBs	604	BW decreased with increased dioxin-like compounds in diet; only significant in boys	Maternal educational level, energy, maternal age, prepregnancy BMI, parity, smoking during pregnancy country	Papadopoulou et al., 2014
Norwegian Mother and Child Cohort Study—Maternal dietary intake of dioxins and PCBs	50,651	BW decreased with increased dioxin-like compounds in diet	Maternal age, energy intake, maternal education, prepregnancy BMI, parity, weight gain and smoking during pregnancy, gestational age, child's gender	Papadopoulou et al., 2013a
United States				
California Child Health and Human Development Study	600	No association with birth weight	Race, age, smoking status, BMI, sex, length of gestation, lipids	Kezios et al., 2012
Cord blood in Massachusetts infants (1993–1998)—PCB 118	722	Negative birth weight effects with increasing exposure quartile, non-significant—0, –18, –72, –69.5	Gestational age, infant size, birth year, maternal age, race parity, height, prepregnancy BMI, smoking, local fish consumption	Sagiv et al., 2007
Times Beach and Quail Run cohorts—TCDD Soil contamination in Missouri	Matched sets, ~400 (2:1)	LBW: 1.5 (95% CI 0.2–2.3)	Sex, maternal education, parity, marital status, prepregnancy weight, smoking, history of previous SAB and fetal deaths	Stockbauer et al., 1988
Maternal serum concentrations of PCBs measured before conception for 234 couples living in Michigan and Texas (LIFE cohort)	Girls (n = 117) Boys (n = 113)	β-change in birthweight for 1 SD increase in serum concentration of PCB-167– Girls: –61.69g (–172.52, 49.15) Boys: –129.24 (–228.16, –30.31)	Maternal and paternal serum lipids, serum cotinine, maternal prepregnancy BMI (kg/m2), maternal age, difference in parental age, infant sex, and the individual and partner sum of remaining chemical concentrations in each chemical's respective class	Robledo et al., 2015

continued

TABLE 35 Continued

Primary Exposure	Sample Size	Outcome/Main Findings	Adjustment Covariates	Reference
Vietnam				
People living around contaminated airbase	210	At birth no effect, but birth weight discrepancy grows with months from delivery. Significant at 4 months. Effect only seen in boys	Parity, maternal age, weight, educational period, alcohol use, family income, family smoking, gestational weeks, infant age on the day of examination	Nishijo et al., 2012
People living near a contaminated airbase	58 mother-infant pairs from contaminated region 62 mother-infant pairs non-contaminated region	BW inversely correlated with 2,3,7,8-TeCDD and 2,3,4,7,8-PeCDF congener levels. Proportion of newborns with a BW < 2500 g was threefold higher in the hotspot (12%) than in the control region (4%)		Van Tung et al., 2016

NOTE: BMI, body mass index; BW, birth weight; CI, confidence interval; I-TEQ, International (total) toxic equivalent; LBW, low birth weight; OR, odds ratio; PCB, polychlorinated biphenyls; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDF, polychlorinated dibenzofurans; SAB, spontaneous abortion; SGA, small for gestational age; TCDD, 2,3,7,8-trichlorodibenzo-*p*-dioxin; TEQ, (total) toxic equivalent; VA, US Department of Veterans Affairs.

TABLE 36 Selected Epidemiologic Studies—Birth Defects in Offspring of Subjects[a] (shaded entries are new information for Update 11 [2018])

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Verified birth defects in children born to AFHS veterans			Michalek et al., 1998a
Before service in SEA	nr	0.7 (nr)	
After service in SEA	nr	1.5 (nr)	
High-exposure Ranch Hands relative to comparisons			Wolfe et al.,1995
All anomalies	57	1.0 (0.8–1.3)	
Nervous system	3	nr	
Eye	3	1.6 (0.4–6.0)	
Ear, face, neck	5	1.7 (0.6–4.7)	
Circulatory system, heart	4	0.9 (0.3–2.7)	
Respiratory system	2	nr	
Digestive system	5	0.8 (0.3–2.0)	
Genital system	6	1.2 (0.5–3.0)	
Urinary system	7	2.1 (0.8–5.4)	
Musculoskeletal	31	0.9 (0.6–1.2)	
Skin	3	0.5 (0.2–1.7)	
Chromosomal anomalies	1	nr	
CDC Birth Defects Study—Hospital records reviewed for offspring of 7,924 Vietnam veterans and 7,364 non-Vietnam veterans		**All COIs**	
General Birth Defects Study—hospital records	130	1.0 (0.8–1.3)	CDC, 1989a
Major birth defects	51	1.2 (0.8–1.9)	
Digestive system defects	18	2.0 (0.9–4.6)	
Birth defects—black Vietnam veterans only	21	3.4 (1.5–7.6)	
Vietnam veterans identified through CDC Metropolitan Atlanta Congenital Defects Program			Erikson et al., 1984a,b
Any major birth defects	428	1.0 (0.8–1.1)	
Multiple birth defects with reported exposure	25	1.1 (0.7–1.7)	
EOI-5: spina bifida	1	2.7 (1.2–6.2)	
EOI-5: cleft lip with or without cleft palate	5	2.2 (1.0–4.9)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Reproductive outcomes—interview data			CDC, 1989b
Total anomalies	826	1.3 (1.2–1.4)	
Nervous system defects	33	2.3 (1.2–4.5)	
Ear, face, neck defects	37	1.6 (0.9–2.8)	
Integument	41	2.2 (1.2–4.0)	
Musculoskeletal defects	426	1.2 (1.1–1.5)	
Hydrocephalus	11	5.1 (1.1–23.1)	
Spina bifida	9	1.7 (0.6–5.0)	
Hypospadias	10	3.1 (0.9–11.3)	
Multiple defects	71	1.6 (1.1–2.5)	
Children of veterans reporting high exposure	46	1.7 (1.2–2.4)	

continued

TABLE 36 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
US VA Cohort of Female Vietnam Veterans		**All COIs**	
Female Vietnam-era veterans—deployed vs nondeployed (maternal exposure)			Kang et al., 2000a
"Likely" birth defects	nr	1.7 (1.2–2.2)	
"Moderate-to-severe" birth defects	nr	1.5 (1.1–2.0)	
State Studies of US Vietnam Veterans			
Massachusetts Vietnam-era veterans		**All COIs**	
Vietnam veterans whose children were born at Boston Hospital for Women			Aschengrau and Monson, 1990
All congenital anomalies (crude OR)			
vs men without known military service	55	1.3 (0.9–1.9)	
vs non-Vietnam veterans	55	1.2 (0.8–1.9)	
One or more major malformations (crude OR)			
vs men without known military service	18	1.8 (1.0–3.1)	
vs non-Vietnam veterans	18	1.3 (0.7–2.4)	
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Validation Study		*Expected number of exposed cases*	AIHW, 1999
Down syndrome	67	92 expected (73–111)	
Tracheo-esophageal fistula	10	23 expected (14–32)	
Anencephaly	13	16 expected (8–24)	
Cleft lip or palate	94	64 expected (48–80)	
Absent external body part	22	34 expected (23–45)	
Extra body part	74	74 expected (nr)	
Vietnam veterans vs all other men	127	1.0 (0.8–1.3)	Donovan et al., 1984
National Service veterans—Vietnam service vs no Vietnam service	69	1.3 (0.9–2.0)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Wives of workers with measured serum TCDD in NIOSH cohort	14	nr	Lawson et al., 2004
Dow Workers with Potential TCDD Exposure and reproductive outcomes in offspring of 930 men working with chlorophenol 1939–1975	30	0.9 (0.5–1.4)	Townsend et al., 1982
Monsanto workers in Nitro, West Virginia occupationally exposed and potentially exposed after 1949 explosion (1948–1969)		**Dioxins, phenoxy herbicides**	
Followup of current and retired 2,4,5-T production workers (n = 235; 117 with chloracne exposure), 1948–1969	11	1.3 (0.5–3.4)	Moses et al., 1984
Followup of 2,4,5-T production workers (204 exposed, 163 unexposed), 1948–1969	18	1.1 (0.5–2.2)	Suskind and Hertzberg, 1984

TABLE 36 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
Canada—Pregnancies with one or more birth defects in OFFHS	108	**Herbicides**	Weselak et al., 2008
Use on farm, during 3 months before conception, of:			
Herbicides	24	0.7 (0.4–1.1)	
Male offspring	19	0.9 (0.5–1.6)	
Direct paternal use	19	0.5 (0.3–1.0)	
Phenoxy herbicides	12	0.6 (0.3–1.1)	
Male offspring	9	0.8 (0.4–1.7)	
Direct paternal use	8	0.4 (0.2–0.9)	
2,4-D	10	1.1 (0.6–2.1)	
Male offspring	7	1.3 (0.6–2.8)	
Direct paternal use	6	0.6 (0.3–1.5)	
Dicamba	8	1.7 (0.8–3.5)	
Male offspring	7	2.4 (1.1–5.5)	
Use on farm, during 3 months after conception, of:			
Herbicides	7	0.5 (0.2–1.2)	
Phenoxy herbicides	9	0.8 (0.4–1.5)	
2,4-D	7	1.0 (0.4–2.3)	
Canadian sawmill workers with exposure in upper three quartiles for any job held up to 3 months before conception			Dimich-Ward et al., 1996
Cataracts	11	5.7 (1.4–22.6)	
Genital organs	105	1.3 (0.9–1.5)	
New Zealand—Followup of 2,4,5-T sprayers vs nonsprayers (n = 989)		**Herbicides** 90% CI	Smith et al., 1982
	13	1.2 (0.6–2.5)	
Norway—farmers (maternal, paternal exposure)	4,189	1.0 (1.0–1.1)	Kristensen et al., 1997
United States—Minnesota private pesticide appliers		**Pesticides**	Garry et al., 1996
All births with anomalies	125	1.4 (1.2–1.7)	
Circulatory, respiratory	17	1.7 (1.0–2.8)	
Gastrointestinal	6	1.7 (0.8–3.8)	
Urogenital	20	1.7 (1.1–2.6)	
Musculoskeletal, integumental	30		
Maternal age under 30 years	11	0.9 (0.5–1.7)	
Maternal age over 30 years	19	2.5 (1.6–4.0)	
Chromosomal	8	1.1 (0.5–2.1)	
Other	48		
Maternal age under 35 years	36	1.1 (0.8–1.6)	
Maternal age over 35 years	12	3.0 (1.6–5.3)	
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group)		**TCDD**	
Maternal, paternal, in utero exposure		90% CI	Mastroiacovo et al., 1988
Zones A, B, R—total defects	137	1.0 (0.8–1.1)	
Zones A and B—total defects	27	1.2 (0.9–1.6)	
Zones A and B—mild defects	14	1.4 (0.9–2.2)	

continued

TABLE 36 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Ecological Study of Residents of Chapaevsk, Russia		**Dioxin**	Revich et al., 2001
Congenital malformations	nr	nr, but ns	
Times Beach/Quail Run Cohorts		**Dioxin**	
Persons in Missouri with documented TCDD soil contamination near residence (maternal, paternal, in utero exposure)		**TCDD**	Stockbauer et al., 1988
Total birth defects	17	0.8 (0.4–1.5)	
Major defects	15	0.8 (0.4–1.7)	
Midline defects	4	0.7 (0.2–2.3)	
Other International Environmental Studies			
France—Case-control study (2001–2003 births) of urinary tract defects (n = 304) vs regional controls (n = 226) (Same population as Cordier et al., 2004)		**Dioxin**	Cordier et al., 2010
Maternal exposure to:			
Atmospheric dioxin	63	2.0 (1.2–3.4)	
Above median	33	2.8 (1.3–6.1)	
Below median	30	1.4 (0.7–2.9)	
Dioxin deposits	75	1.8 (1.1–3.0)	
Above median	41	3.0 (1.5–5.9)	
Below median	34	1.2 (0.6–2.2)	
France—Births (1988–1997): maternal residence in municipality with solid-waste incinerator vs not		**Dioxin**	Cordier et al., 2004
Minor anomalies	518	0.9 (0.8–1.1)	
Chromosomal anomalies	204	1.0 (0.9–1.2)	
Monogenic anomalies	83	1.1 (0.8–1.4)	
Unknown or multhyifactoral etiology	964	1.1 (1.0–1.2)	
Specific major anomalies with significant increases reported (of 23 categories reported)			
Facial clefts	152	1.3 (1.1–1.6)	
Renal dysplasia	60	1.6 (1.1–2.2)	
Turkey—Cross-sectional study of MIH in Turkey; n = 109 from industrialized community with high levels of PCDDs and n = 44 from low industrialized community		**PCDDs** Prevalence of MIH 4/44 and 10/109, no difference	Kuscu et al., 2009
United States—Rural or farm residents of Minnesota, Montana, North Dakota, South Dakota (maternal, paternal exposure)		**2,4-D, MCPA**	Schreinemachers, 2003
Any birth anomaly	213	1.1 (0.9–1.3)	
Central nervous system anomalies	12	0.8 (0.5–1.4)	
Circulatory, respiratory anomalies	39	1.7 (1.1–2.6)	
Digestive system anomalies	24	0.9 (0.6–1.5)	
Urogenital anomalies	44	1.0 (0.7–1.5)	
Musculoskeletal, integumental anomalies	70	1.5 (1.1–2.1)	
Chromosomal anomalies	17	0.9 (0.6–1.6)	
United States—Persons exposed to an electric-transformer fire in Binghamton, New York—total birth defects (maternal, paternal exposure)	1	**Chlorophenols** 2.1 (0.1–11.9)	Fitzgerald et al., 1989

TABLE 36 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
United States—National Birth Defects Prevention Study, 1997–2002			Rocheleau et al., 2015
		High herbicide and insecticide	
Isolated congenital heart defect	26	1.90 (1.05–3.44)	
Pulmonary valve stenosis,	5	3.64 (1.31–10.15)	
Right ventricular outflow tract obstruction	7	3.40 (1.41–8.16)	
hypoplastic left heart syndrome without ventricular septal defect or anomalous pulmonary venous return	4	5.11 (1.70–15.35)	
CASE-CONTROL STUDIES			
US Case-Control Studies			
Indiana—ecologic study of the relationship between pesticide exposure and use and hypertrophic pyloric stenosis (HPS) identified by the Indiana Birth Defects Registry from 2005–2009		**Pesticides in general; herbicides**	Markel et al., 2015
Total pesticide levels in county of residence		r = 0.029, p = 0.004	
Herbicide use		r = 0.029, p = 0.005	
North Carolina—Case-control study drawn from a cohort of geocoded singleton livebirths (n = 335,729) 2003–2005. Cases = 6,358, controls = 298,548		**Pesticide**	Rappozzo et al., 2016
Atrial Septal Defect			
90th percentile and above	nr	1.70 (1.34–2.14)	
Patent Ductus Arteriosus			
90th percentile and above	nr	1.50 (1.22–1.85)	
Arkansas—hypospadias as function of mother's residence within 500 m of agricultural pesticide use during gestation weeks 6–16		**Dicamba**	Meyer et al., 2006
Dicamba (lb)			
0	nr	1.0	
> 0– < 0.04	nr	0.5 (0.3–1.0)	
≥ 0.04	nr	0.9 (0.4–2.1)	
California—San Joaquin Valley, California. Cases (n = 193) were born 1997–2006 with gastroschisis confirmed by clinical geneticists. Controls (n = 974) comprised nonmalformed live-born infants randomly selected from birth hospitals in the study area		**2,4-D dimethylamine salt**	Shaw et al., 2014
OR association of pesticide exposure with gastroschisis adjusted for race/ethnicity, prepregnancy body mass index, any use of folic acid containing supplements, and smoking during the month before and the first 2 months of pregnancy	8	1.7 (0.7–4.1)	
California—San Joaquin Valley, California. Cases (n = 367) were born 1997–2006 with anotia/microtia, anorectal atresia/stenosis, transverse limb deficiency, craniosynostosis, or diaphragmatic hernia. Controls (n = 785) comprised nonmalformed live-born infants randomly selected from birth hospitals in the study area		**Dichlorophenoxy acid or ester**	Carmichael et al., 2016
Transverse limb deficiency	7	2.5 (1.1–6.0)	
Anotia/microtia	12	3.4 (1.6–7.6)	

continued

TABLE 36 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
California—US National Birth Defects Prevention Study (8 counties in San Joaquin Valley), residential proximity to agricultural pesticide applications during early pregnancy (785 controls)		**2,4-D**	
Atrial septal defect (n = 132 cases)	14	2.3 (1.2–4.5)	Carmichael et al., 2014
Pulmonary valve stenosis (n = 53 cases)	6	2.9 (1.0–7.9)	
Anencephaly (n = 73 cases)	7	2.0 (0.8–5.1)	Yang et al., 2014
Cleft palate (n = 117 cases)	4	nr	
Cleft lip and palate (n = 277 cases)	16	1.1 (0.6–2.1)	
Spina bifida (n = 123 cases)	4	nr	
Gastroschisis (n = 156 cases)	11	1.6 (0.8–3.2)	Shaw et al., 2014
Hypospadias and maternal occupational herbicide exposure; JEM to determine exposure from conception through first trimester of pregnancy (647 cases vs 1,496 controls)		**Herbicides**	Rocheleau et al., 2011b
Second- or third-degree hypospadias	178	1.0 (0.5–2.1)	
California—Hypospadias and residential proximity to commercial pesticide applications (690 cases, 2,195 controls)	5	**2,4-D** 2.1 (0.8–5.6)	Carmichael et al., 2013
Maryland—Baltimore mothers in the BWIS exposed to herbicides during first trimester (maternal exposure)	8	**Herbicides** 2.8 (1.2–6.9)	Loffredo et al., 2001
International Case-Control Studies			
Denmark—Hospital diagnosis of cryptorchidism and farming.		**Pesticides/herbicides** HR	Jorgensen et al., 2014
Maternal farming	157	1.31 (1.12–1.53)	
Maternal horticultural worker	72	1.20 (0.95–1.52)	
Paternal farmers	742	1.04 (0.96–1.12)	
Paternal horticultural worker	72	1.20 (0.96–1.51)	
Denmark/Finland—Relationship between congenital cryptorchidism and PCBs and dioxins in adipose tissue (14 samples)		**Dioxins**	Koskenniemi et al., 2015
OR for relationship between cryptorchidism and POP exposure after adjustment for the country of origin, age at operation and the duration of breastfeeding,			
total-TEQ		3.2 (1.3–9.1)	
∑ PCDD/Fs		3.7 (1.5–10.9)	
∑ PCBs		1.9 (0.9–4.0)	
∑ PBDEs		0.86 (0.47–1.54)	
Denmark/Finland—Relationship between congenital cryptorchidism and PCBs and dioxins in breast milk (130 samples)		**Dioxin, PCBs** ns	Krysiak-Baltyn et al., 2012
Denmark/Finland—Relationship between congenital cryptorchidism and PCBs and dioxins in placentas; 112 Finnish subjects (56 cases, 56 controls) and 168 Danish subjects (39 cases, 129 controls)		**Dioxin, PCBs** ns	Virtanen et al., 2012
Finland—Followup of participants from previous case-control study of cleft lip and palate, n = 167 placenta tissue analyzed for PCDD/Fs and children assessed for MIH		**PCDDs, PCDFs** 24/167 with MIH TEQ of PCDDs not association with MIH; duration of breast feeding not association with MIH	Laisi et al., 2008

TABLE 36 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Japan—Investigated multiple pregnancy outcomes in Japan-infant deaths from congenital defects	42	**Dioxin** nr, but ns	Tango et al., 2004
Guam—Village-level estimates of alleged Agent Orange exposure and infant mortality due to congenital anomalies		**Agent Orange**	Noel et al., 2015
Regression coefficient for agent orange spraying and mortality from congenital anomalies		2.02 (0.08, 3.96)	
New Zealand—Residents of areas subject to aerial 2,4,5-T spraying		**2,4,5-T** 90% CI	Hanify et al., 1981
All birth malformations excluding dislocated or dislocatable hip	164	1.7 (1.4–2.1)	
All heart malformations	20	3.9 (2.1–7.4)	
Hypospadias, epispadias	18	5.6 (2.7–11.7)	
Talipes	52	1.7 (1.2–2.3)	
Cleft lip	6	0.6 (0.3–1.3)	
Isolated cleft palate	7	1.4 (0.6–3.2)	
Spain—Residents of agricultural areas—at least median score on chlorophenoxy-herbicide exposure duration (months) index	14	**Herbicides** 3.1 (0.6–16.9)	García et al., 1998
Brazil—Hospital-based case-control study. Cases (n = 137) were children age < 5 years with a congenital malformation. Controls (n = 274) were age matched children diagnosed with other conditions			Ueker et al., 2016
Living close to crop spraying with pesticides		1.61 (0.88–3.03)	
Pesticide use at work		1.52 (0.65–3.53)	
Paternal application of pesticides		2.75 (1.05–7.19)	
France—Case-control study comprised 408 boys with isolated hypospadias and 302 controls identified at multiple institutions in the south of France between 2009 and 2014			Kalfa et al., 2015
Maternal exposure to herbicides		1.00 (0.007–13.97)	
The Netherlands—Infants born in Zeeburg, Amsterdam, clinics 1963–1965 with orofacial cleft (maternal exposure)		**Dioxin**	ten Tusscher et al., 2000
Births in 1963	5	nr, but said to be significant	
Births in 1964	7	nr, but said to be significant	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; AFHS, Air Force Health Study; aOR, adjusted odds ratio; BWIS, Baltimore–Washington Infant Study; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; JEM, job-exposure matrix; IARC, International Agency for Research on Cancer; MCPA, 4-chloro-2-methylphenoxyacetic acid; MIH, molar incisor hypomineralization; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; ns, not significant; OFFHS, Ontario Farm Family Health Study; OR, odds ratio; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzodioxins; PCDF, polychlorinated dibenzofurans; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEQ, (total) toxic equivalent; VA, US Department of Veterans Affairs.

[a]Unless otherwise indicated, studies show paternal exposure.

[b]Given when available; results other than estimated risk explained individually.

TABLE 37 Selected Epidemiologic Studies—Neural-Tube Defects in Offspring of Subjects[a] (shaded entries are new information for Update 11 [2018])

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Air Force Operation Ranch Hand personnel—neural-tube defects	4[c]	nr	Wolfe et al., 1995
CDC Birth Defects Study—Hospital records reviewed for offspring of 7,924 Vietnam veterans and 7,364 non-Vietnam veterans		**All COIs**	
Vietnam veterans identified through CDC Metropolitan Atlanta Congenital Defects Program			Erickson et al., 1984a,b
Service in Vietnam			
Spina bifida	19	1.1 (0.6–1.7)	
Anencephaly	12	0.9 (0.5–1.7)	
Military records indicate opportunity for exposure			
Spina bifida	20	2.7 (1.2–6.2)	
Anencephaly	7	0.7 (0.2–2.8)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
VES cohort—reproductive outcomes			CDC, 1989a
Spina bifida			
Vietnam veterans' children	9	1.7 (0.6–5.0)	
Non-Vietnam veterans' children	5	1.0	
Anencephaly			
Vietnam veterans' children	3	nr	
Non-Vietnam veterans' children	0	1.0	
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Validation Study		*Expected number of exposed cases*	AIHW, 1999
Spina bifida—maximums	50	33 (22–44)	
Anencephaly	13	16 (8–24)	
Australian Vietnam veterans—neural-tube defects		**All COIs**	ADVA, 1983
	16	0.9 (nr)	
OCCUPATIONAL—HERBICIDE-USING WORKERS			
Norwegian farmers—spina bifida (maternal, paternal exposures)		**Herbicides**	Kristensen et al., 1997
Tractor spraying equipment	28	1.6 (0.9–2.7)	
Tractor spraying equipment, orchards, greenhouses[d]	5	2.8 (1.1–7.1)	
United States—birth defects in children born to licensed pesticide appliers in Minnesota linked to state birth registries		**Herbicides, pesticides**	Garry et al., 1996
Central nervous system defects	6	1.1 (0.5–2.4)	
ENVIRONMENTAL			
Times Beach/Quail Run Cohorts		**Dioxin**	
Persons in Missouri with documented TCDD soil contamination near residence (maternal, paternal, in utero exposure)		**TCDD**	Stockbauer et al., 1988
Central nervous system defects	3	3.0 (0.3–35.9)	

TABLE 37 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Other International Environmental Studies			
France—Population-based birth defects registry in Rhône-Alpes region (1988–1997): maternal residence in municipality with solid-waste incinerator vs not	49	**Dioxin** 0.9 (0.6–1.2)	Cordier et al., 2004
CASE-CONTROL STUDIES			
Canada—British Columbian sawmill workers with exposure in upper three quartiles for any job held up to 3 months before conception		**Herbicides**	Dimich-Ward et al., 1996
Spina bifida, anencephaly	22	2.4 (1.1–5.3)	
Spina bifida only	18	1.8 (0.8–4.1)	
New Zealand—Residents of areas subject to aerial 2,4,5-T spraying		**2,4,5-T** 90% CI	Hanify et al., 1981
Anencephaly	10	1.4 (0.7–2.9)	
Spina bifida	13	1.1 (0.6–2.1)	
The Netherlands—Children of Dutch farmers who were born with spina bifida (1980–1992), 470 cases vs 456 healthy controls		**Herbicides, pesticides**	Blatter et al., 1997
Spina bifida—moderate, heavy exposure			
Pesticide use	8	1.7 (0.7–4.0)	
Herbicide use	7	1.6 (0.6–4.0)[e]	
US National Birth Defects Prevention Study—California (8 counties in San Joaquin Valley), residential proximity to agricultural pesticide applications during early pregnancy (785 controls)		**2,4-D**	Yang et al., 2014
Anencephaly (n = 73 cases)	7	2.0 (0.8–5.1)	
Spina Bifida (n = 123 cases)	4	nr	
		Insecticides and herbicides	Makelarski et al., 2014
Spina Bifida (n = 310 cases)	14	2.1 (1.0–4.1)	
		Insecticides, herbicides and fungicides	Pettigrew et al., 2014
Spina Bifida (n = 291 cases)	10	0.8 (0.4–1.5)	
		Herbicides, adjusted for other pesticides	
Spina Bifida (n = 291 cases)	15	0.6 (0.3–125)	

NOTE: 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; nr, not reported; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VES, Vietnam Experience Study.

[a]Unless otherwise indicated, studies show paternal exposure.

[b]Given when available; results other than estimated risk explained individually.

[c]Of four neural-tube defects reported in Ranch Hand offspring, two were spina bifida (high dioxin exposure), one spina bifida (low dioxin), one anencephaly (low dioxin); no neural-tube defects reported in comparison cohort; 454 postservice births studied in Ranch Hand veterans; 570 in comparison cohort.

[d]Greenhouse workers would not have been exposed to chemicals of interest.

[e]Calculated from data presented in the paper.

TABLE 38 Selected Epidemiologic Studies—Childhood Cancer[a] (shaded entries are new information for Update 11 [2018])

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
Intergroup Rhabdomyosarcoma Study—Cases (n = 319) and population-based controls (n = 319) were matched on race, sex, and age; ORs adjusted for race, sex, age, family income, father's education and recreational drug use, length of pregnancy, and maternal spotting/bleeding/ cramping during pregnancy		**All COIs**	Grufferman et al., 2014
Maternal military service	10	2.75 (0.71–10.62)	
Paternal military service	93	0.85 (0.58–1.25)	
Paternal service during 1962–1970	53	0.78 (0.50–1.21)	
Reported potential wartime exposure to herbicides	9	1.72 (0.55–5.41)	
CDC Birth Defects Study—Hospital records reviewed for offspring of 7,924 Vietnam veterans and 7,364 non-Vietnam veterans		**All COIs**	
Vietnam veterans identified through CDC Metropolitan Atlanta Congenital Defects Program			Erickson et al., 1984b
"Other" neoplasms	87	1.8 (1.0–3.3)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
VES cohort—reproductive outcomes			CDC, 1988a
Cancer	25	1.5 (0.7–2.8)	
Leukemia	12	1.6 (0.6–4.0)	
US veterans—case-control study of children's leukemia			Wen et al., 2000
AML, ALL			
Father ever served in Vietnam, Cambodia	117	1.2 (0.9–1.6)	
< 1 year in Vietnam or Cambodia	61	1.4 (0.9–2.0)	
> 1 year in Vietnam or Cambodia	49	1.2 (0.8–1.7)	
AML only			
Father ever served in Vietnam, Cambodia	40	1.7 (1.0–2.9)	
< 1 year in Vietnam or Cambodia	13	2.4 (1.1–5.4)	
> 1 year in Vietnam or Cambodia	16	1.5 (0.7–3.2)	
International Vietnam Veteran Studies			
Australian Vietnam Veterans' children—revised validation study		**All COIs**	
AML	12[c]	1.3 (0.8–4.0)	ADVA, 2005b
Australian Vietnam veterans' children—validation study—AML			*AIHW, 2000*
This study, which incorrectly calculated expected number of AML cases, is updated by AIHW, 2001 above			
Tasmanian Veterans with Service in Vietnam		**All COIs**	
Cancer in children of Australian Vietnam veterans	4	nr	Field and Kerr, 1988

TABLE 38 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
OCCUPATIONAL—HERBICIDE-USING WORKERS			
France, Germany, and United Kingdom—Pooled analysis of three population-based case-control studies of childhood cancer: France (2003–2004), Germany (1988–1994), United Kingdom (1991–1996)		**Pesticides**	Febvey et al., 2016
All CNS Tumors			
Mothers exposure during pregnancy	12	0.76 (0.41–1.41)	
Paternal exposure around conception	57	0.71 (0.53–0.95)	
Astrocytomas			
Maternal exposure during pregnancy	12	0.46 (0.11–1.90)	
Paternal exposure around conception	57	0.87 (0.53–1.43)	
Embryonal Tumors			
Mothers exposure during pregnancy	12	0.67 (0.21–2.13)	
Paternal exposure around conception	57	0.68 (0.40–1.17)	
Ependymomas			
Maternal exposure during pregnancy	12	1.71 (0.53–5.53)	
Paternal exposure around conception	57	0.44 (0.16–1.20)	
Other CNS Tumors			
Maternal exposure during pregnancy	12	0.75 (0.27–2.06)	
Paternal exposure around conception	57	0.73 (0.46–1.16)	
Canada—Sawmill Workers in British Columbia; 26,487 workers for ≥ 1 year at 14 mills using chlorophenates 1950–1985		**Chlorophenates, not TCDD**	
Workers having a live birth within 1 year after the initiation of employment			Heacock et al., 1998
Leukemia			
All workers' offspring—incidence	11	1.0 (0.5–1.8)	
Chlorophenate exposure: high- vs low-exposure subjects	5	0.8 (0.2–3.6)	
Brain cancer			
All workers' offspring—incidence	9	1.3 (0.6–2.5)	
Chlorophenate exposure: high- vs low-exposure subjects	5	1.5 (0.4–6.9)	
United States—US Agricultural Health Study—prospective study of licensed pesticide sprayers in Iowa and North Carolina: commercial (n = 4,916), private/farmers (n = 52,395, 97.4% men), and spouses of private sprayers (n = 32,347, 0.007% men), enrolled 1993–1997; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Offspring of male pesticide applicators in Iowa from AHS			Flower et al., 2004
Maternal exposure to chlorophenoxy herbicides	7	0.7 (0.3–1.5)	
Paternal exposure to chlorophenoxy herbicides	28	1.3 (0.6–2.6)	
Maternal exposure to 2,4-D	7	0.7 (0.3–1.6)	
Paternal exposure to 2,4-D	26	1.3 (0.7–2.4)	

continued

TABLE 38 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Seveso residents 0–19 years old—10-year followup, morbidity, all exposure zones			Pesatori et al., 1993
All cancers	17	1.2 (0.7–2.1)	
Ovary, uterine adnexa	2	nr (0 cases expected)	
Brain	3	1.1 (0.3–4.1)	
Thyroid	2	4.6 (0.6–32.7)	
HL	3	2.0 (0.5–7.6)	
Lymphatic leukemia	2	1.3 (0.3–6.2)	
Myeloid leukemia	3	2.7 (0.7–11.4)	
Seveso residents 0–19 years old—10-year followup, mortality, all exposure zones			Bertazzi et al., 1992
All cancers	10	7.9 (3.8–13.6)	
Leukemias	5	3.9 (1.2–1.8)	
Lymphatic leukemia	2	1.6 (0.1–4.5)	
Myeloid leukemia	1	0.8 (0.0–3.1)	
Leukemia, others	2	1.6 (0.1–4.6)	
Central nervous system tumors	2	1.6 (0.1–4.6)	
Other International Environmental Studies			
North America, Europe and Australia—Childhood Leukemia International Consortium: harmonized data from childhood cancer studies in three countries with self-reported home herbicide use during pregnancy		**Home herbicide use**	Bailey et al., 2015
Acute lymphoblastic (lymphocytic) leukemia		1.23 (1.04–1.45)	
Acute myeloid leukemia		0.84 (0.56–1.26)	
Canada—ALL in children (0–9 years old) in households using herbicides (1980–1993)		**Herbicides**	Infante-Rivard et al., 1999
Exposure during pregnancy	118	1.8 (1.3–2.6)	
Exposure during childhood	178	1.4 (1.1–1.9)	
England—Renal cancer in subjects (1–15 years of age) with paternal occupation in agriculture	21	**Herbicides, pesticides** 0.9 (0.2–3.8)	Pearce and Parker, 2000
Norway—Cancer in children of agricultural workers (n = 1,275) identified in cancer registries (1965–1991)		**Pesticides**	Kristensen et al., 1996
Children with AML whose parents purchased pesticides	12	1.4 (0.6–2.9)	
CASE-CONTROL STUDIES			
US Case-Control Studies			
Children's Oncology Group/Willis Eye Institute —Case-control study of retinoblastoma; 282 cases (186 unilateral and 96 bilateral); ORs adjusted for mother's race, mother's age, mother's work status, and whether the father was living at home at start of pregnancy		**Pesticides, herbicides**	Omidakhsh et al., 2017
Parental home use of "weed killer"		2.3 (0.9–5.4) [unilateral]	
Lawn/Garden use of weed control products		2.3 (0.9–5.4) [unilateral]	

TABLE 38 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
Professional lawn or landscape services		3.4 (0.6–18.0) [bilateral]	
Weed control products on garden or lawn		1.0 (0.3–3.3) [bilateral]	
Children's Oncology Group—Studies association between infant leukemia and maternal herbicide exposure (443 cases vs 324 population controls)		**Herbicides** ns	Slater et al., 2011
Children's Oncology Group—Childhood GCTs residential exposure to herbicides 6 months before conception, during gestation, through breastfeeding period		**Pesticides**	Chen Z et al., 2006
Maternal exposure	47	1.3 (0.9–1.7)	
Daughters	36	1.4 (1.0–2.0)	
Sons	11	1.0 (0.5–1.8)	
Paternal exposure	90	1.0 (0.7–1.3)	
Daughters	32	1.2 (0.7–2.0)	
Sons	58	1.0 (0.7–1.4)	
Children's Oncology Group—Parental occupational exposure to pesticide and GCTs, 1993–2001 (253 cases vs 394 controls)		**Pesticides**	Chen et al., 2005
Maternal	32	1.1 (0.7–1.6)	
Paternal	39	0.9 (0.6–1.3)	
Children's Cancer Group—exposure to pesticides, weed killers—AML		**Pesticides**	Buckley et al., 1989
Any paternal exposure	27	2.3 (p = 0.5)	
Paternal exposure over 1,000 days	17	2.7 (1.0–7.0)	
Maternal exposure over 1,000 days	7	undefined	
California (Northern California Childhood Leukemia Study)—exposure to "outdoor herbicides" and ALL (and variants in metabolic genes) 669 children diagnosed with ALL and 1021 controls, ORs for risk of pesticide exposure and adjustment for child's sex, age, ethnicity, mother's race and household income		**Pesticides/herbicides**	Gunier et al., 2017
Paternal occupational exposure to any pesticides		1.7 (1.2–2.5)	
Paternal occupational exposure to pesticides and ALL in children ≤ 4 years of age		2.3 (1.3–4.1)	
Maternal pesticide exposure		1.3 (0.8–2.4)	
		Herbicides	
Exposure to 2,4-D measured in house dust (252 cases, 306 controls)	236	1.0 (0.9–1.1)	Metayer et al., 2013
Outdoor herbicide use before birth (377 cases, 448 controls)		1.5 (1.0–2.0)	Chokkalingam at al., 2012
California—Maternal exposure to agricultural pesticide in class of "probable human carcinogens" (including cacodylic acid) during 9 months before delivery		**Pesticides**	Reynolds et al., 2005
All sites	223	1.0 (0.9–1.2)	
Leukemias	179	1.2 (0.9–1.5)	
Central nervous system tumors	31	0.9 (0.5–1.4)	
New York State—Neuroblastoma risk in children, age ≤ 14 years of age (1976–1987)		**Pesticides**	Kerr et al., 2000
Maternal occupational exposure to insecticides	40	2.3 (1.4–3.7)	
Paternal exposure to dioxin	7	6.9 (1.3–68.4)	

continued

TABLE 38 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
International Case-Control Studies			
Australia—ALL in offspring and parental occupational exposure to pesticides			Glass et al., 2012
Paternal exposure to phenoxy herbicides (327 cases, 751 controls)	8	0.9 (0.4–2.2)	
Maternal exposure to phenoxy herbicides (378 cases, 854 controls)	2	1.9 (0.3–11.8)	
Canada and United States—Study of Wilm's tumor		**Herbicides**	Cooney et al., 2007
Maternal report of household use of herbicides from month before conception through child's diagnosis	112	1.0 (0.7–1.4)	
Canada and United States—Neuroblastoma risk in children (538 cases, 504 controls) from 139 hospitals in the United States and Canada (exposures as reported by both parents)		**Herbicides, pesticides**	Daniels et al., 2001
Pesticides in home (used ever)	nr	1.6 (1.0–2.3)	
Herbicides in garden	nr	1.9 (1.1–3.2)	
Pesticides in garden	nr	2.2 (1.3–3.6)	
Costa Rica—parental occupational exposure to pesticide, childhood leukemia		**Herbicides**	Monge et al., 2007
Parental exposures in year before conception to:			
Herbicides	53	1.2 (0.8–1.7)	
Phenoxyacetic acids	28	1.0 (0.6–1.6)	
Picloram (all ALL)	11	1.6 (0.7–3.4)	
High vs low	8	6.3 (1.0–38.6)	
Maternal exposures to:			
Herbicides			
In year before conception	9	2.0 (0.8–5.0)	
In 1st trimester	8	5.3 (1.4–20.0)	
In 2nd trimester	8	5.3 (1.4–20.0)	
In 3rd trimester	7	2.3 (0.8–6.8)	
Phenoxyacetic acids in year before conception	4	1.3 (0.4–4.8)	
West Germany—population-based study of childhood cancer (1993–1997) (2,358 cases vs 2,588 controls)		**Pesticides**	Meinert et al., 2000
Leukemia			
Paternal exposure year before pregnancy	62	1.5 (1.1–2.2)	
Paternal exposure during pregnancy	57	1.6 (1.1–2.3)	
Maternal exposure year before pregnancy	19	2.1 (1.1–4.2)	
Maternal exposure during pregnancy	15	3.6 (1.5–8.8)	
Lymphomas			
Paternal exposure year before pregnancy	11	1.5 (0.7–3.1)	
Paternal exposure during pregnancy	10	1.6 (0.7–3.6)	
Maternal exposure year before pregnancy	3	2.9 (0.7–13.0)	
Maternal exposure during pregnancy	4	11.8 (2.2–64.0)	

TABLE 38 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[b]	Reference
France—Hematopoietic malignancies in children < 15 years of age (2003–2004)		**Herbicides**	Rudant et al., 2007
Maternal household herbicide use during pregnancy			
Acute leukemia	53	1.5 (1.0–2.2)	
Without paternal exposure	4	5.0 (1.3–19.0)	
All ALL	nr	1.7 (1.2–2.5)	
Common B-cell ALL	nr	1.9 (1.3–2.9)	
Mature B-cell ALL	nr	1.5 (0.3–6.4)	
T-cell ALL	nr	0.5 (0.1–2.0)	
AML	nr	1.2 (0.5–2.8)	
HL	9	1.1 (0.5–2.4)	
Without paternal exposure	0	nr	
Nodular sclerosis	nr	1.3 (0.5–3.1)	
Mixed cell	nr	0.8 (0.1–6.6)	
NHL	14	1.5 (0.8–2.7)	
Without paternal exposure	0	nr	
Burkitt's lymphoma	nr	1.7 (0.7–4.0)	
B-cell lymphoblastic	nr	0.7 (0.2–3.0)	
T-cell lymphoblastic	nr	2.6 (0.7–9.0)	
Anaplastic large cell	nr	1.4 (0.3–2.8)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; AHS, Agricultural Health Study; AIHW, Australian Institute for Health and Welfare; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; GCT, germ-cell tumor; HL, Hodgkin lymphoma; ICD, *International Classification of Diseases*; NHL, non-Hodgkin's lymphoma; nr, not reported; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; VES, Vietnam Experience Study.

[a]Unless otherwise indicated, studies show paternal exposure.

[b]Given when available; results other than estimated risk explained individually.

[c]Of the 12, nine were observed, three additional cases estimated to have occurred in portion of cohort whose data were not validated.

TABLE 39 Selected Epidemiologic Studies—Parkinson's Disease and Parkinson's-Like Conditions (shaded entries are new information for Update 11 [2018])

Reference and Country	Cases in Study Group	Comparison Group	Exposure Assessment	Exposure(s)	n	OR (95% CI)	Diagnosis of Neurologic Dysfunction
Kang et al., 2014 US	10 PD deaths (2,260 in Vietnam cohort and 1,781 in near-Vietnam cohort	5,313 nondeployed US female Vietnam veterans	Vietnam veterans—information obtained from death certificates, VA Records, Social Security Death master File, NCHS National Death Index	All COIs	10 PD cases (8 PD cases in nurses)	Vietnam cohort: 1.3 (0.3–4.6) Nurses only: 0.8 (0.2–3.5)	Diagnosis from death records
van der Mark et al., 2014 US	444 cases	876 matched controls	JEM and an algorithm derived from the AHS were used to derive cumulative exposure to herbicides; a crop-based method was used to estimate exposure to particular pesticides	JEM group (medium) JEM group (high) AHS-algorithm group (medium) AHS-algorithm group (high) 2,4-D (low) 2,4-D (high)		1.3 (0.7–2.4) 0.3 0.6–2.5) 1.2 (0.6–2.3) 1.5 (0.8–3.0) 1.1 (0.5–2.4) 1.7 0.8–3.5)	Neurologist review of medical records
Weisskopf et al., 2012 US	101 PD cases	349 (186 matched controls)	PCBs analyzed in serum	Mono-ortho dioxin-like PCBs (PCBs 105, 118, 156, 157, 167, 189)		PCB 118: 0.4 (0.4–1.0) Dioxin-like PCBs; 0.3 (0.1–0.9)	Neurologist review of medical records
Yang et al., 2016 Korea	143 PD cases with AO exposure	500 PD cases with no AO exposure	Korean Vietnam veterans	Agent Orange based on self-report and military record verified "perceived exposure index"		Tested mean differences by exposure status: Significant differences ($p<0.05$) were observed for: • Total UPDRS motor subscale • Contralateral CN • Ipsilateral CN • Contralateral AP • Ipsilateral AP • Contralateral PP • Ipsilateral PP • Asymmetry index AP • Asymmetry index PP • Putamen/caudate ratio Caudate/ putamen ratio	Meeting step I and step II criteria according to the PD society brain bank

Yi et al., 2014a Korea	474 PD cases	VV with low exposure (69,305) vs VV with high exposure (42,421)	Korean Vietnam veterans—prevalence data obtained from Korea National Health Insurance claims (January 2000–September 2005)	AO (based on self-report and proximity of veteran's military unit to AO-sprayed area)	213 cases with high exposure; 261 cases with low exposure	PD and high vs low exposure: HR = 1.2 (1.0–1.4) Log EOI scores: HR = 1.0 (1.0–1.1) Secondary PD and high vs low exposure: HR = 1.3 (0.9–1.7) Log EOI scores: HR = 1.0 (0.9–1.1)	Insurance claim data
Yi et al., 2014b Korea	25 PD deaths; total population 17,529	VV with low exposure (7,973) vs VV with high exposure (9,556)	Vietnam Veterans (Korean Veterans Health Study)—cause of death ascertained from National Statistical Office (1992–2005)	Agent Orange (based on self-report and proximity of veteran's military unit to AO-sprayed area)	13 high exposure deaths; 12 low exposure deaths	PD and high vs low exposure: HR = 0.9 (0.4–2.0) Log EOI scores: HR = 1.0 (0.8–1.2)	Diagnosis from death records
Kenborg et al., 2012 Denmark	28 PD cases from male members of Danish Union of Gardeners (n = 3,124)	Incidence of PD in general population of Denmark	Hospital diagnosis of PD between 1977–2008	Pesticides (including phenoxy herbicides)	28 11 16 1	Hospitalization: 1.1 (0.8–1.7) Born before 1915: 1.6 (0.8–2.8) Born 1915–1934: 1.2 (0.7–1.9) Born 1935 or later: 0.3 (0.0–1.6) 1.8 (0.97–3.4) 1.8 (0.95–3.3)	Not specified
Rugbjerg at al., 2011; Canada	403 PD cases from pharmacy database	405 matched controls	Initial screening phone-interview followed by an in-person physical assessment employing a checklist and record of symptoms, reviewed by a neurologist specializing in movement disorders	Herbicides Neurotoxic pesticides (including 2,4-D, 2,4,5-T)	33 35	1.8 (0.97–3.4) 1.8 (0.95–3.3)	Parkinsonian tremor, rigidity, bradykinesia, masked facies, micrographia, or postural imbalance

continued

TABLE 39 Continued

Reference and Country	Cases in Study Group	Comparison Group	Exposure Assessment	Exposure(s)	n	OR (95% CI)	Diagnosis of Neurologic Dysfunction
Firestone et al., 2010 (updates and expands Firestone et al., 2005) Washington, US	Enrolled cases increased from 250 (in original study) to 404	526 unrelated controls	Structured face-to-face interviews; demographic information collected, job descriptions (if held for more than 6 months) and workplace exposures to various industrial toxicants identified from a checklist were recorded	2,4-D	8	0.8 (0.3–2.0)	≥ 2 of 4 cardinal signs; must have bradykinesia or resting tremor, may have ogwheel rigidity, or postural reflex impairment
Elbaz et al., 2009 France	224 PD cases	557 controls	Initial self assessment, plus individual interview with occupational specialist	Phenoxy herbicides	na	1.8 (0.9–3.3)	≥ 2 cardinal signs (rest tremor, bradykinesia, rigidity, impaired postural reflexes)
				Age of onset > 65 years	na	2.9 (1.1–7.3)	
Tanner et al., 2009 US	519 cases; consecutively eligible subjects between July 1, 2004, and May 31, 2007	521 controls frequency matched to cases by age, sex, and location	Telephone interviewers collected information about exposures before the reference age; employment history—industry, location, processes, materials, and job tasks. Toxicant exposure collected for some jobs	2,4-D	16	2.6 (1.0–6.5)	Enrolling investigator determined diagnosis and type of parkinsonism, Unified Parkinson Disease Rating Scale score, and clinical features
Brighina et al., 2008 US (Mayo Clinic)	833 PD sequential cases from clinic; median age = 67.7 year, 208 cases ≤ 59.8 year	472 unaffected siblings and 361 unrelated controls	Self–report down to specific herbicides; 2,4-D said to be most prevalent in cases, but published analysis not that detailed	For youngest quartile at diagnosis:			PD diagnosed by movement disorder specialist
				Pesticides (ever):	87	1.8 (1.1–2.9)	
				Herbicides (ever):		2.5 (1.3–4.5)	
				Phenoxy herbicides		1.5 (1.0–2.2)	
				Insecticides (ever):		1.0 (0.6–1.7)	
				Fungicides (ever):		1.0 (0.3–3.2)	

Dhillon et al., 2008 US (University of Texas)	100 PD cases recruited from a medical center's neurological institute in East Texas	84 controls without PD recruited from the same medical center	Professionally administered questionnaire used to determine military history (including spraying herbicides/ pesticides), personal use/mixing and average duration of exposure to herbicides and specific pesticides, among other exposures	Ever personally used/ mixed or applied:			PD diagnosed by neurologist specializing in movement disorders using standard clinical/lab diagnostic criteria
				Herbicide use-home or agricultural	34	0.8 (0.4–1.4)	
				2,4-D	17	1.2 (0.6–2.8)	
				2,4,5-T	4	0.5 (0.1–1.6)	
				Silvex or other 2,4,5-TP products	1	0.3 (0.0–2.7)	
Hancock et al., 2008 US (Duke University, NC)	319 cases	296 unaffected relatives and others	All comparisons referent to those who never applied any pesticide	Pesticide application:	200	1.6 (1.1–2.3)	
				Insecticides:		1.8 (1.2–2.8)	
				Botanical:	7	5.9 (0.6–56)	
				Organophosphate:	53	1.9 (1.1–3.6)	
				Herbicides:		1.6 (1.0–2.5)	
				Chlorophenoxy:	15	2.1 (0.7–6.2)	
				Phosophonoglycine:	57	1.5 (0.9–2.5)	
				Triazine:	5	1.1 (0.3–3.6)	
Kamel et al., 2007b US (Agricultural Health Study) [Updates Kamel et al., 2005]	83 prevalent cases at enrollment; 78 incident cases during followup among private applicators and spouses	79,557 without PD at enrollment; 55,931 without PD followed up	Self-report of individual herbicides (2,4-D; 2,4,5-T; 2,4,5-TP) on detailed self-administered questionnaires at enrollment or telephone interview for followup	For incident cases:			
				2,4-D:	49	1.0 (0.5–2.1)	
				2,4,5-T:	24	1.8 (1.0–3.3)	
				2,4,5-TP:	7	0.9 (0.4–1.8)	
				Dicamba:	32	1.5 (0.8–2.8)	
				Paraquat:	11	1.0 (0.5–1.9)	
				Trifuralin:	32	1.7 (1.0–3.2)	
				Cyanazine	26	1.0 (0.5–1.8)	
				For prevelent cases:			
				2,4-D:	47	0.9 (0.5–1.8)	
				2,4,5-T:	16	0.9 (0.5–1.7)	
				2,4,5-TP:	4	0.8 (0.3–1.9)	
				Dicamba:	26	0.9 (0.5–1.6)	
				Paraquat:	14	1.8 (1.0–3.4)	
				Trifuralin:	31	0.9 (0.5–1.6)	
				Cyanazine	30	2.6 (1.4–4.9)	

continued

TABLE 39 Continued

Reference and Country	Cases in Study Group	Comparison Group	Exposure Assessment	Exposure(s)	n	OR (95% CI)	Diagnosis of Neurologic Dysfunction
Firestone et al., 2005 Washington, US (Updated by Firestone et al., 2010)	250 (156 men) newly diagnosed 1992–2002 at Group Health Cooperative	388 (241 men)	Interview determining occupational and home-based pesticide exposure characterized by chemical name or brand, duration, and frequency	Occupational, men only			Controlled for age, sex, smoking
				Pesticides:	19	1.0 (0.5–1.9)	
				Insecticides:	15	0.9 (0.4–1.8)	
				Fungicides:	2	0.4 (0.1–3.9)	
				Herbicides:	9	1.4 (0.5–3.9)	
				Paraquat:	2	1.7 (0.2–12.8)	
				Home use, all subjects			
				Pesticides:	178	1.0 (0.7–1.4)	
				Insecticides:	141	0.8 (0.6–1.1)	
				Fungicides:	14	0.6 (0.3–1.1)	
				Herbicides:	116	1.1 (0.8–1.5)	
Behari et al., 2001 India	377 (301 men, 76 women)	377 matched for age (± 3 years), but not sex	Structured interview	McNemar chi-square:			
				Herbicides:		p = 0.010	
				(protective effect—not confirmed by multivariate analysis)			
				Insecticide:		p = 0.169	
				Rodenticide:		p = 0.662	
Engel et al., 2001 US	238	72	Self-administered questionnaire for occupational exposure [cross-sectional, but otherwise fairly high-quality design]	[prevalence ratios]			
				Any pesticide:		0.8 (0.5–1.2)	Neurologic exam by trained nurse
				Herbicides:		0.9 (0.6–1.3)	
				Insecticides:		0.9 (0.6–1.5)	
				Fungicides:		0.8 (0.6–1.3)	
Kuopio et al., 1999 Finland	123 (onset of PD before 1984; 63 men, 60 women)	246 matched on sex, age (± 2 years), and urban/rural	Interview—pesticides or herbicides regularly or occasionally used	Pesticide use:	39	1.0 (0.6–1.7)	Neurologic exam
				Occasional use:	26	1.2 (0.7–2.0)	
				Regular use:	13	0.7 (0.3–1.3)	
				Herbicide use:	33	1.4 (0.8–2.5)	
				Occasional use:	20	1.7 (0.9–3.2)	
				Regular use:	13	0.8 (0.4–1.7)	
Taylor et al., 1999 US Boston Medical Center	140	147 controls referred by cases	Interview—exposure recorded as total days for lifetime	Logistic analysis adjusted for age, sex, family history, education, smoking, water source, head injury, depression			Neurologic exam
				Pesticides:		1.0 (0.9–1.2)	
				Herbicides:		1.1 (0.7–1.7)	

Gorell et al., 1998 US	144 (age > 50 years)	464	Interview—herbicide and insecticide use while working on a farm or gardening	All occupations contributing exposure to:		Standard criteria of PD by history
				Herbicides:	4.1 (1.4–12.2)	
				Insecticides:	3.6 (1.8–7.2)	
				Fungicides:	1.6 (0.5–5.5)	
Liou et al., 1997 Taiwan	120	240 hospital controls matched for age (± 2 years) and sex	Interview—occupational exposures to herbicides or pesticides	Pesticides vs no pesticides:	2.9 (2.3–3.7)	Neurologic exam
				But no paraquat use:	2.2 (0.9–5.6)	
				Paraquat use:	4.7 (2.0–12))	
				Paraquat use vs no paraquat:	3.2 (2.4–4.3)	
Seidler et al., 1996 Germany	380 (age < 66 years with PD after 1987)	755 (379 neighborhood, 376 regional; neighborhood controls may be over-matched)	Interview—dose-years = years of application weighted by use	Pesticides:	2.1 (1.6–2.6)	Neurologic exam
				Herbicides—high dose:	2.4 (1.0–6.0)	
				Dose trend		
				vs neighbor controls	p = 0.06	
				vs regional controls	p < 0.001	
				Insecticides—high dose:	2.1 (0.9–4.8)	
				Dose trend		
				vs neighbor controls	p = 0.12	
				vs regional controls	p < 0.001	
Hertzman et al., 1994 Canada	127 (71 men and 56 women)	245 (121 with cardiac disease; 124 voters)	Interview—occupation with probable pesticide exposure	Cases vs voters—among men		Neurologic exam
				Pesticides:		
				Herbicides:	2.3 (1.1–4.9)	
				Chlorophenoxys:	1.2 (0.6–2.5)	
				Paraquat:	1.2 (0.6–2.4)	
				Insecticides:	1.3 (0.3–4.6)	
				Fungicides:	0.3 (0.1–0.9)	
Butterfield et al., 1993 US	63 young onset cases (age < 50 years)	68	Questionnaire—pesticide or insecticide use 10 times in any year	Herbicides:	3.2 p = 0.033	Standard criteria of PD by history
				Insecticides:	5.8 p < 0.001	
				Dwelling fumigated:	5.3 p = 0.45	

continued

TABLE 39 Continued

Reference and Country	Cases in Study Group	Comparison Group	Exposure Assessment	Exposure(s)	n	OR (95% CI)	Diagnosis of Neurologic Dysfunction
Semchuk et al., 1992 Calgary, Alberta, Canada	130 living cases from register of Calgary residents (population-based)	260 community controls matched for age (± 2.5 years) and sex, identified by RDD	Interview—self-report of exposure for each job held > 1 month	Pesticides:	32	2.3 (1.3–4.0)	Neurologic exam confirming idiopathic PD without dementia (average 7.8 years from diagnosis)
				Herbicides:	17	3.1 (1.3–7.0)	
				Exposed during age interval:			
				16–25 years		1.4 (0.5–4.3)	
				26–35 years		4.8 (1.5–15.0)	
				36–45 years		3.8 (1.2–13.0)	
				46–55 years		4.9 (1.3–19.0)	
				Insecticides:	17	2.1 (1.0–4.1)	
				Fungicides:	16	1.6 (0.8–3.3)	
Stern et al., 1991 US (NJ and PA)	69—all young onset cases identified (age < 40 years); 80—random selection of old onset cases (age > 59 years)	149 nominated by each case or picked from hospital; matched by age (± 6 years), sex, and race	Interview—self-report of insecticide and pesticide use by self or others in home or garden	Insecticides:		0.7 (0.3–1.4)	Review of medical records, responsive to PD medication (under treatment average of 8.2 years), without major cognitive impairment
				Onset < 40 years:		0.6 (0.2–1.7)	
				Onset > 59 years:		0.8 (0.3–2.1)	
				Herbicides:		1.1 (0.7–1.7)	
				Onset < 40 years:		0.9 (0.5–1.7)	
				Onset > 59 years:		1.3 (0.7–2.4)	
				Adjusted for smoking, head injury, rural residence:			
				Insecticides:		0.5 (0.2–1.1)	
				Herbicides:		0.9 (0.6–1.5)	
Hertzman et al., 1990 British Columbia, Canada	57 prevalent PD patients (age < 79 years) (50–54 had confirmed PD, not clear exactly how many)	122 aged 50–79 who responded from electoral rolls	Questionnaire—ever worked in an orchard	Work in orchards:	4/57	3.7 (1.3–10.3) (p = 0.01)	Neurologic exam confirmed diagnostic criteria in 55 of 69 cases identified by asking physicians in area
				Paraquat:			

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TP, 2-(2,4,5-trichlorophenoxy) propionic acid or Silvex; AHS, Agricultural Health Study; CI, confidence interval; COI, chemical of interest; EOI, Exposure Opportunity Index; HR, hazard ratio; JEM, job-exposure matrix; NCHS, National Center for Health Statistics; OR, odds ratio; PCB, polychlorinated biphenyl; PD, Parkinson disease; RDD, random-digit dialing; VA, US Department of Veterans Affairs; VV, Vietnam veteran.

TABLE 40 Selected Epidemiologic Studies—Amyotrophic Lateral Sclerosis (shaded entries are new information for Update 11 [2018])

Reference and Country	Study Group	Comparison Group	Exposure Assessment	Significant Association with Pesticides[a]	Exposure of Interest/ Estimated Risk (95% CI)	Neurologic Dysfunction
Beard et al., 2017 US	446 selected from the National Registry of Veterans with ALS	616	US Vietnam Veterans—self-report of service in Vietnam War and use of Agent Orange	—	IP-weighted HR for ALS survival and "mixing and application of Agent Orange" HR = 0.62 (0.32–1.20) IP-weighted OR for ALS survival "exposure to Agent Orange in the field" HR = 0.66 (0.42–1.05)	ALS diagnosis extracted from medical record, ALS Functional Rating Scale-Revised
Beard et al., 2016 US	621 selected from the National Registry of Veterans with ALS	958 Controls matched on age of the diagnosis of the case	US Vietnam Veterans—self-report of service in Vietnam War and use of Agent Orange	—	IP-weighted OR for ALS and "mixing and application of Agent Orange" OR=1.15 (0.38–3.44) IP-weighted OR for ALS and "exposure to Agent Orange in the field" OR = 2.80 (1.44–5.44) IP-weighted OR for ALS and mixing and application of Agent Orange OR=1.15 (0.38–3.44) exposure to pesticides on clothing or bedding: OR = 1.83 (0.99, 3.40)	ALS diagnosis extracted from medical record, ALS Functional Rating Scale-Revised
Su et al., 2016 US	156	128	Measurement of PCBs in blood, including PCB 118	—	OR = 0.69 (0.48–1.01)	Diagnosis of definitive, probable, probable with laboratory support, or possible ALS by revised El Escorial criteria
Yi et al., 2014a Korea	290	111,436	Korean Vietnam veterans—self-report and proximity of veteran's military unit to AO-sprayed area	+	Low (158) vs high (132) exposure:	Yi et al., 2014a

continued

TABLE 40 Continued

Reference and Country	Study Group	Comparison Group	Exposure Assessment	Significant Association with Pesticides[a]	Exposure of Interest/ Estimated Risk (95% CI)	Neurologic Dysfunction
Yi et al., 2014b Korea	17	17,529	Korean Vietnam veterans—vital status and cause of death and proximity of veteran's military unit to AO-sprayed area		Low (9) vs high (8) exposure: HR = 0.8 (0.3–2.2) Log EOI score: HR = 0.9 (0.7–1.2)	Spinal muscular atrophy (G12)
Kamel et al., 2012 US (AHS)	41	84,698	Self-administered questionnaire		Herbicides: 1.6 (0.7–3.7) 2,4-D: 1.0 (0.5–2.1) 2,4,5-T: 1.3 (0.5–3.2)	ALS cases identified via linkage with National Death Index
Pamphlett, 2012 Australia (followup to Morahan and Pamphlett, 2006)	614	778	Questionnaire	+	Herbicide/pesticide exposure: Men: 1.8 (1.3–2.4) Women: 1.4 (1.0–2.0)	Self-reported and fulfilled probable or definite revised El Escorial criteria
Morahan and Pamphlett, 2006 Australia	179	179	Questionnaire—exposure to environmental toxicants	+	Herbicide, pesticide exposure: 1.6 (1.0–2.4); industrial exposure: 5.6 (2.1–15.1)	Self-reported
ADVA, 2005c Australia	nr	nr	Deployment to Vietnam	+	4.7 (1.0–22.8)	
Weisskopf et al., 2005 US	nr	nr	Self-administered questionnaire	+	1.5 (1.1–2.1); p = 0.007	Self-reported military services, death certificates
Burns et al., 2001 US	1,567	40,600	Industrial hygienist ranked jobs for exposure to 2,4-D to derive of years exposure and cumulative exposure	+	3.45 (1.1–11.1)	Death certificates
McGuire et al., 1997 US	174	348	Self-reported lifetime job history, workplace exposures reviewed by panel of four industrial hygienists	+	Herbicide exposure: 2.4 (1.2–4.8); significant trend analysis for dose–effect relationship with agricultural chemicals: p = 0.03	New diagnosis of ALS 1990–1994 in western Washington state
Chancellor et al., 1993 Scotland	103	103	Required regular occupational exposure to pesticides for 12 months or more		1.4 (0.6–3.1)	Scottish Motor Neuron Register

Savettieri et al., 1991 Italy	46	92	Continual exposure to agricultural chemicals	3.0 (0.4–20.3)	Cases reviewed by neurologists
Deapen and Henderson, 1986 US	518	518	Ever worked in presence of pesticides	2.0 (0.8–5.4)	ALS Society of America

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; AHS, Agricultural Health Study; ALS, amyotrophic lateral sclerosis; AO, Agent Orange; CI, confidence interval; EOI, Exposure Opportunity Index; HR, hazard ratio; IP, Inverse Probability; nr, not reported; OR, odds ratio.

[a]For the objective of the VAO review series, only associations with herbicides are of possible relevance; only phenoxy herbicides, cacodylic acid, and picloram are of specific interest.

TABLE 41 Selected Epidemiologic Studies—Diabetes and Related Health Outcomes (shaded entries are new information for Update 11 [2018])

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
AFHS—followup through 2004			Michalek and Pavuk, 2008
Calendar period in Vietnam			
During or before 1969	130	1.7 (p = 0.005)	
Background (serum TCDD ≤ 10 ppt)	39	1.3 (0.8–2.0)	
Low (10–91 ppt)	40	1.9 (1.2–2.9)	
High (> 91 ppt)	51	2.0 (1.3–3.1)	
After 1969	50	0.9 (p = 0.45)	
Spraying during tour			
≥ 90 days	170	1.3 (p = 0.04)	
Background (serum TCDD ≤ 10 ppt)	42	1.0 (0.7–1.4)	
Low (10–91 ppt)	60	1.5 (1.0–2.0)	
High (> 91 ppt)	68	1.6 (1.1–2.2)	
< 90 days	10	0.6 (p = 0.12)	
AFHS—Ranch Hand–comparison subject pairs—within-pair differences; lower Ranch Hand insulin sensitivity with greater TCDD levels			Kern et al., 2004
1997 examination (29 pairs)		(p = 0.01)	
2002 examination (71 pairs)		(p = 0.02)	
Air Force Ranch Hand veterans (n = 343)	92	ns	
AFHS—comparison veterans only, OR by quartiles of serum dioxin concentration			Longnecker and Michalek, 2000[b]
Quartile 1: < 2.8 ng/kg	26	1.0	
Quartile 2: 2.8– < 4.0 ng/kg	25	0.9 (0.5–1.7)	
Quartile 3: 4.0– < 5.2 ng/kg	57	1.8 (1.0–3.0)	
Quartile 4: ≥ 5.2 ng/kg	61	1.6 (0.9–2.7)	
AFHS—through 1992 examination cycle Ranch Hand veterans—high-exposure group			Henriksen et al., 1997[b]
Glucose abnormalities	60	1.4 (1.1–1.8)	
Diabetes prevalence	57	1.5 (1.2–2.0)	
Use of oral medications for diabetes	19	2.3 (1.3–3.9)	
Serum insulin abnormalities	18	3.4 (1.9–6.1)	
Ranch hand vs comparisons to evaluate low testosterone as a risk factor for incident diabetes in a multivariate model adjusted for BMI and birth year			Mazur et. al., 2014
Diabetes mellitus	183	p > 0.05	

TABLE 41 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
US VA Cohort of Army Chemical Corps—Expanded as of 1997 to include all Army men with chemical MOS (2,872 deployed vs 2,737 nondeployed) serving during Vietnam era (7/1/1965–3/28/1973)		**All COIs**	
Incidence—Self-reported diabetes diagnosed by doctor			
CATI survey of stratified sample: 1,499 deployed (795 with TCDD measured) vs 1,428 nondeployed (102 with TCDD measured)			Kang et al., 2006
Deployed vs nondeployed	226	1.2 (0.9–1.5)	
Sprayed herbicides in Vietnam (n = 662) vs never (n = 811)	123	1.5 (1.1–2.0)	
Mortality—diabetes			
Through 2005			Cypel and Kang, 2010
Deployed veterans (2,872) vs nondeployed (2,737)	27	1.8 (0.7–4.4)	
ACC deployed men in Kang et al. (2006) reported sprayed herbicide vs did not spray	ns	2.2 (0.6–8.0)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Followup—deployed vs nondeployed			CDC, 1988a
Interviewed—self-reported diabetes	155	1.2 ($p > 0.05$)	
Subset with physical examinations			
Self-reported diabetes	42	1.1 ($p > 0.05$)	
Fasting serum glucose		Geometric means 93.4 vs 92.4 mg/dL $p < 0.05$)	
US VA Cohort of Female Vietnam-era Veterans served in Vietnam (n = 4,586; nurses only = 3,690); nondeployed (n = 5,325; nurses only = 3,282)		**All COIs**	
Mortality			
Through 2010—Vietnam-era veterans	33	0.7 (0.4–1.5)	Kang et al., 2014
Vietnam nurses only	25	1.0 (0.4–2.2)	
International Vietnam Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Incidence			
Validation Study—Expected number of exposed cases (95% CI)			
Men		Cases expected	CDVA, 1998a[b]
Self-report of doctor's diagnosis	2,391		
(proportion of respondents)	(6%)	1,780 (1,558–2,003)	
Women		*Cases expected*	CDVA, 1998a[b]
Self-report of doctor's diagnosis	5		
(proportion of respondents)	(2%)	10 (9–11)	

continued

TABLE 41 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
Mortality			
All branches, return–2001	55	0.5 (0.4–0.7)	ADVA, 2005a
Navy	12	0.5 (0.3–0.9)	
Army	37	0.5 (0.4–0.7)	
Air Force	6	0.5 (0.2–1.0)	
1980–1994			CDVA, 1997a
Sample of 1,000 Male Australian Vietnam Veterans—prevalence		**All COIs**	
450 interviewed 2005–2006 vs respondents to 2004–2005 national survey	55	1.0 (0.8–1.3)	O'Toole et al., 2009
641 interviewed 1990–1993 vs respondents to 1989–1990 national survey (self-report of doctor diagnosis)	12	1.6 (0.4–2.7)	O'Toole et al., 1996b
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Mortality 1966–2001	6	0.3 (0.1–0.7)	ADVA, 2005c
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)			Cox et al., 2015
Number of first-observed conditions compared to number expected based on New Zealand national hospitalization rates		SHR (99% CI)	
Thyroid disease	7	1.41 (0.04–2.78)	
Diabetes	151	1.14 (0.90–1.38)	
Gout and other crystal diseases	40	1.50 (0.89–2.12)	
Korean Vietnam Veterans		**All COIs**	
Korean veterans of Vietnam era: 1,224 deployed vs 154 nondeployed—incidence	154	2.7 (1.1–6.7)	Kim JS et al., 2003
Korean Vietnam Veterans Health Study—on basis of individual EOI scores categorized as high or low exposure		**All COIs**	
Prevalence (2000–2005)			Yi et al., 2014a
Categorized high (n = 42,421) vs low (n = 69,305)			
All diabetes [E10–E14]	12,942 vs 19,891	1.0 (1.0–1.1) p = 0.006	
Type 1 diabetes [E10]	2,099 vs 2,981	1.1 (1.0–1.2) p = 0.001	
Type 2 diabetes [E11]	10,881 vs 16,725	1.0 (1.0–1.1) p = 0.015	
OR per unit of $\log_{10}$ EOI (n = 111,726)			
All diabetes [E10–E14]	32,833	p = 0.014	
Type 1 diabetes [E10]	5,080	p = 0.120	
Type 2 diabetes [E11]	27,606	p = 0.029	
Mortality (1992–2005)			Yi et al., 2014b
All diabetes [E10–E14]			
Categorized high (n = 85,809) vs low (n = 94,442)	376 vs 327	1.0 (0.9–1.2); p = 0.859	
HR per unit of $\log_{10}$ EOI (n = 180,639)	703	p = 0.414	

TABLE 41 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Diabetes—mortality	33	2.3 (0.5–9.5)	Vena et al., 1998
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 month in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Incidence			
BASF workers potentially exposed to TCDD following an accident involving trichlorophenol		p = 0.06	Ott et al., 1994
Through 1989 (n = 158 men exposed within 1 year of accident vs 161 other BASF employees 1953–1969)	10	0.5 (0.2–1.0)	Zober et al., 1994
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
245 Workers randomly selected for study consented to send a blood sample			't Mannetje et al., 2018
OR Diabetes worked in highly exposed job, adjusted for age (continuous), gender, smoking (ever, former, current), BMI (< 25, 25–30, ≥ 30, missing), Māori ethnicity	13	3.98 (1.03–15.4)	
OR Diabetes serum TCDD ≥ 10 pg/g lipid, adjusted for age (continuous), gender, smoking (ever, former, current), BMI (< 25, 25–30, ≥ 30, missing), Māori ethnicity	7	3.05 (0.87–10.67)	
Mortality 1969–2004			McBride et al., 2009a
TCP production workers			
(Preliminary) NIOSH Cross-Sectional Medical Study		**Dioxin/phenoxy herbicides**	
Workers exposed to 2,4,5-T, derivatives			Calvert et al., 1999[b]
Serum TCDD pg/g of liquid			
< 20	7	2.1 (0.8–5.8)	
20–75	6	1.5 (0.5–4.3)	
75–238	3	0.7 (0.2–2.6)	
238–3,400	10	2.0 (0.8–4.9)	
Dioxin-exposed workers in two chemical plants		1.1, p = < 0.003	Sweeney et al., 1997/1998
NIOSH/Ranch Hand Comparison—Ranch Hand veterans, workers exposed to TCDD-contaminated products compared with nonexposed comparison cohorts		**Dioxin/phenoxy herbicides**	
Ranch Hands	147	1.2 (0.9–1.5)	Steenland et al., 2001
Workers	28	1.2 (0.7–2.3)	
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Highly exposed industrial cohort (n = 5,132)			Steenland et al., 1999[b]
Diabetes as underlying cause	26	1.2 (0.8–1.7)	
Diabetes among multiple causes	89	1.1 (0.9–1.3)	

continued

TABLE 41 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
Chloracne subcohort (n = 608)	4	1.1 (0.3–2.7)	
Dioxin exposed workers—mortality[c]			Steenland et al., 1992[b]
Diabetes as underlying cause	16	1.1 (0.6–1.8)	
Diabetes among multiple causes	58	1.1 (0.8–1.4)	Sweeney et al., 1992
NIOSH production workers	26	1.6 (0.9–3.0)	
Monsanto Plant—Nitro, West Virginia		**Dioxin/phenoxy herbicides**	
2.4.5-T, TCP production workers with chloracne	22	2.3 (1.1–4.8)	
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, Michigan) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)	16	1.1 (0.6–1.8)	Collins et al., 2009b
1940–1982 (n = 2,187 men)	4	0.7 (0.2–1.9)	Cook et al., 1987
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, Washington, and Wichita, Kansas) and workers who made PCP and TCP at two additional plants (in Midland, Michigan, and Sauget, Illinios)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122)	18	0.8 (0.5–1.2)	
PCP and TCP (n = 720)	8	1.1 (0.5–2.2)	
PCP (no TCP) (n = 1,402)	10	0.6 (0.3–1.2)	
Dow PCP Production Workers (1937–1989 in Midland, Michigan) (not in IARC and NIOSH cohorts)			
1937–2011 Potential dioxin exposure (n = 2,192), TCP production (n = 1,419), PCP production (n = 577), Both TCP and PCP (n = 196)		**2,4,5-T; 2,4,5-TCP; PCP**	Collins et al., 2016
TCP/PCP	27	0.97 (0.64-1.42)	
TCP (includes 196 PCP workers)	19	0.92 (0.55-1.43)	
PCP (includes 196 TCP workers)	9	0.97 (0.44-1.84)	
		Low chlorinated dioxins; 2,4-D	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	8	1.1 (0.5–2.2)	Collins et al., 2009a
Mortality 1940–1989 (n = 770)	4	1.2 (0.3–3.0)	Ramlow et al., 1996
Other Studies of Industrial Workers (not related to IARC or NIOSH phenoxy cohorts)			
Czechoslovakia Production Workers—Production workers admitted to hospital in Prague	11	**2,4,5-T, TCP** nr	Pazderova-Vejlupkova et al., 1981
German Production Workers—West German chemical production workers	nr	**Dioxin, phenoxy herbicides** nr	Von Benner et al., 1994
Japanese Waste-Incinerator Workers—Workers exposed to PCDD at municipal waste incinerator	8	**Dioxin, phenoxy herbicides** nr, but ns	Kitamura et al., 2000
678 male workers from 2000–2007 at 36 waste incineration sites throughout Japan		**PCDDs**	Yamamoto et al., 2015
< 4.34 pg TEQ/g lipid	3	1.0 (referent)	
≥ 4.34 pg TEQ/g lipid	7	2.33 (0.50–10.86)	
≥ 6.09 pg TEQ/g lipid	10	3.18 (0.71–14.23)	

TABLE 41 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
≥ 8.98 pg TEQ/g lipid	25	6.70 (1.61–27.91) p-trend < 0.05	
		PCDFs	
< 2.16 pg TEQ/g lipid	3	1.0 (referent)	
≥ 2.16 pg TEQ/g lipid	7	1.56 (0.31–7.77)	
≥ 3.10 pg TEQ/g lipid	10	4.20 (0.99–17.81)	
≥ 4.51 pg TEQ/g lipid	25	5.69 (1.32–24.53) p-trend < 0.05	
		Coplanar PCBs	
< 2.60 pg TEQ/g lipid	2	1.0 (referent)	
≥ 2.60 pg TEQ/g lipid	9	3.30 (0.60–18.04)	
≥ 4.45 pg TEQ/g lipid	14	4.84 (0.91–25.68)	
≥ 7.30 pg TEQ/g lipid	20	5.36 (1.00–28.72) p-trend < 0.05	
		Total dioxins	
< 9.76 pg TEQ/g lipid	3	1.0 (referent)	
≥ 9.76 pg TEQ/g lipid	4	1.28 (0.24–6.85)	
≥ 13.70 pg TEQ/g lipid	16	4.44 (1.04–18.94)	
≥ 21.67 pg TEQ/g lipid	22	4.98 (1.17–21.17) p-trend < 0.05	
United Kingdom Production Workers—TCP production workers	2	**Dioxin, phenoxy herbicides** nr	May, 1982
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
New Hampshire pulp and paper workers, 883 white men working ≥ 1 year, mortality through July 1985	9	1.4 (0.7–2.7)	Henneberger et al., 1989
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
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; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Incidence			
Self-reported incidence diabetes in 13,637 wives of licensed applicators (10 year followup) (adjusted hazard ratio)			Starling et al., 2014
Ever use of 2,4,5-T or 2,4,5-TP	19	1.6 (1.0–2.5)	
Ever use of 2,5-D	185	1.1 (0.9–1.3)	
Self-reported incidence diabetes (1999–2003) in licensed applicators			Montgomery et al., 2008
2,4-D	73	0.9 (0.8–1.1)	
2,4,5-T	28	1.0 (0.9–1.2)	

continued

TABLE 41 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
Self-reported gestational diabetes in wives of licensed applicators			Saldana et al., 2007
Documented exposure during 1st trimester		*ORs read from graph*	
2,4-D	10	~1.0 (ns)	
2,4,5-T	3	~5 (p < 0.05)	
2,4,5-TP	2	~7 (p < 0.05)	
Dicamba	7	~3 (p ~ 0.06)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Applicators (n = 1,641)	98	0.5 (0.3–0.5)	
Spouses (n = 676)	42	0.4 (0.3–0.6)	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	26	0.3 (0.2–0.5)	
Spouses of private applicators (> 99% women)	18	0.6 (0.4–1.0)	
ITALY			
Trento, electric arc furnace workers (n = 331) Cohort followed from 1979 to 2009 (6,731 person-years), morbidity analyses limited to 225 workers		**Dioxin (detected in foundry dust)**	Cappelletti et al., 2016
RR adjusted for age, compared to general population in Trento			
Diabetes	25	2.39 (1.67–3.41)	
ENVIRONMENTAL			
Seveso, Italy, Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Incidence			
Children residing in Seveso at time of incident—development of diabetes			Baccarelli et al., 2005b
101 with chloracne	1	nr	
211 without chloracne	2	nr	
Mortality			
25-year followup to 2001—men and women			Consonni et al., 2008
Zone A	3	1.0 (0.3–3.1)	
Zone B	26	1.3 (0.9–1.9)	
Zone R	192	1.3 (1.1–1.5)	
20-year followup to 1996			Bertazzi et al., 2001
Zones A and B—men	6	0.8 (0.3–1.7)	
Zones A and B—women	20	1.7 (0.1–2.7)	
15-year followup to 1991—men			Bertazzi et al., 1998[b]
Zone B	6	1.2 (0.5–2.7)	
15-year followup to 1991—women			Bertazzi et al., 1998[b]
Zone A	2	1.8 (0.4–7.0)	
Zone B	13	1.8 (1.0–3.0)	
15-year followup to 1991			Pesatori et al., 1998[b]
Zone R men	37	1.1 (0.8–1.6)	
Zone R women	74	1.2 (1.0–1.6)	

TABLE 41 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
Seveso (Italy) Women's Health Study—981 women who were infants to 10–40 years of age when exposed—incidence		**TCDD**	
806 women with serum TCDD levels from 1976 followed through 2009			Warner et al., 2013
Diabetes —Log_{10} TCDD (ppt)	54	0.8 (0.5–1.3)	
Metabolic syndrome —Log_{10} TCDD (ppt)	172	1.1 (0.8–1.4)	
≤ 12 years of age	16	2.0 (1.3–3.3)	
> 12 years of age	156	1.0 (0.7–1.4)	
UNITED STATES			
Mohawk Nation at Akwesasne—Mohawk adults (n = 601), a population with high consumption of locally sourced fish, recruited 1995–2001 following industrial pollution of PCBs in the St. Lawrence River			Aminov et al., 2016a,b
Associations between diabetes prevalence and quartiles of PCBs, models adjusted for age, gender, BMI, total lipids, and total pesticides, MDL given concentrations of the MDL/$\sqrt{2}$		**Dioxin-like PCBs**	
Quartile 1	12	1.0 (referent)	
Quartile 2	13	0.49 (0.18–1.34)	
Quartile 3	28	0.93 (0.33–2.59)	
Quartile 4	58	1.82 (0.61–5.40)	
Associations between diabetes prevalence and quartiles of PCBs, adjusted for total pesticides as well as age, gender, BMI, serum concentrations of total lipids		**Non-/mono-ortho PCBs**	
Quartile 1	9	1.0 (referent)	
Quartile 2	13	1.03 (0.37, 2.86)	
Quartile 3	31	2.37 (0.84, 6.73)	
Quartile 4	58	4.55 (1.48, 13.95)	
Gila River Indian Community—Nested case-control study within longitudinal diabetes study (1965–2007). Men and women with examination data from 1969–1974 and were non-diabetic at baseline. Cases (n = 149) developed diabetes by 2007, controls (n = 151) remained disease free			Grice et al., 2017
ORs are per one SD in the log(PCB) adjusted for age, sex, BMI, 2hPG, sample water loss, storage time, cholesterol and triglycerides		**Dioxin-like PCBs**	
PCB-167		1.11 (0.80–1.55)	
PCB-157		1.06 (0.75–1.49)	
PCB-156		1.06 (0.73–1.53)	
PCB-118		1.16 (0.82–1.65)	
PCB-105		1.14 (0.81–1.60)	

continued

TABLE 41 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
National Health and Nutrition Examination Survey		**Dioxin, dioxin-like PCBs**	
NHANES 1999–2004—2,588 participants (Total TEQ)			
OR for association of dioxins and dioxin-like chemicals with diabetes-related nephropathy, adjusted for age, gender, race/ethnicity, BMI Z-score, poverty income ratio, energy adjusted fruit and vegetable consumption, and physical activity			
1,2,3,6,7,8-HxCDD, fg/g			Everett et al., 2016
< 121.41		1.0 (referent)	
121.41–299.45		0.2 (0.1–0.5)	
≥ 299.46		51.1 (4.1–641.6)	
1,2,3,4,6,7,8-HpCDD, fg/g			
< 161.08		1.0 (referent)	
161.08–367.07		0.5 (0.2–1.0)	
≥ 367.08		3.7 (0.7–20.3)	
1,2,3,4,6,7,8,9-OCDD, fg/g			
< 1,945.82		1.0 (referent)	
1,945.82–2,908.62		0.7 (0.2–2.9)	
≥ 2,908.63		2.9 (0.5–17.0)	
2,3,4,7,8-PeCDF, fg/g			
< 54.02		1.0 (referent)	
≥ 54.02		0.9 (0.2–5.3)	
PCB 126, fg/g			
< 86.48		1.0 (referent)	
86.48–214.53		0.8 (0.4–1.5)	
≥ 214.54		8.9 (2.0–39.7)	
PCB 169, fg/g			
< 133.01		1.0 (referent)	
133.01–167.32		< 0.001	
≥ 167.33		9.4 (1.02–87.6)	
PCB 118, ng/g			
< 0.042		1.0 (referent)	
0.042–0.089		0.7 (0.2–2.7)	
≥ 0.090		7.0 (0.7–72.4)	
PCB 156, ng/g			
< 0.048		1.0 (referent)	
0.048–0.055		< 0.001	
≥ 0.056		17.9 (2.1–152.6)	
One of four chemicals elevated			
None elevated		1.0 (referent)	
One or more elevated		7.1 (1.8–28.1)	
OR for association of dioxins and dioxin-like chemicals with pre-diabetes, adjusted for age, gender, race/ethnicity, BMI Z-score, poverty income ratio, energy adjusted fruit and vegetable consumption, and physical activity			
1,2,3,6,7,8-HxCDD, fg/g			
< 121.41		1.0 (referent)	
121.41–299.45		0.7 (0.0–15.8)	
≥ 299.46		< 0.001	

TABLE 41 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
1,2,3,4,6,7,8-HpCDD, fg/g			
< 161.08		1.0 (referent)	
161.08–367.07		0.3 (0.1–0.9)	
≥ 367.08		0.9 (0.3–3.1)	
1,2,3,4,6,7,8,9-OCDD, fg/g			
< 1,945.82		1.0 (referent)	
1,945.82–2,908.62		0.4 (0.1–2.7)	
≥ 2,908.63		0.6 (0.2–2.4)	
2,3,4,7,8-PeCDF, fg/g			
< 54.02		1.0 (referent)	
≥ 54.02		< 0.001	
PCB 126, fg/g			
< 86.48		1.0 (referent)	
86.48–214.53		0.3 (0.1–1.0)	
≥ 214.54		< 0.001	
PCB 169, fg/g			
< 133.01		1.0 (referent)	
133.01–167.32		< 0.001	
≥ 167.33		< 0.001	
PCB 118, ng/g			
< 0.042		1.0 (referent)	
0.042–0.089		1.8 (0.6–5.2)	
≥ 0.090		< 0.001	
PCB 156, ng/g			
< 0.048		1.0 (referent)	
0.048–0.055		—	
≥ 0.056		< 0.001	
One of four chemicals elevated			
None elevated		1.0 (referent)	
One or more elevated		< 0.001	
Diabetes with nephropathy		2.4 (1.6–3.5)	Everett and Thompson, 2014
Diabetes without nephropathy		1.4 (1.1–1.9)	Everett et al., 2007
NHANES 1999–2002 participants			
Total diabetes (self-report or HbA1c > 6.1%)			
HxCDD (TEF = 0.1)			
> 42.0–99.1 pg/g		1.8 (1.1–2.8)	
> 99.1 pg/g		2.0 (0.9–4.4)	
PCB 126 (TEF = 0.1)			
> 31.3–83.8 pg/g		1.7 (1.0–2.7)	
> 83.8 pg/g		3.7 (2.1–6.5)	
NHANES 1999–2002 participants			Lee DH et al., 2006
HpCDD > 90th percentile vs nondetectable	46	2.7 (1.3–5.5)	
OCDD > 90th percentile vs nondetectable	31	2.1 (0.9–5.2)	
Anniston (Alabama) Community Health Survey—774 residents of an area with high level of PCBs		**PCBs**	
Association between diabetes and PCB levels in serum	202		Silverstone et al., 2012
Dioxin TEQs		1.2 (0.9–2.0)	

continued

TABLE 41 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS)—Prospective (cross-sectional) study of residents (≥ 70 years of age) living in Uppsala, Sweden, between April 2001 and June 2004 (n = 989; 725 in diabetes analysis)		**PCBs**	
Risk elevations compared to the lowest exposure quintiles:			Lee DH et al., 2011b
Second quintile, PCB 105		5.2 (1.3–84.4)	
Fourth quintile, PCB 118		10.7 (1.1–25.5)	
Fourth quintile, PCB 157		3.5 (1.0–12.4)	
Third quintile, PCB 189		3.5 (1.0–11.9)	
Coronary Artery Risk Development in Young Adults (CARDIA) Study		**Pesticides, PCBs**	
Nested case-control study within CARDIA study, relationship between persistent organic pollutants and type 2 diabetes (nested cases = 90 of 116 study participants who provided blood samples in 1987/88 exam and later developed diabetes)			Lee DH et al., 2010
Quartile 1 of PCB 156 (model 2, adjusted)		referent	
Quartile 2		1.3 (0.5–3.5)	
Quartile 3		0.9 (0.3–2.6)	
Quartile 4		0.8 (0.2–2.9)	
Quartile 1 of PCB 157 (model 2, adjusted)		referent	
Quartile 2		1.0 (0.4–2.5)	
Quartile 3		0.5 (0.2–1.5)	
Quartile 4		0.5 (0.1–1.7)	
Quartile 1 of PCB 167 (model 2, adjusted)		referent	
Quartile 2		0.9 (0.4–2.2)	
Quartile 3		1.0 (0.4–2.5)	
Quartile 4			
Other Environmental Studies			
BELGIUM			
Flemish Environment and Health Survey (2002–2006) random sample of men (n = 775) and women (n = 808) aged 50–65. Followup survey completed, November 2011, to assess health conditions		**PCBs**	Van Larebeke et al., 2015
HCB OR doubling of (ng/g fat) exposure and diabetes adjusted for BMI, education, cholesterol		1.49 (1.06–2.10)	
OR doubling of (pg TEQ/g fat) ln **dioxin-like activity** and diabetes adjusted for BMI, education, cholesterol		0.20 (0.09–0.47)	
PCB-118 OR doubling of (ng/g fat) exposure and diabetes adjusted for BMI, education, cholesterol		1.81 (1.01–3.22)	
Belgium residents (142 women, 115 men) exposed to dioxin, PCBs		**Dioxin, PCBs**	Fierens et al., 2003a
Subjects in top decile for dioxin		5.1 (1.2–21.7)	
CANADA			
Fasting plasma levels (pg/ml) from non-diabetic, obese, post-menopausal women from Montreal—36 "metabolically healthy" vs 40 "metabolically abnormal," categorized on the basis of insulin sensitivity		**dioxin-like PCBs, OCDD**	Gauthier et al., 2014
Sum PCBs 105, 118, 156, 157, 189		$p < 0.001$	
OCDD		$p = 0.161$	

TABLE 41 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
Population-based survey in Saskatchewan	28	**Herbicides** nr	Masley et al., 2000
Adult Inuit Health Survey (2007–2008) of Inuit participants from the Canadian Arctic (n = 2,172). Self-reported diabetes for 147 participants			Singh et al., 2017 (supplemental Table 2)
ORs for self-reported diabetes and lipid standardized plasma PCBs adjusted for age, gender, log BMI, √HDL, √omega3/omega6, and education			
PCB-105			
Q1		referent	
Q2		0.95 (0.42–2.16)	
Q3		0.79 (0.36–1.74)	
Q4		2.15 (1.04–4.67)	
PCB-118			
Q1		referent	
Q2		1.20 (0.52–2.96)	
Q3		1.00 (0.43–2.48)	
Q4		2.58 (1.12–6.44)	
PCB-156			
Q1		referent	
Q2		1.32 (0.58–3.23)	
Q3		1.06 (0.44–2.71)	
Q4		2.62 (1.04–7.02)	
ΣDioxin-like PCBs			
Q1		referent	
Q2		0.73 (0.31–1.76)	
Q3		0.84 (0.37–1.98)	
Q4		2.12 (0.91–5.16)	
TAIWAN			
Residents near a closed PCP factory with known dioxin release (n = 2,898); 425 had diabetes			Huang et al., 2015
PCDD/Fs (pg WHO98-TEQDF/g lipid) adjusted for age and BMI		**PCDD/Fs**	
< 20	86	1.0 (referent)	
20–63	246	2.2 (1.6–3.0)	
≥ 64	93	3.6 (2.4–5.4)	
Residence years adjusted for PCDD/Fs, age, and BMI			
< 30		1.0 (referent)	
30–39		1.7 (1.1–2.5)	
40–49		1.7 (1.1–2.6)	
50–59		3.3 (2.2–4.9)	
60–69		3.1 (1.9–4.9)	
≥ 70		3.7 (2.2–6.1)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, 2,4-dichlorophenoxypropanoic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,4,5-TP, 2-(2,4,5-trichlorophenoxy) propionic acid; ACC, Army Chemical Corps; AFHS, Air Force Health Study; BMI, body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; CATI, computer-assisted telephone interviewing; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; HbA1c, hemoglobin A1c; HpCDD, 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin; HxCDD, 1,2,3,6,7,9-hexachlorodibenzo-*p*-dioxin; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; IU, international unit; MCPA, 2 methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-

continued

TABLE 41 Continued

2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; MDL, mean dioxin level; MOS, military occupational specialty; NHANES, National Health and Nutrition Examination Survey; n, number; NIOSH, National Institute for Occupation Safety and Health; nr, not reported; ns, not significant; OCDD, 1,2,3,4,6,7,8,9-octachlorodibenzo-*p*-dioxin; OR, odds ratio; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDD/Fs, chlorinated dioxins and furans combined; PCP, pentachlorophenol; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; ppt, parts per trillion; SEA, Southeast Asia; SHR, standardized hospitalization ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCDF, tetrachlorodibenzofuran; TCP, trichlorophenol; TEF, toxicity equivalency factor; TEQ, (total) toxic equivalent; VA, US Department of Veterans Affairs.

[a]Given when available; results other than estimated risk explained individually.

[b]Study is discussed in greater detail in *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes* (IOM, 2000).

[c]Includes some subjects covered in other references cited in the category occupational cohorts.

TABLE 42 Selected Epidemiologic Studies—Circulatory Disorders (Shaded entries are new information for Update 11 [2018])[a]

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[c]	*Reference*/Comments
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Through 1999—Ranch Hand personnel (n = 1,262) vs SEA veterans (n = 19,078)—circulatory disease—mortality			*Ketchum and Michalek, 2005*
Ranch Hand subjects vs all SEA veterans			
Pilots and navigators	18	1.1 (0.7–1.8)	Not adjusted for known risk factors
Administrative officers	2	1.8 (0.4–7.8)	
Enlisted flight engineers	6	0.5 (0.2–1.1)	
Ground crew	40	1.7 (1.2–2.4)	
Atherosclerosis	28	1.7 (1.1–2.5)	
Hypertensive disease	2	2.5 (0.6–10.8)	
Stroke	5	2.3 (0.9–6.0)	
Subjects with serum TCDD measures			Adjusted for smoking and family history of heart disease
SEA comparison group	31	1.0	
Background (0.6–10.0 ppt)	8	0.8 (0.4–1.8)	
Low (10.0–29.2 ppt)	12	1.8 (0.9–3.5)	
High (18.0–617.8 ppt)	9	1.5 (0.7–3.3)	
US VA Cohort of Army Chemical Corps—Expanded as of 1997 to include all Army men with chemical MOS (2,872 deployed vs 2,737 nondeployed) serving during Vietnam era (07/01/1965–03/28/1973)		**All COIs**	
Self-reported circulatory disorders diagnosed by doctor			
2013 Mail or CATI health survey of 3,086 ACC veterans Hypertension ORs and 95% CIs, adjusted for Vietnam service status, rank, age at the time of the survey, tobacco use, alcohol use, race, and BMI			*Cypel et al., 2016*
Herbicide sprayer vs non-sprayer	1,085	1.74 (1.44–2.11)	
Vietnam service vs no service	1,146	1.26 (1.05–1.53)	
Vietnam sprayers vs Vietnam nonsprayers	740	1.77 (1.35–2.30)	
non-Vietnam sprayers vs non-Vietnam nonsprayers	345	1.72 (1.31–2.26)	
Vietnam sprayers vs non-Vietnam sprayers	740	1.29 (0.95–1.74)	
Vietnam nonsprayers vs non-Vietnam nonsprayers	406	1.25 (0.99–1.59)	
Vietnam nonsprayers vs non-Vietnam sprayers	406	0.73 (0.53–0.99)	
Vietnam sprayers vs non-Vietnam nonsprayers	740	2.21 (1.76–2.77)	

continued

TABLE 42 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[c]	*Reference*/Comments
CATI survey of stratified sample: 1,499 deployed (795 with TCDD measured) vs 1,428 nondeployed (102 with TCDD measured)			*Kang et al., 2006* Diagnoses not confirmed by medical record review. Adjusted for age, race, rank, BMI, and smoking. Serum TCDD levels measured in subset of subjects; self-reported sprayers had significantly higher concentrations, so that category regarded as valid surrogate for elevated exposure
Vietnam veterans vs non-Vietnam veterans			
Hypertension requiring medication	496	1.1 (0.9–1.3)	
Heart disease diagnosed by physician	243	1.1 (0.9–1.4)	
Sprayers vs nonsprayers			
All (diabetics, nondiabetics)			
Hypertension requiring medication	247	1.3 (1.0–1.6)	
Heart disease diagnosed by physician	129	1.4 (1.1–1.9)	
All veterans, contribution of spraying to logistic regression model			
All (diabetics, nondiabetics)			
Hypertension requiring medication		1.3 (1.1–1.6)	
Heart disease diagnosed by physician		1.5 (1.2–1.9)	
Nondiabetics only			
Hypertension requiring medication		1.2 (1.0–1.5)	
Heart disease diagnosed by physician		1.5 (1.1–2.0)	
Controlling for diabetic status			
Hypertension requiring medication		1.3 (1.0–1.6)	
Heart disease diagnosed by physician		1.5 (1.1–1.9)	
Mortality—Circulatory disorders			
Vietnam veterans vs non-Vietnam veterans—through 2005			*Cypel and Kang, 2010*
Deaths, causes of deaths from national death registries. Adjustment for race, rank duration of service, and age			
Circulatory system disease	184	1.2 (0.9–1.6)	
Hypertension	5	0.9 (0.2–3.9)	
Cerebrovascular disease	27	1.5 (0.7–3.3)	
Sprayers vs nonsprayers (subset studied in Kang et al., 2006)			
Circulatory system disease	ns	1.2 (0.6–2.3)	
Hypertension	ns	2.4 (0.2–28.5)	
Cerebrovascular disease	ns	2.1 (0.4–12.3)	
894 ACC members assigned to Vietnam in 1966–1971—1987 (vs US male population)			*Thomas and Kang, 1990*
Circulatory diseases (ICD 390–458)	6	0.6	Not adjusted for known risk factors
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Incidence			
Deployed vs nondeployed			*CDC, 1988a*
Hypertension after discharge			Not adjusted for known risk factors
Interviewed	2,013	1.3 ($p < 0.05$)	
Examined	623	1.2 ($p < 0.05$)	

TABLE 42 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[c]	*Reference*/Comments
Mortality			
Deployed vs nondeployed (1965–2000)	185	1.0 (0.8–1.2)	*Boehmer et al., 2004*
Circulatory disease			
Year of death			
1970–1984	nr	0.6 (0.3–1.2)	Adjusted for age, race, military occupation
1985–2000 (partition at 1970 arbitrary)	nr	1.1 (0.9–1.3)	
Discharged before 1970	nr	0.8 (0.6–1.1)	
Discharged after 1970	125	1.4 (1.0–2.0)	
Ischemic heart disease			
0–15 years since discharge	8	0.8 (0.3–1.6)	
> 15 years since discharge	117	1.1 (0.9–1.5)	
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/1965–3/1/1973		**All COIs**	
1965–1988—mortality (PMR)			*Watanabe and Kang, 1996*
Served in Vietnam vs never deployed to SEA			
Circulatory disease			Not adjusted for known risk factors
Army	5,756	0.97 (p > 0.05)	
Marine Corps	1,048	0.92 (p < 0.05)	
US VA Study of Male Vietnam Veterans Wounded in Combat		**All COIs**	
Mortality through 1981—US wounded Vietnam veterans vs US men (focus on suicide)			*Bullman and Kang, 1996*
Circulatory disease	246	0.7 (0.6–0.9)	
US VA Cohort of Female Vietnam-era Veterans served in Vietnam (n = 4,586; nurses only = 3,690); nondeployed (n = 5,325; nurses only = 3,282)		**All COIs**	
Mortality (deployed vs nondeployed)			
Through 2010—Vietnam-era veterans			*Kang et al., 2014*
Heart disease (angina pectoris, myocardial infarction, coronary artery disease, congestive heart failure) (n = 451)	167	0.8 (0.7–1.0)	
Cerebrovascular disease (total n = 94)	36	0.9 (0.6–1.3)	
Hypertension (total n = 12)	5	0.7 (0.2–2.3)	
Vietnam nurses only			
Heart disease (angina pectoris, myocardial infarction, coronary artery disease, congestive heart failure) (total = 343)	na	0.8 (0.6–1.0)	
Cerebrovascular disease (total n = 68)	na	0.8 (0.5–1.3)	
Hypertension (total n = 8)	na	0.7 (0.2–3.1)	
Through 2004—mortality			*Cypel and Kang, 2008*
Circulatory system diseases			Adjusted for duration of service, year of birth, race
Vietnam vs non-SEA veterans	129	0.8 (0.6–1.0)	
Nurses only	102	0.8 (0.6–1.0)	
US American Legion Cohort		**All COIs**	
American Legionnaires serving during Vietnam era—morbidity			*Stellman SD et al., 1988b*
Service in SEA vs not, with medically diagnosed			Not age adjusted
High blood pressure	592	1.1 (p > 0.05)	
Heart disease	97	1.5 (p < 0.05)	Age adjusted

continued

TABLE 42 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[c]	*Reference*/Comments
State Studies of US Vietnam Veterans			
Massachusetts Vietnam-era veterans—(1958–1973)—mortality (1972–1983); deployed vs nondeployed			*Kogan and Clapp, 1985* (state report)
Deaths 1972–1983 (PMR)			Not adjusted for age; VVs thought to be younger
Circulatory system (except cerebrovascular)	139	0.9 (p > 0.05)	
Cerebrovascular	28	1.1 (p > 0.05)	
Deaths 1978–1983 (PMR)			Expected less "diluted" effect for later time
Circulatory system (except cerebrovascular)	85	0.8 (p < 0.05)	
Cerebrovascular	19	1.6 (p < 0.05)	
Wisconsin Vietnam-era veterans—923 white male Vietnam veteran's with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans (all diseases of circulatory system)			*Anderson et al., 1986a,b*
White male Vietnam veterans vs	100		
National population		0.69 (p < 0.05)	
State population		0.62 (p < 0.05)	
Non-veterans		0.58 (p < 0.05)	
All veterans		0.86 (p > 0.05)	
Vietnam-era veterans		1.0 (0.8–1.2)	
International Vietnam Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Mortality—All branches, return–2001			
Circulatory disease	1,767	0.9 (0.8–0.9)	*ADVA, 2005a*
1963–1979	186	0.7 (0.6–0.8)	
1980–1990	546	0.9 (0.8–1.0)	Pattern of increasing risks with time could indicate dissipation of healthy warrior effect
1991–2001	1,035	0.9 (0.9–1.0)	
Ischemic heart disease	1,297	0.9 (0.9–1.0)	
1963–1979	124	0.7 (0.6–0.8)	
1980–1990	421	1.0 (0.9–1.0)	
1991–2001	753	1.0 (0.9–1.1)	
Stroke	223	0.8 (0.7–0.9)	
1963–1979	35	0.8 (0.5–1.1)	
1980–1990	59	0.7 (0.5–0.9)	
1991–2001	129	0.8 (0.7–1.0)	
1980–1994			*CDVA, 1997a*
Circulatory disease		1.0 (0.9–1.1)	Not adjusted for known risk factors
Ischemic heart disease		1.0 (0.9–1.1)	
Cerebral hemorrhage		0.8 (0.5–1.2)	
Sample of 1,000 Male Australian Vietnam Veterans—prevalence		**All COIs**	
450 interviewed 2005–2006 vs respondents to 2004–2005 national survey			*O'Toole et al., 2009*
Hypertensive disease	192	1.1 (1.0–1.3)	
Ischemic heart disease			Prevalence ratios calculated with age-adjustment
Angina	44	2.3 (1.7–3.0)	
Without angina	59	4.1 (3.1–5.0)	
Cerebrovascular disease	12	2.4 (1.2–3.5)	

TABLE 42 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[c]	*Reference*/Comments
641 interviewed 1990–1993 vs respondents to 1989–1990 national survey			*O'Toole et al., 1996b*
Hypertensive disease	nr	2.2 (1.7–2.6)	
Heart disease	nr	2.0 (0.9–3.1)	
Other circulatory diseases	nr	2.4 (1.6–3.2)	
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Mortality			
1966–2001			*ADVA, 2005c*
Circulatory disease	208	1.1 (0.9–1.3)	
Ischemic heart disease	159	1.2 (0.9–1.5)	
Stroke	15	0.6 (0.3–1.2)	
1982–1994 (deployed vs nondeployed)			*CDVA, 1997b*
Circulatory disease	77	1.0 (0.7–1.3)	Not adjusted for known risk factors
Ischemic heart disease	57	1.0 (0.7–1.4)	
Cerebral hemorrhage	3	1.0 (0.1–5.7)	
Other	17	0.9 (0.4–1.7)	
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	
Standardized hospitalization ratio for the number first observed for a condition compared to those expected based on New Zealand national hospitalization rates			*Cox et al., 2015*
Acute myocardial infarction	331	1.16 (1.00–1.33)	
Coronary atherosclerosis	659	1.27 (1.14–1.39)	
Chest pain	350	1.35 (1.16–1.53)	
Cardiac arrest	9	1.54 (0.22–2.86)	
Dysrhythmia	261	1.27 (1.07–1.48)	
Congestive heart failure	121	1.02 (0.78–1.26)	
Acute cerebrovascular disease	170	1.31 (1.05–1.56)	
Peripheral atherosclerosis	70	1.17 (0.81–1.53)	
Aneurysm	45	1.47 (0.91–2.04)	
Phlebitis	51	1.67 (1.07–2.28)	
Syncope	100	1.47 (1.18–1.76)	
Coronary Heart Disease Mortality (1988–2008)	104	0.8 (0.7–1.0)	*McBride et al., 2013*
Korean Vietnam Veterans Health Study		**All COIs**	
Prevalence (01/2000–09/2005) (n = 111,726)			*Yi et al., 2014a*
Diseases of the circulatory system [I00–I99]			
Categorized high (n = 42,421) vs low (n = 69,305)	25,613 vs 40,518	1.0 (1.0–1.0) p = 0.937	ORs adjusted for age, military rank, smoking, drinking frequency, physical activity, domestic herbicide experience, education, household income, BMI
Hypertensive disease [I10–I13]	19,597 vs 30,701	1.0 (1.0–1.0) p = 0.715	
Essential (primary) hypertension [I10]	18,946 vs 29,619	1.0 (1.0–1.0) p = 0.908	
Ischemic heart disease [I20–I25]	8,044 vs 12,226	1.0 (1.0–1.1) p = 0.025	
Acute myocardial infarction [I21–I23]	1,248 vs 1,891	1.0 (1.0–1.1) p = 0.539	
Heart failure [I50]	1,460 vs 2,156	1.0 (1.0–1.1) p = 0.769	
Stroke [I60–I64]	4,330 vs 6,024	1.1 (1.0–1.1) p < 0.001	
Atherosclerosis [I70]	1,036 vs 1,629	1.0 (0.9–1.1) p = 0.714	
Log EOI scores			

continued

TABLE 42 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[c]	*Reference*/Comments
Diseases of the circulatory system [I00–I99]	66,131	p = 0.929	
Hypertensive disease [I10–I13]	50,298	p = 0.704	
Essential (primary) hypertension [I10]	48,565	p = 0.518	
Ischemic heart disease [I20–I25]	20,270	p = 0.012	
Acute myocardial infarction [I21–I23]	3,139	p = 0.699	
Heart failure [I50]	3,616	p = 0.402	
Stroke [I60–I64]	10,354	p < 0.001	
Atherosclerosis [I70]	2,665	p = 0.584	
Mortality (1992–2005) (n = 180, 639)			*Yi et al., 2014b*
Diseases of the circulatory system [I00–I99] Categorized high (n = 85,809) vs low (n = 69,305)	1,716 vs 1,464	1.0 (1.0–1.1) p = 0.289	HRs adjusted for age at cohort entry, military rank during Vietnam service
Hypertension [I10–I13]	110 vs 82	1.2 (0.9–1.6) p = 0.278	
Ischemic heart disease [I20–I25]	437 vs 406	1.0 (0.9–1.1) p = 0.897	
Acute myocardial infarction [I21]	352 vs 347	0.9 (0.8–1.1) p = 0.383	
Cerebrovascular diseases [I60–I69]	879 vs 739	1.0 (0.9–1.1) p = 0.785	
Log EOI scores	3,180	p = 0.028	
Hypertensive disease [I10–I13]	192	p = 0.108	
Ischemic heart disease [I20–I25]	843	p = 0.729	
Acute myocardial infarction [I21]	699	p = 0.313	
Cerebrovascular diseases [I60–I69]	1,618	p = 0.353	
Korean Vietnam Veterans—morbidity		**All COIs**	
Deployed vs nondeployed (unadjusted)			
Cox-regression analysis revealed that exposure history to TCDD has not significant impact on long-term cardiac events		p = 0.736	*Kim et al., 2014*
Hospital-based study of ischemic stroke Exposed cases with deployment to Vietnam (n = 91) compared to male ischemic stroke patients 55–75 years who did not serve (n = 288)			*Han et al., 2016*
Hypertension	60	65.9% vs 72.2%, p = 0.290	
Hyperlipidemia	6	6.6% vs 24.0%, p ≤ 0.001	
Atrial fibrillation	9	9.9% vs 17.0%, p = 0.132	
Type of stroke,			
Small vessel occlusion	36	39.6 % vs 25.3 %	
Large artery atherosclerosis	26	28.6 % vs 41.7 %	
Cardio embolism	9	9.9 % vs 16.0 %	
Other	20	22.0 % vs 17.0 % 0.014 p-trend type of stroke subtype	

TABLE 42 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[c]	*Reference*/Comments
Hypertensive disease [I10–I13]	192	p = 0.108	*Kim JS et al., 2003* Concerns: selection bias, diagnosis quality, low participation, sample pooling made TCDD concentrations useless
Ischemic heart disease [I20–I25]	843	p = 0.729	
Acute myocardial infarction [I21]	699	p = 0.313	
Cerebrovascular diseases [I60–I69]	1,618	p = 0.353	
Deployed vs nondeployed (unadjusted)			
Valvular heart disease	8	p = 0.0019	
Congestive heart failure	5	p = 0.5018	
Ischemic heart disease	34	p = 0.0143	
Hypertension	383	2.3 (1.3–4.0)	
Adjusted for age, smoking, alcohol, BMI, education, marital status			
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates		**Dioxin, phenoxy herbicides**	
Mortality 1939–1992			*Vena et al., 1998* (same dataset as *Kogevinas et al.,1997* [emphasis on cancer])
All male phenoxy herbicide workers			
All circulatory disease (ICD 390–459)	1,738	0.9 (0.9–1.0)	
Ischemic heart disease (ICD 410–414)	1,179	0.9 (0.9–1.0)	
Cerebrovascular disease (ICD 430–438)	254	0.9 (0.8–1.0)	
Other diseases of the heart (ICD 415–429)	166	1.1 (1.0–1.3)	
All female phenoxy herbicide workers			
All circulatory disease (ICD 390–459)	48	1.0 (0.7–1.3)	Not adjusted for known risk factors
Ischemic heart disease (ICD 410–414)	24	1.1 (0.7–1.6)	
Cerebrovascular disease (ICD 430–438)	9	0.7 (0.3–1.4)	
Other diseases of the heart (ICD 415–429)	6	0.9 (0.3–2.0)	
Workers with phenoxy herbicide exposure only			
All circulatory disease (ICD 390–459)	588	0.9 (0.8–0.9)	
Ischemic heart disease (ICD 410–414)	394	0.9 (0.8–0.9)	
Cerebrovascular disease (ICD 430–438)	96	0.9 (0.7–1.1)	
Other diseases of the heart (ICD 415–429)	32	0.9 (0.8–0.9)	
TCDD-exposed workers			
All circulatory disease (ICD 390–459)	1,170	0.9 (0.9–1.0)	
Ischemic heart disease (ICD 410–414)	789	1.0 (0.9–1.0)	
Cerebrovascular disease (ICD 430–438)	162	0.8 (0.7–1.0)	
Other diseases of the heart (ICD 415–429)	138	1.2 (1.0–1.4)	
Contribution of TCDD exposure to Poisson regression analysis			Adjusted for age, timing of exposure
All circulatory disease (ICD 390–459)	1,151	1.5 (1.2–2.0)	
Ischemic heart disease (ICD 410–414)	775	1.7 (1.2–2.3)	
Cerebrovascular disease (ICD 430–438)	161	1.5 (0.8–2.9)	
British MCPA Plant—Production 1947–1982 (n = 1,545) (included in IARC cohort) and spraying 1947–1972 (n = 2,561) (not included in IARC cohort)		**MCPA**	
Mortality through 1983 (hypertensive, ischemic heart disease (ICD 401–414, 428–429)	337		*Coggon et al., 1986*
vs national rates		0.8 (0.7–0.9)	
vs rural adjustment		0.9 (0.8–1.0)	

continued

TABLE 42 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[c]	*Reference*/Comments
British Production Workers at 4 plants (included in IARC cohort)		**Dioxins, but TCDD unlikely; MCPA**	*Coggon et al., 1991*
Mortality—circulatory disease	74	1.2 (0.9–1.5)	
Plant A (1975–1987)	34	1.7 (adjusted = 1.4, p ≈ 0.05)	
Plant B (1969–1987)	5	0.95	
Plant C (1963–1987)	12	0.84	
Plant D (1969–1987)	23	0.97	
Danish Production Workers (3,390 men and 1,069 women involved in production of phenoxy herbicides unlikely to contain TCDD at 2 plants in 1947–1987) (in IARC cohort)		**Dioxins, but TCDD unlikely; 2,4-D, 2,4-DP, MCPA, MCPP**	
Incidence			
Incidence 1943–1987 (men only)			*Lynge, 1993*
Incidence 1943–1982			*Lynge, 1985*
Men			
Women			
Mortality			
Mortality 1955–2006			*Boers et al., 2012*
TCDD plasma level (HRs, by tertile)	93	1.2 (1.1–1.3)	
Background (≤ 0.4)	33	—	
Low (0.4–4.1)	6	0.9 (0.4–2.5)	
Medium (4.1–20.1)	6	1.5 (0.6–4.0)	
High (≥ 20.1)	7	2.7 (1.0–7.2)	
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–2006 (HRs for lagged TCDD plasma levels)			*Boers et al., 2012*
Ischemic heart disease (ICD-9 120–125)	60	1.2 (1.1–1.4)	
Cerebrovascular disease (ICD-9 160–167)	24	0.9 (0.7–1.1)	
Mortality 1955–2006			*Boers et al., 2010*
Ischemic heart disease	43	1.2 (0.7–2.0)	
Accident 1963	17	1.6 (0.7–3.6)	HRs adjusted for age, year of first employment. Referent group is unexposed workers
Main production workers	9	1.0 (0.5–2.2)	
Occasionally exposed	17	1.1 (0.6–2.1)	
Cerebrovascular disease	17	1.2 (0.4–3.6)	
Accident 1963	2	0.3 (0.1–1.4)	
Main production workers	5	1.3 (0.4–4.7)	
Occasionally exposed	10	1.5 (0.5–4.3)	
Mortality 1955–1991 (549 exposed vs 482 nonexposed male workers)			*Hooiveld et al., 1998*
All circulatory disease (ICD 390–459)	45	1.4 (0.8–2.5)	
TCDD > 124 ng/kg	nr	1.5 (0.8–2.9)	Adjusted for age, timing of exposure
Ischemic heart disease (ICD 410–414)	33	1.8 (0.9–3.6)	
TCDD > 124 ng/kg	nr	2.3 (1.0–5.0)	
Cerebrovascular disease (ICD 430–438)	9	1.4 (0.4–5.1)	
TCDD > 124 ng/kg	nr	0.8 (0.2–4.1)	
Other heart disease (ICD 415–429)	3	0.7 (0.1–4.3)	
TCDD > 124 ng/kg	nr	0.4 (0.0–4.9)	

TABLE 42 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[c]	*Reference*/Comments
Dutch production workers in Plant B (414 men exposed during production 1965–1986; 723 unexposed) (in IARC cohort)		**2,4-D; MCPA; MCPP; highly chlorinated dioxins unlikely**	
Mortality 1965–2006			*Boers et al., 2010*
Ischemic heart disease	18	1.6 (0.8–3.1)	HRs adjusted for age, year of first employment. Referent group is unexposed workers
Main production workers	5	1.7 (0.6–4.6)	
Occasionally exposed	13	1.6 (0.7–3.3)	
Cerebrovascular disease	7	1.0 (0.4–2.8)	
Main production workers	1	0.9 (0.1–7.1)	
Occasionally exposed	6	1.1 (0.4–3.2)	
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 month in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992 (circulatory diseases, ICD 390–458)	12	0.7 (0.4–1.3)	*Becher et al., 1996*
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 month in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1965–1989 (circulatory diseases, ICD 390–458)	3	0.3 (0.1–1.0)	*Becher et al., 1996*
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 month in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1956–1989 (circulatory diseases, ICD 390–458)	32	0.8 (0.5–1.1)	*Becher et al., 1996*
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Mortality—1953–1992			*Ott and Zober, 1996b*
Circulatory diseases	37	0.8 (0.6–1.2)	
< 0.1 estimated TCDD μg/kg bw	13	0.8 (0.4–1.4)	
0.1–0.99	11	1.0 (0.5–1.7)	Reliability of estimated body burden is questionable
≥ 1.0	13	0.8 (0.4–1.3)	
Ischemic heart disease	16	0.7 (0.4–1.1)	
< 0.1 estimated TCDD μg/kg bw	7	0.9 (0.3–1.8)	
0.1–0.99	4	0.7 (0.2–1.7)	
≥ 1.0	5	0.6 (0.2–1.3)	
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 month in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–2007			*Manuwald et al., 2012*
Men			
Circulatory system disease		1.2 (1.0–1.3)	
Women			
Circulatory system disease		0.7 (0.6–0.9)	

continued

TABLE 42 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[c]	*Reference*/Comments
Mortality 1952–1992; estimated blood PCDD, PCDF, TCDD from work history, measured in 190 of 1,189 men, divided into 4 lowest quintiles, top 2 deciles			*Flesch-Janys et al., 1995*
Estimated final PCDD, PCDF, TEQs (ng/kg)			
Circulatory disease (ICD 390–459)	156		Gas workers provide a more appropriate comparison group for the data on production workers than the national population data used in *Flesch-Janys, 1997; Flesch-Janys et al., 1998*
1.0–12.2		0.9 (0.6–1.5)	
12.3–39.5		0.9 (0.6–1.5)	
39.6–98.9		1.5 (1.0–2.2)	
99.0–278.5		1.6 (1.1–2.2)	
278.6–545.0		1.6 (1.0–2.6)	
545.1–4,361.9		2.1 (1.2–3.5)	
		p-trend < 0.01	
Ischemic heart disease (ICD 410–414)	76		
1.0–12.2		1.0 (0.5–2.0)	
12.3–39.5		1.0 (0.5–1.8)	
39.6–98.9		1.0 (0.5–1.8)	
99.0–278.5		1.1 (0.6–2.0)	
278.6–545.0		1.7 (0.9–3.3)	
545.1–4,361.9		2.7 (1.5–5.0)	
		p-trend < 0.01	
Estimated final TCDD (ng/kg)			
Circulatory disease (ICD 390–459)	156		
0–2.8		1.2 (0.8–1.8)	Not adjusted for known risk factors
2.81–14.4		0.9 (0.5–1.4)	
14.5–49.2		1.4 (0.9–2.0)	
49.3–156.7		1.6 (1.1–2.4)	
156.8–344.6		1.5 (1.0–2.4)	
344.7–3,890.2		2.0 (1.2–3.3)	
		p-trend = 0.01	
Ischemic heart disease (ICD 410–414)	76		
0–2.8		1.4 (0.8–2.4)	Potential for exposure misclassification
2.81–14.4		0.8 (0.4–1.6)	
14.5–49.2		1.2 (0.7–2.2)	
49.3–156.7		0.9 (0.5–1.8)	
156.8–344.6		1.6 (0.9–3.0)	
344.7–3,890.2		2.5 (1.3–4.7)	
		p-trend < 0.01	
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
245 Workers randomly selected for study consented to send a blood sample			*'t Mannetje et al., 2018*
OR Heart Disease worked in highly exposed job, adjusted for age (continuous), gender, smoking (ever/ex/current), BMI (< 25/25–30/≥ 30/missing), Māori ethnicity	10	2.71 (0.65–11.4)	
OR Heart Disease serum TCDD ≥ 10 pg/g lipid, adjusted for age (continuous), gender, smoking (ever/ex/current), BMI (< 25/25–30/≥ 30/missing), Māori ethnicity	5	1.64 (0.41–6.57)	

TABLE 42 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[c]	*Reference*/Comments
Mortality 1969–2004			*McBride et al., 2009*
Ever-exposed workers—stroke	15	1.1 (0.6–1.9)	
Ever-exposed workers—ischemic heart disease	61	1.1 (0.9–1.5)	
Ischemic heart disease:			Adjusted for age, sex, hire year, birth year
TCDD exposure ppt-months			
0–68.3	14	1.0 (referent)	
68.4–475.0	18	1.2 (0.6–2.6)	
475.1–2,088.7	15	1.3 (0.6–2.9)	
> 2,088.7	14	0.9 (0.4–2.4)	
Production Workers (713 men and 100 women worked > 1 month in 1969–1984)			
Mortality 1969–2000			*'t Mannetje et al., 2005*
Circulatory disease	51	1.0 (0.7–1.3)	
Hypertensive disease	0	0.0 (0.0–3.5)	Not adjusted for known risk factors
Ischemic heart disease	38	1.0 (0.7–1.4)	
All-causes (SMR)	nr	1.0 (0.8–1.2)	
Sprayers (697 men and 2 women on register of New Zealand applicators, 1973–1984)			
Mortality 1973–2000			*'t Mannetje et al., 2005*
Circulatory disease	33	0.5 (0.4–0.7)	
Hypertensive disease	1	0.8 (0.0–4.5)	Not adjusted for known risk factors
Ischemic heart disease	22	0.5 (0.3–0.8)	
All-causes (SMR)	nr	0.6 (0.5–0.8)	
(Preliminary) NIOSH Cross-Sectional Medical Study—490 workers from chemical plants in Newark, New Jersey, and Verona, Missouri, 1951–1969 (morbidity)		**Dioxin/phenoxy herbicides**	*Calvert et al., 1998*
Verified conditions			
TCDD-exposed (281) vs nonexposed (260)			Not adjusted for known risk factors
Myocardial infarction	17	1.3 (0.6–2.8)	
Current systolic hypertension	64	1.1 (0.7–1.6)	
Current diastolic hypertension	77	1.2 (0.8–1.8)	
TCDD effect vs nonexposed in logistic model. Self-reported, verified conditions combined			
Myocardial infarction			Adjusted for age, sex, BMI, smoking, drinking, diabetes, triglycerides, total cholesterol, HDL, family history of heart disease, and chemical plant
Serum TCDD < 238 pg/g of lipid	nr	1.1 (0.3–4.5)	
Serum TCDD ≥ 238 pg/g of lipid	nr	1.1 (0.2–5.1)	
Hypertension			
Serum TCDD < 238 pg/g of lipid	nr	1.3 (0.9–2.0)	
Serum TCDD ≥ 238 pg/g of lipid	nr	1.1 (0.6–1.9)	
Verified conditions			
Current systolic hypertension			
Serum TCDD < 238 pg/g of lipid	nr	1.1 (0.7–1.8)	
Serum TCDD ≥ 238 pg/g of lipid	nr	1.2 (0.6–2.3)	
Current diastolic hypertension			
Serum TCDD < 238 pg/g of lipid	nr	1.4 (0.9–2.1)	
Serum TCDD ≥ 238 pg/g of lipid	nr	1.0 (0.5–1.9)	

continued

TABLE 42 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[c]	*Reference*/Comments
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993			*Steenland et al., 1999*
Cerebrovascular disease (ICD 430–438)	69	1.0 (0.7–1.2)	Not adjusted for known risk factors
Ischemic heart disease (ICD 410–414)	456	1.1 (1.0–1.2)	
Chloracne subcohort (n = 608) vs US population; exposure subcohort (n = 3,538)	92		Adjusted for age
< 19 cumulative TCDD	nr	1.0	
19–138	nr	1.2 (0.8–2.0)	
139–580	nr	1.3 (0.8–2.2)	No units given for exposure derived from job-exposure matrix
581–1,649	nr	1.3 (0.8–2.1)	
1,650–5,739	nr	1.4 (0.9–2.2)	
5,740–20,199	nr	1.6 (1.0–2.6)	
≥ 20,200	nr	1.8 (1.1–2.9)	
		p-trend = 0.05 p-trend log < 0.001	
Monsanto workers (n = 240) involved in 2,4,5-T production (1948–1969) and 163 unexposed workers, results of clinical examination July 1979—morbidity		**Dioxin, phenoxy herbicides**	*Suskind and Hertzberg, 1984*
Hypertension	70	(p > 0.05)	Adjusted for age
Coronary artery disease	22	(p > 0.05)	
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, Michigan) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)			*Collins et al., 2009b*
Ischemic heart disease	218	1.1 (0.9–1.2)	No adjustment discussed
Cerebrovascular disease	37	1.0 (0.7–1.4)	
March 1955–1977 (n = 884 workers); mortality			*Zack and Gaffey, 1983*
Circulatory disease (ICD 390–458)	92	1.11 (p > 0.05)	Not adjusted for known risk factors
Atherosclerosis and CHD (ICD 410–413)	79	1.33 (p > 0.05)	
March 1949–1978 (n = 121); mortality—121 TCP workers with chloracne			*Zack and Suskind, 1980*
Circulatory disease (ICD 390–458)	17	0.68 (p > 0.05)	Not adjusted for known risk factors
Atherosclerosis and CHD (ICD 410–413)	13	0.73 (p > 0.05)	
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, Washington, and Wichita, Kansas) and workers who made PCP and TCP at two additional plants (in Midland, Michigan, and Sauget, Illinois)		**2,4,5-T; 2,4,5-TCP**	*Ruder and Yiin, 2011*
1940–2005 (n = 2,122)			
Rheumatic heart disease (ICD-9 390–398)	4	0.6 (0.2–1.6)	
Ischemic heart disease (ICD-9 410–414)	350	1.0 (0.9–1.2)	
Hypertension with heart disease (ICD-9 402, 404)	6	0.4 (0.2–1.0)	
Cerebrovascular disease (ICD-9 430–438)	64	1.0 (0.7–1.2)	
PCP and TCP (n = 720)			
Rheumatic heart disease (ICD-9 390–398)	0	0.0 (0.0–1.9)	
Ischemic heart disease (ICD-9 410–414)	120	1.1 (0.9–1.3)	
Hypertension with heart disease (ICD-9 402, 404)	0	0.0 (0.0–1.0)	
Cerebrovascular disease (ICD-9 430–438)	20	1.0 (0.6–1.5)	

TABLE 42 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[c]	*Reference*/Comments
PCP (no TCP) (n = 1,402)			
Rheumatic heart disease (ICD-9 390–398)	4	0.9 (0.3–2.3)	
Ischemic heart disease (ICD-9 410–414)	230	1.0 (0.9–1.1)	
Hypertension with heart disease (ICD-9 402, 404)	6	0.6 (0.2–1.3)	
Cerebrovascular disease (ICD-9 430–438)	44	0.9 (0.7–1.2)	
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan) (subset of all TCP-exposed workers)		**2,4-D, lower chlorinated dioxins**	
Through 1994 (n = 1,517), circulatory disease			*Burns et al., 2001*
0 years latency	158	1.0 (0.8–1.1)	
≥ 20 years latency	130	1.1 (0.9–1.2)	
Dow PCP Production Workers (1937–1989 in Midland, Michigan) (*not* in IARC and NIOSH cohorts)		**Low chlorinated dioxins, 2,4-D**	
1937–2011 Potential dioxin exposure (n = 2,192), TCP production (n = 1,419), PCP production (n = 577), Both TCP and PCP (n = 196)		**2,4,5-T; 2,4,5-TCP PCP**	*Collins et al., 2016*
TCP/PCP, Cerebrovascular disease (I60–I69)	68	1.03 (0.80–1.30)	
TCP (includes 196 PCP workers), Cerebrovascular disease (I60–I69)	49	1.07 (0.79–1.41)	
PCP (includes 196 TCP workers), Cerebrovascular disease (I60–I69)	27	1.07 (0.70–1.55)	
TCP/PCP, Ischemic heart disease (I20–I25)	371	1.10 (0.99–1.22)	
TCP (includes 196 PCP workers), Ischemic heart disease (I20–I25)	256	1.07 (0.95–1.21)	
PCP (includes 196 TCP workers), Ischemic heart disease (I20–I25)	150	1.20 (1.01–1.41)	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)			*Collins et al., 2009a*
Ischemic heart disease	99	1.0 (0.8–1.3)	No adjustment discussed
Cerebrovascular disease	17	0.9 (0.5–1.2)	
Mortality 1940–1989 (n = 770)			*Ramlow et al., 1996*
Circulatory disease (ICD 390–458)	115	1.0 (0.8–1.1)	
Arteriosclerotic heart disease (ICD 410–413)	86	1.0 (0.8–1.3)	
Cerebrovascular disease (ICD 430–438)	15	1.0 (0.6–1.7)	
Other Studies of Industrial Workers (not related to IARC or NIOSH phenoxy cohorts)			
Italy			
Trento, electric arc furnace workers (n = 331). Cohort followed from 1979–2009 (6,731 person-years)		**Dioxin (detected in foundry dust)**	*Cappelletti et al., 2016*
Ischemic heart disease (crude)	4	1.27 (0.35–3.26)	
Morbidity analysis limited to 235 living workers adjusted for age, compared to general population in Trento			
Cardiovascular Disease	5	1.74 (1.07–2.82)	
Non-complicated Hypertension	30	2.44 (1.75–3.40)	
Complicated Hypertension	14	2.22 (1.35–3.65)	

continued

TABLE 42 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[c]	*Reference*/Comments
Japanese Waste-Incinerator Workers—Workers exposed to PCDD at municipal waste incinerator		**Dioxin, phenoxy herbicides**	*Kitamura et al., 2000*
Hypertension by PCDD, PCDF	14 of 94	No increases observed	Adjusted for age, BMI, smoking
678 male workers from 2000–2007 at 36 waste incineration sites throughout Japan		**PCDDs**	*Yamamoto et al., 2015*
< 4.34 pg TEQ/g lipid	3	1.0 (referent)	
≥ 4.34 pg TEQ/g lipid	7	1.35 (0.84–2.19)	
≥ 6.09 pg TEQ/g lipid	10	1.16 (0.71–1.91)	
≥ 8.98 pg TEQ/g lipid	25	1.66 (1.00–2.78)	
		p-trend < 0.05	
		PCDFs	
< 2.16 pg TEQ/g lipid	3	1.0 (referent)	
≥ 2.16 pg TEQ/g lipid	7	1.34 (0.82–2.19)	
≥ 3.10 pg TEQ/g lipid	10	1.74 (1.06–2.87)	
≥ 4.51 pg TEQ/g lipid	25	1.90 (1.12–3.25)	
		p-trend < 0.05	
		Coplanar PCBs	
< 2.60 pg TEQ/g lipid	2	1.0 (referent)	
≥ 2.60 pg TEQ/g lipid	9	1.26 (0.76–2.09)	
≥ 4.45 pg TEQ/g lipid	14	1.66 (0.99–2.79)	
≥ 7.30 pg TEQ/g lipid	20	2.31 (1.33–4.02)	
		p-trend < 0.05	
		Total dioxins	
< 9.76 pg TEQ/g lipid	3	1.0 (referent)	
≥ 9.76 pg TEQ/g lipid	7	1.01 (0.62–1.66)	
≥ 13.70 pg TEQ/g lipid	10	1.62 (0.97–2.70)	
≥ 21.67 pg TEQ/g lipid	25	1.92 (1.21–3.28)	
		p-trend < 0.05	
OCCUPATIONAL—PAPER AND PULP WORKERS		**TCDD**	
IARC cohort of pulp and paper workers—60,468 workers from 11 countries, TCDD among 27 agents assessed by JEM			*McLean et al., 2006*
Exposure to nonvolatile organochlorine compounds—circulatory disease (mortality)			Not adjusted for known risk factors
Never	2,727	0.9 (0.8–1.0)	
Ever	2,157	1.0 (1.0–1.0)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
ITALIAN Licensed Pesticide Users—male farmers in southern Piedmont licensed 1970–1974			
Italian rice growers with documented phenoxy use (1960–1980)—mortality (1957–1992) (n = 1,487)		**Phenoxy herbicides**	*Gambini et al., 1997*
Myocardial infarction	67	0.7 (0.6–0.9)	
Other ischemic heart diseases	72	0.4 (0.3–0.5)	
Stroke	155	1.0 (0.8–1.1)	

TABLE 42 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[c]	*Reference*/Comments
THE NETHERLANDS			
Dutch Licensed Herbicide Sprayers—1,341 certified before 1980		**Herbicides**	
Through 2000			*Swaen et al., 2004*
Circulatory disease	70	0.7 (0.5–0.9)	
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; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Parameter estimate phenoxy herbicide exposure and 1 unit change in BMI at followup		β = 0.03 p = 0.0222	*Laverda et al., 2015*
Study of myocardial infarction			*Mills et al., 2009*
Mortality among 54,069 male applicators			
2,4-D	73	0.9 (0.7–1.1)	Adjusted for age, state, smoking. Incidence analysis further adjusted for body mass index
2,4,5-T	32	1.0 (0.8–1.2)	
2,4,5-TP	14	1.1 (0.8–1.4)	
Dicamba	42	0.9 (0.8–1.2)	
Non-fatal incidence among 32,024 male applicators—year 5 survey			
2,4-D	78	1.2 (1.0–1.4)	
2,4,5-T	37	1.2 (1.0–1.4)	
2,4,5-TP	14	1.1 (0.9–1.4)	
Dicamba	47	1.1 (0.9–1.3)	
Enrollment through 2001—mortality			*Blair et al., 2005a,b*
Private applicators (farmers), spouses			Adjusted for age, race, state, sex, and calendar year of death
Circulatory disease	619	0.5 (0.5–0.6)	
Enrollment through 2007, vs state rates			*Waggoner et al., 2011*
Applicators (n = 1,641)			
Rheumatic heart disease	8	0.7 (0.3–1.4)	
Hypertension with heart disease	40	0.5 (0.4–0.7)	
Hypertension without heart disease	15	0.4 (0.2–0.6)	
Ischemic heart disease	1,099	0.5 (0.5–0.6)	
Cerebrovascular disease	236	0.5 (0.5–0.6)	
Spouses (n = 676)			
Rheumatic heart disease	7	0.7 (0.3–1.5)	
Hypertension with heart disease	7	0.3 (0.1–0.6)	
Hypertension without heart disease	6	0.3 (0.1–0.7)	
Ischemic heart disease	211	0.5 (0.4–0.5)	
Cerebrovascular disease	105	0.6 (0.5–0.7)	

continued

TABLE 42 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[c]	*Reference*/Comments
US Department of Agriculture Workers—nested case-control study of white men dying 1970–1979		**Herbicides**	
Forest conservationists		p-trend < over years worked	*Alavanja et al., 1989* Not adjusted for known risk factors
Ischemic heart disease (ICD 410–414)	543	1.0 (0.9–1.1)	
Cerebrovascular disease (ICD 430–438)	99	0.9 (0.8–1.1)	
Florida Licensed Pesticide Applicators		**Herbicides**	*Blair et al., 1983* Not adjusted for known risk factors
Pesticide applicators in Florida licensed 1965–1966 (n = 3,827)—mortality through 1976			
Circulatory diseases (ICD 390–458)			
ENVIRONMENTAL			
Seveso, Italy, Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
25-year followup to 2001			*Consonni et al., 2008*
Zone A, sexes combined			
All circulatory diseases (ICD 390–459)	45	1.1 (0.8–1.4)	Adjusted for gender, age, period
Chronic rheumatic heart diseases (ICD 393–398)	3	5.7 (1.8–18.0)	
Hypertension (ICD 400–405)	5	2.2 (0.9–5.3)	
Ischemic heart diseases (ICD 410–414)	13	0.8 (0.5–1.4)	
Acute myocardial infarction (ICD 410)	6	0.6 (0.3–1.4)	
Chronic ischemic heart diseases (ICD 412, 414)	7	1.1 (0.5–2.3)	
Cerebrovascular diseases (ICD 430–438)	11	0.9 (0.5–1.6)	
Zone B, sexes combined			
All circulatory diseases (ICD 390–459)	289	1.0 (0.9–1.1)	
Chronic rheumatic heart diseases (ICD 393–398)	1	0.3 (0.0–2.2)	
Hypertension (ICD 400–405)	11	0.7 (0.4–1.3)	
Ischemic heart diseases (ICD 410–414)	102	1.0 (0.8–1.2)	
Acute myocardial infarction (ICD 410)	54	0.9 (0.7–1.1)	
Chronic ischemic heart diseases (ICD 412, 414)	47	1.1 (0.8–1.4)	
Cerebrovascular diseases (ICD 430–438)	101	1.2 (1.0–1.5)	
Zone R, sexes combined			
All circulatory diseases (ICD 390–459)	2,357	1.1 (1.0–1.1)	
Chronic rheumatic heart diseases (ICD 393–398)	24	1.0 (0.6–1.5)	
Hypertension (ICD 400–405)	144	1.2 (1.0–1.4)	
Ischemic heart diseases (ICD 410–414)	842	1.1 (1.0–1.1)	
Acute myocardial infarction (ICD 410)	447	1.0 (0.9–1.1)	
Chronic ischemic heart diseases (ICD 412, 414)	390	1.2 (1.0–1.3)	
Cerebrovascular diseases (ICD 430–438)	695	1.1 (1.0–1.2)	

TABLE 42 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[c]	*Reference*/Comments
National Health and Nutrition Examination Survey			
NHANES 1999–2004 participants over 70 years		**PCBs**	
CVD death			*Kim et al., 2015*
Tertile 1 PCB Exposure	11	referent	Adjusted for age, sex, race, smoking, physical activity, and BMI
Tertile 2 PCB Exposure	13	1.06 (0.47–2.40)	
Tertile 3 PCB Exposure	26	2.37 (1.10–5.09)	
NHANES 2011–2012—9,756 participants, 3,035 with hypertension		**2,4-D**	*Shiue et al., 2014* Adjusted for urine creatinine, age, sex, ethnicity, and BMI
OR 2,4-Dichlorophenol and hypertension		1.02 (0.88–1.19)	
Total arsenic		1.13 (0.99–1.29)	
Trimethylarsine oxide		2.47 (1.27–4.81)	
Dimethylarsonic acid		1.42 (1.12–1.79)	
NHANES 1999–2004—9,756 adults ≥ 40 years of age (1,176 males and 1,185 females) followed for mortality through 2006 (average 4.6 years)		**Dioxin, dioxin-like PCBs**	*Lin et al., 2012* Adjusted for age, gender, BMI, race, smoking, drinking
CVD [ICD-10 I00–I78]—75 deaths			
< 25th percentile (13.3 pg TEQ/g lipid)		1.0	
25th–75th percentile (13.3–27.9 pg TEQ/g lipid)		1.5 (0.6–3.4)	
>75th percentile (≥ 27.9 pg TEQ/g lipid)		1.7 (0.6–4.5)	
		p-trend = 0.59	
increase per 1 pg in dioxin TEQ/g lipid		1.1 (0.8–1.5)	
NHANES 1999–2002—newly diagnosed hypertension; 524 adults (≥ 40 years of age) excluding treated hypertensives		≥ 75th percentile vs < 25th percentile	*Ha et al., 2009*
Men			
PCDDs	23	2.3 (0.7–7.8)	
		p-trend = 0.15	
PCDFs	21	1.9 (0.7–4.9)	
		p-trend = 0.17	
Dioxin-like PCBs	27	1.7 (0.8–6.6)	Adjusted for age, race, income, BMI, cigarette smoking, serum cotinine, alcohol, exercise
		p-trend = 0.11	
Women			
PCDDs	33	5.0 (1.2–21.5)	
		p-trend = 0.08	
PCDFs	30	4.2 (1.3–14.3)	
		p-trend = 0.01	
Dioxin-like PCBs	28	1.1 (0.3–3.5)	
		p-trend = 0.93	
26.1–59.1		1.1 (0.9–1.4)	
> 59.1		1.8 (1.2–2.6)	
PCB 156 (ng/g of lipid) (TEF = 0.0005)			
≤ 12.5		1.0	
12.6–15.4		1.3 (0.9–1.9)	
> 15.4		1.2 (0.8–1.9)	
PCB 169 (pg/g of lipid) (TEF = 0.01)			
≤ 27.0		1.0	
27.1–46.4		1.1 (0.9–1.5)	
> 46.4		1.3 (0.9–1.9)	

continued

TABLE 42 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[c]	*Reference*/Comments
NHANES 1999–2002—self-reported cardiovascular disease (excluding hypertension)—889 nondiabetics ≥ 40 years of age		≥ 75th percentile vs < 25th percentile	*Ha et al., 2007*
Men			
HxCDD	18	2.5 (0.8–7.7)	Adjusted for age, race, income, BMI, cigarette smoking, serum cotinine, alcohol, exercise HDL, total cholesterol, triglycerides hypertension, C-reactive protein
HpCDD	18	2.4 (0.5–10.3)	
OCDD	16	2.1 (0.6–7.7)	
PCDDs	23	2.2 (0.8–6.1)	
PCDFs	19	0.7 (0.3–1.7)	
Dioxin-like PCBs	22	1.7 (0.6–5.5)	
Women			
HxCDD	21	2.8 (0.9–8.6)	
HpCDD	14	1.9 (0.3–10.8)	
OCDD	17	0.7 (0.2–2.8)	
PCDDs	19	2.0 (0.7–6.4)	
PCDFs	15	1.0 (0.3–2.8)	
Dioxin-like PCBs	23	5.0 (1.2–20.4)	
NHANES 1999–2004—prevalent hypertension (self-report that told by doctor, ≥ 140/90 mmHg or antihypertensive medications)—3,398–3,712 individuals depending on congener			*Everett et al., 2008b* superseded *Everett et al., 2008a* on 1999–2002 and n = 2,074–2,556
PCB 126 (ng/g of lipid) (TEF = 0.1)			
≤ 26.1		1.0	
26.2–59.1		1.1 (0.9–1.4)	
> 59.1		1.8 (1.2–2.6)	
PCB 169 (ng/g of lipid) (TEF = 0.01)			Adjusted for age, gender, race/ethnicity, smoking status, BMI, exercise, total cholesterol, family history of myocardial infarction
≤ 27.0		1.0	
27.1–46.4		1.1 (0.9–1.5)	
> 46.4		1.3 (0.9–1.9)	
PCB 118 (ng/g of lipid) (TEF = 0.0001)			
≤ 12.5		1.0	
12.6–27.5		1.4 (1.1–1.8)	
> 27.5		2.0 (1.3–3.0)	
PCB 156 (ng/g of lipid) (TEF = 0.0005)			
≤ 12.5		1.0	
12.6–15.4		1.3 (0.9–1.9)	
> 15.4		1.2 (0.8–1.9)	
NHANES 1999–2002—721 nondiabetics ≥ 20 with fasting blood samples and measured persistent organic pollutants high blood pressure (≥ 130/85 hg)	nr	≥ 75th percentile vs those with nondetectable level	*Lee et al., 2007c*
PCDDs		1.7 (1.0–3.1)	
HxCDD		1.2 (0.7–2.2)	Adjusted for age, race, sex, income, cigarette smoking, serum cotinine, alcohol consumption, exercise
HpCDD		2.6 (1.3–5.0)	
OCDD		1.1 (0.6–2.0)	
PCDFs		1.9 (1.2–3.3)	
PeCDF		1.3 (0.7–2.4)	
HxCDF		2.3 (1.3–4.0)	
HpCDF		1.4 (0.8–2.3)	
Dioxin-like PCBs		1.4 (0.8–2.7)	
PCB 74		1.2 (0.6–2.4)	
PCB 118		1.8 (1.0–3.5)	
PCB 126		2.1 (1.2–3.7)	
PCB 169		0.6 (0.3–1.1)	

TABLE 42 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[c]	*Reference*/Comments
UNITED STATES			
Superfund site caused by wood-treatment facility in Pensacola, Florida—47 workers, residents—prevalence		**Dioxin/phenoxy herbicides**	*Karouna-Renier et al., 2007*
Hypertension defined by self-report, medication use, or two readings of systolic blood pressure greater than 140 mmHg or diastolic blood pressure greater than 90 mmHg		1.1 (1.1–1.2) [error likely; published OR, lower confidence limit identical to 3 decimal places]	Adjusted for age, race, sex, BMI, tobacco and alcohol use, worker status
Other International Environmental Studies			
BELGIUM			
Flemish Environment and Health Survey (2002–2006) random sample of men (n = 775) and women (n = 808) aged 50–65. Followup survey completed, November 2011, to assess health conditions.			*Van Larebeke et al., 2015*
OR doubling of (pg TEQ/g fat) ln dioxin-like activity and **atheromata,** adjusted for BMI, education, cholesterol		1.16 (0.98–1.38)	
OR 90th percentile to 10th		1.60 p = 0.083	
OR doubling of (pg TEQ/g fat) ln dioxin-like activity and **hypertension**, adjusted for BMI, education, cholesterol		1.17 (1.03–1.32)	
OR 90th percentile to 10th		1.61 p = 0.014	
OR doubling of (Ln **HCB,** ng/g fat) ln dioxin-like activity and **hypertension,** adjusted for BMI, education, cholesterol, alcohol consumption		1.43 (1.12–1.81)	
OR 90th percentile to 10th		2.02 p = 0.0038	
CANADA		**Dioxin-like PCBs**	
Inuit adults from Nunavik, Quebec (n = 315) Adjusted for age, sex, fasting glucose, total serum lipids, waist circumference, alcohol consumption, physical activity, omega-3 fatty acid, mercury, lead levels		0.9 (0.8–1.1)	*Valera et al., 2013b*
PCB 105 and hypertensive status		1.4 (1.1–1.9)	
SWEDEN			
Swedish Mammography Cohort—population-based prospective cohort of women est. 1987–1990 (n = 33,446)		**PCBs**	*Bergkvist et al., 2015*
RR myocardial infarction, PCB exposure quartiles, ng/day			
Median, ng/day 101	335	1.0 (referent)	
Median, ng/day 147	307	1.12 (0.91–1.38)	
Median, ng/day 186	279	1.20 (0.90–1.59)	
Median, ng/day 286	465	1.58 (1.10–2.25) p-trend = 0.007	

continued

TABLE 42 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[c]	*Reference*/Comments
β change in total serum cholesterol 2.7 times change in POP concentrations (ng/glipid) subsample n = 598 at age 70 and 75 years		**Dioxins, dioxin-like PCBs**	*Pennell et al., 2014* Adjusted for gender, education, physical exercise, smoking, BMI, change in BMI, total energy intake, percentage of dietary fat
OCDD		0.12 (0.004–0.23)	
PCB 105		-0.011(-0.13–0.11)	
PCB 118		0.02 (-0.11–0.15)	
PCB 156		0.05 (-0.1–0.20)	
PCB 157		0.05 (-0.1–0.20)	
PCB 189		0.03 (-0.07–0.14)	
PIVUS participants and 100 consecutive non-participants, total sample n = 732			
OR prevalent hypertension		**Dioxin-like PCBs**	*Lind et al., 2014* Adjusted for gender, BMI, smoking status, exercise, and education
Hexachlorobenzene		1.14 (0.8–1.63)	
PCB 126		1.1 (0.94–1.3)	
PCB 169		0.86 (0.63–1.17)	
PCB 105		1.23 (0.96–1.6)	
PCB 118		1.26 (0.95–1.67)	
PCB 156		0.9 (0.63–1.3)	
PCB 157		0.9 (0.65–1.26)	
PCB 189		0.87 (0.69–1.09)	
FINLAND			
Finnish fishermen (n = 6,410) and spouses (n = 4,260) registered between 1980 and 2002 compared to national statistics		**TCDD, PCBs, TEQs**	*Turunen et al., 2008*
Ischemic heart disease			Standardized mortality analysis—age adjusted
Men	269	0.7 (0.7–0.8)	
Women	62	0.7 (0.5–0.8)	
Cerebrovascular disease			
Men	67	0.7 (0.5–0.9)	
Women	46	1.0 (0.7–11.3)	
GREENLAND		**dioxin-like PCBs**	
Plasma levels of mono-ortho PCBs 105, 18, and 156 and hypertension status			
Inuit adults residing in Greenland (n = 1,614)	645	1.0 (0.9–1.2)	*Valera et al., 2013a*
Ages 18–39		1.3 (1.0–1.7)	Adjusting for age, sex, BMI, diabetes, physical activity, smoking
Ages ≥ 40 years		0.9 (0.8–1.1)	
JAPAN			
2,264 Japanese from general population not occupationally exposed to dioxins, aged 15–76 years in 2002–2008		**Total Serum TEQ**	*Nakamoto et al., 2013*
Hypertension	638		Adjusted for age, sex, smoking, drinking, region, survey year, BMI
1st quartile		1.0	
2nd quartile		1.3 (0.9–2.0)	
3rd quartile		1.5 (1.1–2.3)	
4th quartile		2.3 (1.5–3.4)	
		p-trend < 0.0001	

TABLE 42 Continued

Study Population	Exposed Cases[b]	Exposure of Interest/ Estimated Relative Risk (95% CI)[c]	*Reference*/Comments
Hyperlipidemia			
1st quartile		1.0	
2nd quartile		1.7 (1.3–2.2)	
3rd quartile		2.4 (1.8–3.3)	
4th quartile		3.4 (2.4–4.8)	
		p-trend < 0.0001	
TAIWAN			
Residents around 12 municipal waste incinerators in Taiwan—prevalence		**Dioxin/phenoxy herbicides**	*Chen HL et al., 2006*
Hypertension diagnosed by a physician	118	5.6 (1.6–19.6)	
Serum PCDD/F (TEQs in logistic model)		0.9 (0.2–3.7)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,4,5-TP, 2-(2,4,5-trichlorophenoxy) propionic acid; 2,5-DCP, 2,5-dichlorophenol; ACC, Army Chemical Corps; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CHD, coronary heart disease; CI, confidence interval; COI, chemical of interest; HDL, high-density lipoprotein; HpCDD, 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin; HpCDF, 1,2,3,4,6,7,8-heptachlorodibenzofuran; HR, hazard ratio; HxCDD, 1,2,3,6,7,8-hexachlorodibenzo-*p*-dixion; HxCDF, 1,2,3,4,7,8-hexachlorodibenzofuran; IARC, International Agency for Research on Cancer; ICD, *International Classification of Diseases*; JEM, job-exposure matrix; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; MOS, months of service; NHANES, National Health and Nutrition Examination Survey; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; OCDD, 1,2,3,4,6,7,8,9-octachlorodibenzo-*p*-dioxin; OR, odds ratio; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDD/F, dioxins and furans combined; PCDF, polychlorinated dibenzofuran; PCP, pentachlorophenol; PeCDF, 2,3,4,7,8-pentachlorodibenzofuran; PMR, proportional mortality ratio; ppt, parts per trillion; SEA, Southeast Asia; SMR, standardized mortality ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dixoin; TCP, trichlorophenol; TEF, toxicity equivalency factor for individual congener; TEQ, (total) toxic equivalent; VA, US Department of Veterans Affairs.

[a]New citations labeled as such and bolded; section shaded for citations with dose-response information on TCDD.

[b]Subjects male unless otherwise noted.

[c]Given when available; results other than estimated risk explained individually.

TABLE 43 Selected Epidemiologic Studies—Noncancerous Respiratory Disease (shaded entries are new information for Update 11 [2018])

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US Air Force Health Study—Ranch Hand veterans vs SEA veterans (unless otherwise noted)		**All COIs**	
Mortality			
Through 1999—Ranch Hand personnel (n =1,262) vs SEA veterans (n = 19,078) (respiratory disease, ICD-9 460–519)	8	1.2 (0.6–2.5)	Ketchum and Michalek, 2005
US VA Cohort of Army Chemical Corps—Expanded as of 1997 to include all Army men with chemical MOS (2,872 deployed vs 2,737 nondeployed) serving during Vietnam era (7/1/65–3/28/73)		**All COIs**	
Incidence—Self-reported respiratory disease diagnosed by doctor			
CATI survey of stratified sample: 1,499 deployed (795 with TCDD measured) vs 1,428 nondeployed (102 with TCDD measured)			Kang et al., 2006
Deployed vs nondeployed	267	1.4 (1.1–1.8)	
Sprayed herbicides in Vietnam (n = 662) vs never (n = 811)	140	1.6 (1.2–2.1)	
Mortality—respiratory disease			
Through 2005			Cypel and Kang, 2010
Deployed veterans (2,872) vs nondeployed (2,737)			
Respiratory system disease	32 vs 8	2.2 (1.0–4.9)	
Pneumonia, influenza	12 vs 6	1.3 (0.5–3.6)	
COPD	20 vs 2	4.8 (1.1–21.2)	
ACC deployed men in Kang et al. (2006) reported sprayed herbicide vs did not spray			
Respiratory system disease	8	2.2 (0.4–11.8)	
Pulmonary disease (COPD)	6	3.6 (0.4–32.1)	
Through 1991 (respiratory system disease)	11 vs 2	2.6 (0.5–12.2)	Dalager and Kang, 1997
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Incidence			
Physical health—ORs from pulmonary-function tests (case definition: ≥ 80% predicted value)			CDC, 1988a
FEV_1	254	0.9 (0.7–1.1)	
FVC	177	1.0 (0.8–1.3)	
FEV_1/FVC	152	1.0 (0.8–1.3)	
Mortality			
1965–2000 (noncancerous respiratory mortality, ICD-9 460–519)	20	0.8 (0.5–1.5)	Boehmer et al., 2004
US VA Proportionate Mortality Study—sample of deceased male Vietnam-era Army and Marine veterans who served 7/4/65–3/1/73		**All COIs**	
1965–1988			Watanabe and Kang, 1996
Army, deployed (n = 27,596) vs nondeployed (n = 31,757)	648	0.8 ($p < 0.05$)	
Marine Corps, deployed (n = 6,237) vs nondeployed (n = 5,040)	111	0.7 ($p < 0.05$)	

TABLE 43 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
US VA Study of Male Vietnam Veterans Wounded in Combat		**All COIs**	
Mortality through December 1991			Bullman and Kang, 1996
Noncancerous respiratory mortality (ICD-9 460–519)	43	0.9 (0.7–1.2)	
US VA Cohort of Female Vietnam-era Veterans served in Vietnam (n = 4,586; nurses only = 3,690); nondeployed (n = 5,325; nurses only = 3,282)		**All COIs**	Kang et al., 2014
Mortality (through 2004)			
Respiratory system disease	195	0.8 (0.6–1.1)	
COPD	87	0.8 (0.5–1.3)	
Vietnam nurses only			
Respiratory system disease	130	0.7 (0.5–1.1)	
COPD	56	0.7 (0.4–1.3)	
US VA Cohort of Monozygotic Twins—Vietnam-era		**All COIs**	
Incidence of respiratory conditions, deployed vs nondeployed			Eisen et al., 1991
Present at time of survey	nr	1.4 (0.8–2.4)	
At any time since service	nr	1.4 (0.9–2.0)	
Required hospitalization	nr	1.8 (0.7–4.2)	
State Studies of US Vietnam Veterans			
923 White male Vietnam veterans with **Wisconsin** death certificate (1968–1978) vs proportions for Vietnam-era veterans (mortality from noncancerous respiratory disease, ICD-8 460–519)			Anderson et al., 1986a,b
Vietnam veterans vs expected deaths calculated from proportions for:	10		
Nonveterans		0.5 (0.3–0.8)	
All veterans		0.8 (0.4–1.5)	
Vietnam-era veterans		1.0 (0.5–1.8)	
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/62–7/1/73 vs Australian population		**All COIs**	
Mortality			
All branches, return–2001			ADVA, 2005a
Respiratory system disease	239	0.8 (0.7–0.9)	
COPD	128	0.9 (0.7–1.0)	
Navy			
Respiratory system disease	50	0.8 (0.6–1.0)	
COPD	28	0.9 (0.6–1.3)	
Army			
Respiratory system disease	162	0.8 (0.7–0.9)	
COPD	81	0.9 (0.7–1.0)	
Air Force			
Respiratory system disease	28	0.6 (0.4–0.9)	
COPD	18	0.8 (0.4–1.2)	
1980–1994			CDVA, 1997a
Noncancerous respiratory mortality (ICD-9 460–519)			
1964–1979	3	0.1 (0.0–0.3)	
1980–1994	92	0.9 (0.7–1.1)	
Chronic obstructive airways disease (ICD-9 460–496)	47	0.9 (0.7–1.2)	

continued

TABLE 43 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
Sample of 1,000 Male Australian Vietnam Veterans—prevalence		**All COIs**	
450 interviewed 2005–2006 vs respondents to 2004–2005 national survey			O'Toole et al., 2009
Chronic lower respiratory disease	nr		
Bronchitis	nr	2.9 (2.2–3.6)	
Emphysema	nr	2.0 (1.3–2.7)	
Asthma	nr	1.3 (1.0–1.6)	
Hay fever, allergic rhinitis	nr	1.2 (0.96–1.4)	
Chronic sinusitis	nr	1.7 (1.5–2.0)	
Other diseases of respiratory system	nr	15.4 (11.7–19.1)	
641 interviewed 1990–1993 vs respondents to 1989–1990 national survey			O'Toole et al., 1996b
Asthma	nr	0.9 (0.5–1.4)	
Bronchitis, emphysema	nr	4.1 (2.8–5.5)	
Other	nr	4.0 (2.2–5.9)	
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Mortality			
1966–2001			ADVA, 2005c
Respiratory diseases	18	1.1 (0.6–2.2)	
COPD	8	1.0 (0.3–2.8)	
1982–1994			CDVA, 1997b
1965–1982	2	2.6 (0.2–30.0)	
1982–1994	6	0.9 (0.3–2.7)	
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	
Mortality (1988–2009)		SHR (99% CI)	Cox et al., 2015
Asthma	33	0.84 (0.46–1.21)	
Pneumonia	174	1.36 (1.09–1.63)	
COPD	300	1.68 (1.43–1.93)	
Mortality (1988–2008)			McBride et al., 2013
Respiratory disease (not COPD)	12	0.4 (0.2–0.7)	
COPD	18	0.8 (0.5–1.2)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores)		**All COIs**	
Prevalence (01/2000–09/2005)—log EOI scores		HRs	Yi et al., 2014a
Diseases of the respiratory system (J00–J99)		1.0 (1.0–1.0)	
Pneumonia not due to influenza (J12–J18)		1.0 (1.0–1.0)	
COPD (J40–J44, J47)		1.0 (1.0–1.0)	
Chronic bronchitis (J41–J42)		1.0 (1.0–1.0)	
Emphysema (J43)		1.0 (1.0–1.0)	
Bronchiectasis (J47)		1.0 (1.0–1.1)	
Asthma (J45–J46)		1.0 (1.0–1.0)	

TABLE 43 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
Prevalence (01/2000–09/2005)—categorized high (n = 36,813) vs low (n = 59,615) (86.8% vs 86.0%)			
Diseases of the respiratory system (J00–J99)		1.0 (1.0–1.1)	
Pneumonia not due to influenza (J12–J18)		1.0 (1.0–1.1)	
COPD (J40–J44, J47)		1.0 (1.0–1.0)	
Chronic bronchitis (J41–J42)		1.1 (1.0–1.1)	
Emphysema (J43)		0.9 (0.8–1.1)	
Bronchiectasis (J47)		1.2 (1.1–1.3)	
Asthma (J45–J46)		1.0 (1.0–1.1)	
Mortality (1992–2005) (adjusted HRs)			Yi et al., 2014b
Diseases of the respiratory system (J00–J98)	446	1.0 (1.0–1.1)	
Pneumonia not due to influenza (J12–J18)	107	1.0 (0.9–1.1)	
COPD (J40–J44, J47)	115	1.0 (1.0–1.3)	
Asthma (J45–J46)	75	1.0 (0.9–1.1)	
Mortality (01/2000–09/2005)—categorized high (n = 266) vs low (n = 180) (86.8% vs 86.0%)			
Diseases of the respiratory system (J00–J98)		1.2 (1.0–1.5)	
Pneumonia not due to influenza (J12–J18)		1.0 (0.7–1.5)	
COPD (J40–J44, J47)		1.7 (1.2–2.6)	
Asthma (J45–J46)		0.9 (0.6–1.4)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
Mortality 1939–1992		**Phenoxy herbicides, chlorophenols**	Kogevinas et al., 1997
21,863 exposed workers			
Men	252	0.8 (0.7–0.9)	
Women	7	1.1 (0.4–2.2)	
British MCPA Plant—Production 1947–1982 (n = 1,545) (included in IARC cohort) and spraying 1947–1972 (n = 2,561) (not included in IARC cohort)		**MCPA**	
Mortality through 1983 (noncancerous respiratory diseases, ICD-9 460–519)	93	0.6 (0.5–0.8)	Coggon et al., 1986
British Production Workers at 4 plants (included in IARC cohort)		**Dioxins, but TCDD unlikely; MCPA**	Coggon et al., 1991
Mortality 1963–1985 (noncancerous respiratory diseases, ICD-9 460–519)	8	0.7 (0.3–1.3)	
Dutch production workers in Plant A and Plant B, combined (Plant A, 1,020 workers; Plant B, 1,036 workers) (in IARC cohort)		**Dioxins, 2,4-D, 2,4-DP, 2,4,5-T, 2,4,5-TCP MCPA, MCPP**	
Mortality 1955–2006 (diseases of the respiratory system)	52	1.0 (0.8–1.2)	Boers et al., 2012
Dutch production workers in Plant A (549 men exposed during production 1955–1985; 594 unexposed) (in IARC cohort)		**Dioxins, 2,4,5-T, 2,4,5-TCP**	
Mortality 1955–2006 (HRs for lagged TCDD plasma levels)			Boers et al., 2012
Diseases of the respiratory system	31	1.0 (0.8–1.3)	
Mortality 1955–2006	19 vs 12	1.0 (0.4–2.3)	Boers et al., 2010

continued

TABLE 43 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
Dutch production workers in Plant B (414 men exposed during production 1965–1986; 723 unexposed) (in IARC cohort)		**2,4-D; MCPA; MCPP; highly chlorinated dioxins unlikely**	
Mortality 1965–2006	6 vs 15	0.5 (0.2–1.2)	Boers et al., 2010
German Production Workers at Bayer Plant in Uerdingen (135 men working > 1 month in 1951–1976) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4,5-TCP**	
Mortality 1951–1992 (ICD-9 460–519)	2	0.9 (0.1–3.1)	Becher et al., 1996
German Production Workers at Bayer Plant in Dormagen (520 men working > 1 month in 1965–1989) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1965–1989 (ICD-9 460–519)	0	0.0	Becher et al., 1996
German Production Workers at BASF Ludwigshafen Plant (680 men working > 1 month in 1957–1987) (in IARC cohort as of 1997) and women—no results		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP**	
Mortality 1956–1989 (ICD-9 460–519)	4	0.6 (0.2–1.6)	Becher et al., 1996
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (*not* part of IARC)		**Focus on TCDD**	
Incidence			
Through 1989 (n = 158 men exposed within 1 year of accident vs 161 other BASF employees 1953–1969)			Zober et al., 1994
All noncancerous respiratory diseases (ICD-9 460–419)	nr	33.7/31.0 (p = 0.22)	
Upper respiratory tract infections (ICD-9 460–478)	nr	12.0/9.0 (p = 0.00)	
Pneumonia, influenza (ICD-9 480–487)	nr	17.4/18.8 (p = 0.08)	
COPD (ICD-9 490–496)	nr	8.0/7.5 (p = 0.31)	
Mortality			
1953–1992 (noncancerous respiratory)	1	0.1 (0.0–0.8)	Ott and Zober, 1996
German Production Workers at Boehringer–Ingelheim Plant in Hamburg (1,144 men working > 1 month in 1952–1984; generation of TCDD reduced after chloracne outbreak in 1954) and women—no results (some additions to observed cancers over Manz et al., 1991) (in IARC cohort as of 1997)		**Dioxins; 2,4,5-T; 2,5-DCP; 2,4,5-TCP**	
Mortality 1952–2007 (ICD-9 codes 460–519)	33	0.6 (0.4–0.9)	Manuwald et al., 2012
Men	25	0.6 (0.4–0.9)	
Women	8	0.7 (0.3–1.4)	
Mortality 1952–1989 (ICD-9 460–519)	10	0.5 (0.3–1.0)	Becher et al., 1996
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)		**Dioxins; 2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP; Picloram**	
Morbidity survey 2008, n = 245			't Mannetje et al., 2018
Asthma			
Worked in a highly exposed job	8	1.13 (0.40–3.22)	
Serum TCDD concentration ≥ 10 pg/g lipid	3	2.62 (0.53–13.0)	
Chronic bronchitis			
Worked in a highly exposed job	3	2.39 (0.17–34.0)	
Serum TCDD concentration ≥ 10 pg/g lipid	1	1.04 (0.07–14.7)	

TABLE 43 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
Mortality 1969–2004			McBride et al., 2009a
Ever-exposed workers	12	0.8 (0.4–1.4)	
Never-exposed workers	2	0.4 (0.0–1.5)	
Production Workers (713 men and 100 women worked > 1 month in 1969–1984)			
Mortality 1969–2000	9	0.9 (0.4–1.8)	't Mannetje et al., 2005
Sprayers (697 men and 2 women on register of New Zealand applicators, 1973–1984)			
Mortality 1973–2000	6	0.7 (0.2–1.2)	't Mannetje et al., 2005
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Through 1993 (noncancerous respiratory, ICD-9 460–519)	86	0.9 (0.7–1.1)	Steenland et al., 1999
Monsanto workers (n = 240) involved in 2,4,5-T production (1948–1969) and 163 unexposed workers, results of clinical examination July 1979—morbidity			Suskind and Hertzberg, 1984
"Abnormal" outcome on pulmonary-functions tests:			
FEV_1 (< 80% predicted)	32	2.81 (p = 0.02)	
FVC (< 80% predicted)	35	2.25 (p = 0.03)	
FEV_1/FVC (< 70%)	32	2.97 (p = 0.01)	
$FEF_{25–75}$ (< 80% predicted)	47	1.86 (p = 0.05)	
All Dow TCP-Exposed Workers (TCP production 1942–1979 or 2,4,5-T production 1948–1982 in Midland, Michigan) (in IARC and NIOSH cohorts)		**2,4,5-T; 2,4,5-TCP**	
1942–2003 (n = 1,615)	44	0.8 (0.6–1.0)	Collins et al., 2009b
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, Washington, and Wichita, Kansas) and workers who made PCP and TCP at two additional plants (in Midland, Michigan, and Sauget, Illinois)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
Respiratory disorders (ICD-9 codes 460–466, 470–478, 480–487, 490–519)			
1940–2005 (n = 2,122)	94	1.0 (0.8–1.3)	
PCP and TCP (n = 720)	21	0.7 (0.5–1.1)	
PCP (no TCP) (n = 1,402)	73	1.2 (0.9–1.5)	
Pneumonia (ICD-9 codes 480–486)			
1940–2005 (n = 2,122)	19	0.7 (0.4–1.0)	
PCP and TCP (n = 720)	8	0.9 (0.4–1.8)	
PCP (no TCP) (n = 1,402)	11	0.5 (0.3–1.0)	
COPD (ICD-9 codes 490–492, 496)			
1940–2005 (n = 2,122)	63	1.4 (1.1–1.8)	
PCP and TCP (n = 720)	10	0.7 (0.3–1.3)	
PCP (no TCP) (n = 1,402)	53	1.7 (1.3–2.2)	
Dow 2,4-D Production Workers (1945–1982 in Midland, Michigan) (subset of all TCP-exposed workers) excluded		**2,4-D, lower chlorinated dioxins**	
Through 1994 (n = 1,517)			Burns et al., 2001
Noncancerous respiratory (ICD-8 460–519)	8	0.4 (0.2–0.7)	
Pneumonia	4	0.6 (0.2–1.4)	

continued

TABLE 43 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
Dow PCP Production Workers (1937–1989 in Midland, Michigan) (not in IARC and NIOSH cohorts)		**TCP/PCP**	
1937–2011 Potential dioxin exposure (n = 2,192), TCP production (n = 1,419), PCP production (n = 577), Both TCP and PCP (n = 196)			Collins et al., 2016
TCP or PCP, non-malignant respiratory disease (J00–J99)	101	0.90 (0.73–1.09)	
TCP, non-malignant respiratory disease (J00–J99)	75	0.92 (0.72–1.15)	
PCP, non-malignant respiratory disease (J00–J99)	35	0.89 (0.62–1.23)	
		Low chlorinated dioxins, 2,4-D	
Mortality 1940–2004 (n = 577, excluding 196 also having exposure to TCP)	19	0.7 (0.4–1.2)	Collins et al., 2009c
Mortality 1940–1989 (n = 770)			Ramlow et al., 1996
Noncancerous respiratory mortality (ICD-8 460–519)	14	0.9 (0.5–1.5)	
Cumulative PCP exposure			
< 1 unit	3	0.6 (0.2–1.9)	
≥ 1 unit	11	0.4 (0.8–2.5)	
Pneumonia (ICD-8 480–486)	6	1.1 (0.4–2.4)	
Emphysema (ICD-8 492)	4	1.3 (0.4–3.3)	
Preliminary NIOSH Cross-sectional Medical Study—workers in production of sodium trichlorophenol, 2,4,5-T ester contaminated with TCDD—morbidity			
Chronic bronchitis and COPD	2	nr	Sweeney et al., 1997/98
ORs for increase in 1 ppt of serum TCDD compared to unexposed workers			Calvert et al., 1991
Chronic bronchitis	nr	0.5 (0.1–2.6)	
COPD	nr	1.2 (0.5–2.8)	
ITALY			
Trento, Italy, Electric Arc Furnace Workers (n = 331) Cohort followed from 1979 to 2009 (6,731 person-years), morbidity analyses limited to 225 workers		**Dioxin (detected in foundry dust)**	Cappelletti et al., 2016
RR adjusted for age, compared to general population in Trento			
Asthma	2	1.08 (0.27–4.31)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
CANADA			
Cross-sectional study of self-reported prevalence of self-reported asthma (n = 83) in male farmers (n = 1,939) in Saskatchewan (1982–1983)		**Phenoxy herbicides** *Asthmatics vs nonasthmatics*	Senthilselvan et al., 1992
Phenoxyacetic herbicide use	71	85.5% vs 88.5%	
Saskatchewan Rural Health Study—8,153 adults completed mailed questionnaires; 482 self-reported cases of doctor-diagnosed chronic bronchitis		**Herbicides**	Pahwa et al., 2012b
Herbicide—ever exposed occupationally	264	1.2 (1.0–1.5)	

TABLE 43 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
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; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
OR asthma exacerbation and adjustment for current exposure			Henneberger et al., 2014
2,4-D		0.8 (0.5–1.3)	
Dicamba		1.0 (0.6–1.6)	
Prevalence of atopic (n = 282) or nonatopic asthma (n = 420) reported by women (> 19 years of age) at enrollment (1993–1997)			Hoppin et al., 2008
Women reporting atopic asthma exposed to:			
2,4-D	52	1.5 (1.1–2.1)	
Dicamba	11	1.1 (0.6–2.1)	
Women reporting nonatopic asthma exposed to:			
2,4-D	66	1.1 (0.8–1.4)	
Dicamba	13	0.7 (0.4–1.3)	
Prevalence of chronic bronchitis at enrollment (n = 654) in private applicators exposed to:			Hoppin et al., 2007a
2,4-D	78	1.1 (0.9–1.4)	
2,4,5-T	28	1.5 (1.3–1.8)	
2,4,5-TP	9	1.7 (1.3–2.3)	
Dicamba	48	1.0 (0.8–1.2)	
Prevalence of chronic bronchitis at enrollment in nonsmoking farm women (n = 21,541) exposed to:		0.9 (0.7–1.1)	Valcin et al., 2007
2,4-D	16	1.2 (0.9–1.6)	
2,4,5-T	1	1.0 (0.4–2.5)	
Dicamba	5	1.1 (0.6–2.0)	
Mortality			
Enrollment through 2007, vs state rates			Waggoner et al., 2011
Respiratory system diseases			
Applicators (n = 1,641)	346	0.4 (0.3–0.4)	
Spouses (n = 676)	92	0.3 (0.2–0.4)	
Pneumonia			
Applicators (n = 1,641)	76	0.4 (0.3–0.5)	
Spouses (n = 676)	17	0.3 (0.2–0.5)	
COPD			
Applicators (n = 1,641)	165	0.3 (0.3–0.4)	
Spouses (n = 676)	50	0.3 (0.2–0.4)	
Asthma			
Applicators (n = 1,641)	8	0.8 (0.3–1.6)	
Other respiratory diseases			
Applicators (n = 1,641)	97	0.6 (0.5–0.7)	
Spouses (n = 676)	21	0.4 (0.3–0.6)	

continued

TABLE 43 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
Enrollment through 2000, vs state rates			Blair et al., 2005a,b
Private applicators (men and women)	50	0.2 (0.2–0.3)	
Spouses of private applicators (> 99% women)	15	0.3 (0.2–0.7)	
US Department of Agriculture Workers—nested case-control study of white men dying 1970–1979 of noncancerous respiratory diseases (ICD-8 460–519)		**Herbicides**	
Forest conservationists	80	0.8 (0.6–1.0)	Alavanja et al., 1989
Florida Licensed Pesticide Applicators (common phenoxy use assumed but not documented; had been listed by Blair et al., 1983)		**Herbicides**	
Pesticide applicators in Florida licensed 1965–1966 (n = 3,827)—mortality through 1976 from noncancerous respiratory diseases (ICD-8 460–519)	2	**Herbicides** 0.9 (nr)	Blair et al., 1983
Any pesticide (dose-response by length of licensure)	8	0.6 (nr)	
< 10 years	8	1.5 (nr)	
10–19 years	4	1.7 (nr)	
≥ 20 years			
ENVIRONMENTAL			
Seveso, Italy, Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Mortality			
25-year followup to 2001—men and women			Consonni et al., 2008
Respiratory disease (ICD-9 460–519)			
Zone A	9	1.4 (0.7–2.7)	
Zone B	48	1.0 (0.8–1.4)	
Zone R	341	1.0 (0.9–1.1)	
COPD (ICD-9 490–493)			
Zone A	7	2.5 (1.2–5.3)	
Zone B	26	1.3 (0.9–1.9)	
Zone R	175	1.2 (1.0–1.4)	
20-year followup to 1996			Bertazzi et al., 2001
Respiratory disease (ICD-9 460–519)	44	1.0 (0.8–1.4)	
Zone A	9	1.9 (1.0–3.6)	
Zone B	35	1.3 (0.9–2.0)	
COPD (ICD-9 490–493)	29	1.5 (1.1–2.2)	
Zone A	7	3.3 (1.6–6.9)	
Zone B	22	1.3 (0.9–2.0)	
15-year followup to 1991—men			Bertazzi et al., 1998
Respiratory disease (ICD-9 460–519)			
Zone A	5	2.4 (1.0–5.7)	
Zone B	13	0.7 (0.4–1.2)	
Zone R	133	1.1 (0.9–1.3)	
COPD (ICD-9 490–493)			
Zone A	4	3.7 (1.4–9.8)	
Zone B	9	1.0 (0.5–1.9)	
Zone R	74	1.2 (0.9–1.5)	

TABLE 43 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
15-year followup to 1991—women			Bertazzi et al., 1998
Respiratory disease (ICD-9 460–519)			
Zone A	2	1.3 (0.3–5.3)	
Zone B	10	1.0 (0.5–1.9)	
Zone R	84	1.0 (0.8–1.2)	
COPD (ICD-9 490–493)			
Zone A	1	2.1 (0.3–14.9)	
Zone B	8	2.5 (1.2–5.0)	
Zone R	37	1.3 (0.9–1.9)	
10-year followup to 1986—men (Zones A, B, R)			Bertazzi et al., 1989a
Respiratory disease (ICD-9 460–519)	55	1.0 (0.7–1.3)	
Pneumonia (ICD-9 480–486)	14	0.9 (0.5–1.5)	
COPD (ICD-9 490–493)	31	1.1 (0.8–1.7)	
10-year followup to 1986—women (Zones A, B, R)			Bertazzi et al., 1989a
Respiratory disease (ICD-9 460–519)	24	1.0 (0.7–1.6)	
Pneumonia (ICD-9 480–486)	9	0.8 (0.4–1.6)	
COPD (ICD-9 490–493)	8	1.0 (0.5–2.2)	
Cross-sectional study of residents near wood treatment plant (creosote, PCP) in Mississippi, who were plaintiffs (n = 199) in lawsuit vs subjects in comparable area (n = 115) without known exposures		**Dioxin, furans** Prevalence in exposed vs nonexposed	Dahlgren et al., 2003b
Chronic bronchitis			
By history		21.7% vs 4.3% ($p < 0.0001$)	
Diagnosed by physician		17.8% vs 5.8% ($p < 0.0001$)	
Chronic bronchitis			
By history		40.5% vs 11.0% ($p < 0.0001$)	
Diagnosed by physician		13.1% vs 12.0% ns	
Other International Environmental Studies			
JAPAN			
2,253 Japanese from general population not occupationally exposed to dioxins, aged 15–76 years in 2002–2008		**Total Serum TEQ**	Nakamoto et al., 2013
Asthma (40 cases in men; 53 cases in women)	93		
1st quartile		1.0	
2nd quartile		1.1 (0.6–2.0)	
3rd quartile		1.0 (0.5–1.9)	
4th quartile		1.1 (0.5–2.4)	
		p-trend = 0.88	

continued

TABLE 43 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
SWEDEN			
Swedish fishermen (high consumption of fish with persistent organochlorines)		**Organochlorine compounds**	Svensson et al., 1995a
Mortality			
East coast	4	0.5 (0.1–1.2)	
West coast	43	0.8 (0.6–1.1)	

NOTE: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, dichlorprop; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,4,5-TP, 2-(2,4,5-trichlorophenoxy) propionic acid; 2,5-DCP, 2,5-dichlorophenol; CATI, computer-assisted telephone interviewing; CI, confidence interval; COI, chemical of interest; COPD, chronic obstructive pulmonary disease; EOI, Exposure Opportunity Index; $FEF_{25–75}$, forced midexpiratory flow; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD-8, *International Classification of Diseases, 8th revision*; ICD-9, *International Classification of Diseases, 9th revision*; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MCPB, 4-(4-chloro-2-methylphenoxy)butanoic acid; MCPP, methylchlorophenoxypropionic acid; MOS, months of service; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; ns, not significant; OR, odds ratio; PCP, pentachlorophenol; SEA, Southeast Asia; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Given when available; results other than estimated risk explained individually.

TABLE 44 Selected Epidemiologic Studies—COPD and Pulmonary Function (shaded entries are new information for Update 11 [2018])

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
VIETNAM VETERANS			
US Vietnam Veterans			
US VA Cohort of Army Chemical Corps—Expanded as of 1997 to include all Army men with chemical MOS (2,872 deployed vs 2,737 nondeployed) serving during Vietnam era (July 1, 1965–March 28, 1973)		**All COIs**	
Through 2005—Mortality			Cypel and Kang, 2010
Deployed veterans (2,872) vs nondeployed (2,737)			
Respiratory system disease	32 vs 8	2.2 (1.0–4.9)	
COPD	20 vs 2	4.8 (1.1–21.2)	
ACC deployed men in Kang et al. (2006) reported sprayed herbicide vs did not spray			
Respiratory system disease	8	2.2 (0.4–11.8)	
Pulmonary disease (COPD)	6	3.6 (0.4–32.1)	
US CDC Vietnam Experience Study—Cross-sectional study, with medical examinations, of Army veterans: 9,324 deployed vs 8,989 nondeployed		**All COIs**	
Incidence			
Physical health—ORs from pulmonary-function tests (case definition: ≥ 80% predicted value)			CDC, 1988a
FEV_1	254	0.9 (0.7–1.1)	
FVC	177	1.0 (0.8–1.3)	
FEV_1/FVC	152	1.0 (0.8–1.3)	
US VA Cohort of Female Vietnam-era Veterans served in Vietnam (n = 4,586; nurses only = 3,690); nondeployed (n = 5,325; nurses only = 3,282)		**All COIs**	Kang et al., 2014
Mortality (through 2004)			
Through 2004—COPD	87	0.8 (0.5–1.3)	
Vietnam nurses only—COPD	56	0.7 (0.4–1.3)	
International Vietnam-Veteran Studies			
Australian Vietnam Veterans—58,077 men and 153 women served on land or in Vietnamese waters during 5/23/1962–7/1/1973 vs Australian population		**All COIs**	
Mortality			
All branches, return–2001			ADVA, 2005a
Respiratory system disease	239	0.8 (0.7–0.9)	
COPD	128	0.9 (0.7–1.0)	
Navy			
Respiratory system disease	50	0.8 (0.6–1.0)	
COPD	28	0.9 (0.6–1.3)	
Army			
Respiratory system disease	162	0.8 (0.7–0.9)	
COPD	81	0.9 (0.7–1.0)	
Air Force			
Respiratory system disease	28	0.6 (0.4–0.9)	
COPD	18	0.8 (0.4–1.2)	
1980–1994			CDVA, 1997a
Noncancerous respiratory mortality (ICD-9 460–519)			
Chronic obstructive airways disease (ICD-9 460–496)	47	0.9 (0.7–1.2)	

continued

TABLE 44 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
Australian Conscripted Army National Service (18,940 deployed vs 24,642 nondeployed)		**All COIs**	
Mortality			
1966–2001			ADVA, 2005c
Respiratory diseases	18	1.1 (0.6–2.2)	
COPD	8	1.0 (0.3–2.8)	
New Zealand Vietnam War Veterans (2,783 male survivors of deployment in 1964–1975)		**All COIs**	
Mortality (1988–2009)		SHR (99%CI)	Cox et al., 2015
COPD	300	1.68 (1.43–1.93)	
Mortality (1988–2008)			McBride et al., 2013
Respiratory disease (not COPD)	12	0.4 (0.2–0.7)	
COPD	18	0.8 (0.5–1.2)	
Korean Vietnam Veterans Health Study—entire population categorized with high exposure (n = 85,809) vs low exposure (n = 94,442) (individual EOI scores)		**All COIs**	
Prevalence (January 2000–September 2005)—log EOI scores		HRs	Yi et al., 2014a
Diseases of the respiratory system (J00–J99)		1.0 (1.0–1.0)	
COPD (J40–J44, J47)		1.0 (1.0–1.0)	
Prevalence (01/2000–09/2005)—categorized high (n = 36,813) vs low (n = 59,615) (86.8% vs 86.0%)			
Diseases of the respiratory system (J00–J99)		1.0 (1.0–1.1)	
COPD (J40–J44, J47)		1.0 (1.0–1.0)	
Mortality (1992–2005) (adjusted HRs)			Yi et al., 2014b
Diseases of the respiratory system (J00–J98)	446	1.0 (1.0–1.1)	
COPD (J40–J44, J47)	115	1.0 (1.0–1.3)	
Mortality (January 2000–September 2005)—categorized high (n = 266) vs low (n = 180) (86.8% vs 86.0%)			
Diseases of the respiratory system (J00–J98)		1.2 (1.0–1.5)	
COPD (J40–J44, J47)		1.7 (1.2–2.6)	
OCCUPATIONAL—INDUSTRIAL			
IARC Phenoxy Herbicide Cohort—Workers exposed to any phenoxy herbicide or chlorophenol (production or spraying) vs respective national mortality rates			
BASF Cleanup Workers from 1953 accident (n = 247); 114 with chloracne, 13 more with erythema; serum TCDD levels (not part of IARC)		**Focus on TCDD**	
Incidence			
Through 1989 (n = 158 men exposed within 1 year of accident vs 161 other BASF employees 1953–1969)			Zober et al., 1994
All noncancerous respiratory diseases (ICD-9 460–419)	nr	33.7/31.0 (p = 0.22)	
COPD (ICD-9 490–496)	nr	8.0/7.5 (p = 0.31)	

TABLE 44 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
NIOSH Mortality Cohort (12 US plants, 5,172 male production and maintenance workers 1942–1984) (included in IARC cohort as of 1997)		**Dioxins, phenoxy herbicides**	
Monsanto workers (n = 240) involved in 2,4,5-T production (1948–1969) and 163 unexposed workers, results of clinical examination July, 1979—morbidity			Suskind and Hertzberg, 1984
"Abnormal" outcome on pulmonary-functions tests:			
FEV_1 (< 80% predicted)	32	2.81 (p = 0.02)	
FVC (< 80% predicted)	35	2.25 (p = 0.03)	
FEV_1/FVC (< 70%)	32	2.97 (p = 0.01)	
$FEF_{25–75}$ (< 80% predicted)	47	1.86 (p = 0.05)	
All Dow PCP-Exposed Workers—all workers from the two plants that only made PCP (in Tacoma, Washington and Wichita, Kansas) and workers who made PCP and TCP at two additional plants (in Midland, Michigan and Sauget, Illinois)		**2,4,5-T; 2,4,5-TCP**	Ruder and Yiin, 2011
1940–2005 (n = 2,122)	63	1.4 (0.1–1.8)	
PCP and TCP (n = 720)	10	0.7 (0.3–1.3)	
PCP (no TCP) (n = 1,402)	53	0.7 (0.3–2.2)	
Preliminary NIOSH Cross-sectional Medical Study—workers in production of sodium trichlorophenol, 2,4,5-T ester contaminated with TCDD—morbidity			
Chronic bronchitis and COPD	2	nr	Sweeney et al., 1997, 1998
ORs for increase in 1 ppt of serum TCDD compared to unexposed workers			Calvert et al., 1991
Chronic bronchitis	nr	0.5 (0.1–2.6)	
COPD	nr	1.2 (0.5–2.8)	
OCCUPATIONAL—HERBICIDE-USING WORKERS (not related to IARC sprayer cohorts)			
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; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
Mortality (COPD)			
Enrollment through 2007, vs state rates		SMR	Waggoner et al., 2011
Applicators (n = 1,641)	165	0.3 (0.3–0.4)	
Spouses (n = 676)	50	0.3 (0.2–0.4)	
Enrollment through 2000, vs state rates			Blair et al., 2005a
Private applicators (men and women)	50	0.2 (0.2–0.3)	
Spouses of private applicators (> 99% women)	15	0.3 (0.2–0.7)	

continued

TABLE 44 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Estimated Relative Risk (95% CI)[a]	Reference
ENVIRONMENTAL			
Seveso, Italy Residential Cohort—Industrial accident July 10, 1976 (723 residents Zone A; 4,821 Zone B; 31,643 Zone R; 181,574 local reference group) (ICD-9 171)		**TCDD**	
Mortality			
25-year followup to 2001—men and women			Consonni et al., 2008
COPD (ICD-9 490–493)			
Zone A	7	2.5 (1.2–5.3)	
Zone B	26	1.3 (0.9–1.9)	
Zone R	175	1.2 (1.0–1.4)	
20-year followup to 1996			Bertazzi et al., 2001
COPD (ICD-9 490–493)	29	1.5 (1.1–2.2)	
Zone A	7	3.3 (1.6–6.9)	
Zone B	22	1.3 (0.9–2.0)	
15-year followup to 1991—men			Bertazzi et al., 1998
COPD (ICD-9 490–493)			
Zone A	4	3.7 (1.4–9.8)	
Zone B	9	1.0 (0.5–1.9)	
Zone R	74	1.2 (0.9–1.5)	
15-year followup to 1991—women			Bertazzi et al., 1998
COPD (ICD-9 490–493)			
Zone A	1	2.1 (0.3–14.9)	
Zone B	8	2.5 (1.2–5.0)	
Zone R	37	1.3 (0.9–1.9)	
10-year followup to 1986—men (Zones A, B, R)			Bertazzi et al., 1989a
COPD (ICD-9 490–493)	31	1.1 (0.8–1.7)	
10-year followup to 1986—women (Zones A, B, R)			Bertazzi et al., 1989a
COPD (ICD-9 490–493)	8	1.0 (0.5–2.2)	

NOTE: 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COI, chemical of interest; COPD, chronic obstructive pulmonary disease; EOI, Exposure Opportunity Index; $FEF_{25\text{-}75}$, forced midexpiratory flow; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD-9, *International Classification of Diseases, 9th revision*; MOS, months of service; NIOSH, National Institute for Occupational Safety and Health; nr, not reported; OR, odds ratio; PCP, pentachlorophenol; SHR, standardized hospitalization rate; SMR, standardized mortality ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCP, trichlorophenol; VA, US Department of Veterans Affairs.

[a]Given when available; results other than estimated risk explained individually.

TABLE 45 Selected Epidemiologic Studies—Thyroid Homeostasis (shaded entries are new information for Update 11 [2018])

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); THS, total T4, T3%			Pavuk et al., 2003
THS 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— prevalence		**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)		**All COIs**	
Prevalence (01/2000–09/2005)—log EOI scores		HRs	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 non-toxic 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)	

continued

TABLE 45 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Reported Results[a]	Reference
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, New Jersey, and Verona, Missouri, employed > 15 years earlier and matched controls (n = 260)			Calvert et al., 1999
TSH mU/1		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)	
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 = 0.3–5.0μIU/ml	
Based on local levels		0.2	
Based on individual sampling LDs		–0.03	
Based on back extrapolation		–1.4 (p < 0.05)	
T4 vs estimated serum TCDD level	32	Normal = 0.045–2.125μg/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 = 0.9–1.9μg/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)	

TABLE 45 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Reported Results[a]	Reference
NEW ZEALAND			
New Zealand Phenoxy Herbicide Production Workers and Sprayers (1,599 men and women working any time in 1969–1988 at Dow plant in New Plymouth) (in IARC cohort)			
Morbidity survey 2008, n = 245			't Mannetje et al., 2018
Thyroid disorder			
Worked in a highly exposed job	6	0.95 (0.19–4.67)	
Serum TCDD concentration ≥ 10 pg/g lipid	5	4.00 (0.76–21.0)	
Hypothyroid			
Worked in a highly exposed job	1	0.16 (0.01–2.43)	
Serum TCDD concentration ≥ 10 pg/g lipid	1	1.77 (0.13–25.0)	
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; followups with CATIs 1999–2003 and 2005–2010		**Phenoxy herbicides**	
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	0.4 (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)	

continued

TABLE 45 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Reported Results[a]	Reference
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	
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 (–0.61–0.37)	
TSH	402	–0.09 (–0.38–0.20)	
Men (2000–2001)			
T4	497	–0.47 (–0.97–0.04)	
TSH	497	–0.02 (–0.20–0.16)	
Women (1999–2000)			
T4	310	–0.19 (–0.70–0.33)	
TSH	309	–0.15 (–0.14–0.44)	
Men (1999–2000)			
T4	386	–0.58 (–1.26–0.10)	
TSH	385	–0.06 (–0.15–0.35)	
Other Environmental Studies			
CANADA			
Cross-sectional study of Inuit residents (≥ 18 years of age) of Nunavik (Québec, Canada)	607	**dioxin-like PCBs**/ correlation of dioxin-like 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		**dioxin-like PCBs**/ dioxin-like PCB congeners β 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	**dioxin-like chemicals**	Foster et al., 2005
TSH correlation coefficient		ns (value nr)	
T4 correlation coefficient		ns (value nr)	

TABLE 45 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Reported Results[a]	Reference
CHINA—cross-sectional study of a Chinese community in the vacinity of an electronic-waste recycling plant—maternal serum T4 levels at 16 weeks gestation (correnlations with contaminant levels in cord blood)		**PCDDs, PCDFs, dioxin-like PCBs**	Zhang J et al., 2010
Dioxin-like 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 years 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 years in 2002–2008		**Total Serum TEQ**	Nakamoto et al., 2013
Thyroid disease (10 cases in men; 63 cases in women)	73		
1st quartile		1.0	
2nd quartile		1.0 (0.5–2.4)	
3rd quartile		1.2 (0.5–2.7)	
4th quartile		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, dioxin-like 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)	
KOREA—105 pregnant Korean women provided blood samples the day before delivery		**dioxin-like 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 ≤ 0.001)	
T3		–0.5 (p ≤ 0.001)	
UNITED STATES			
CHAMACOS Study—334 pregnant women from Salinas Valley, California, providing blood at 26 weeks gestation		**dioxin-like PCBs**	Chevrier et al., 2008
		β (95% CI)	
Free T4 vs:			
PCB TEQs (pg/g)		–0.05 (–0.16–0.06)	
Mono-ortho PCBs (ng/g)		–0.09 (–0.19–0.01)	
PCB 118 (ng/g)		–0.05 (–0.15–0.06)	
PCB 156 (ng/g)		–0.06 (–0.13– 0.01)	

continued

TABLE 45 Continued

Study Population	Exposed Cases[a]	Exposure of Interest/ Reported Results[a]	Reference
Total T4 vs:			
PCB TEQs (pg/g)		0.26 (–0.45–0.96)	
Mono-ortho PCBs (ng/g)		–0.13 (–0.78–0.53)	
PCB 118 (ng/g)		–0.26 (–0.43–0.95)	
PCB 156 (ng/g)		–0.05 (–0.52–0.42)	
Adult men recruited from Massachusetts infertility clinic (2000–2003)	341	**dioxin-like 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]	
Sportfish anglers from New York exposed to dioxin-like compounds in diet	38	**PCDDs, PCDFs, dioxin-like 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; CATI, computer-assisted telephone interviewing; CI, confidence interval; COI, chemical of interest; dl, dioxin-like; EOI, Exposure Opportunity Index; HR, hazard ratio; IARC, International Agency for Research on Cancer; LD, level of detection; NA, not available; NHANES, National Health and Nutrition Examination Survey; nr, no relationship; ns, nonsignificant; PCB, polychlorinated biphenyls; PCDD, polychlorinated dibenzo-*p*-dioxins; PCDD/Fs, chlorinated dioxins and furans combined; PCDF, polychlorinated dibenzofurans; ppt, parts per trillion; RH, Ranch Hand; SE, standard error; SEA, Southeast Asia; 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.

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