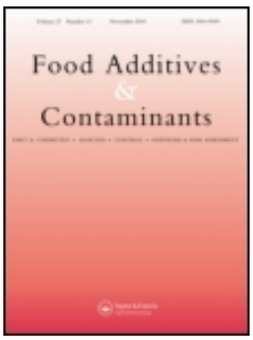

Food Additives & Contaminants

ISSN: 0265-203X (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/tfac19

Human health effects after exposure to 2,3,7,8-TCDD

Marie Haring Sweeney & Paolo Mocarelli

To cite this article: Marie Haring Sweeney & Paolo Mocarelli (2000) Human health effects after exposure to 2,3,7,8-TCDD, Food Additives & Contaminants, 17:4, 303-316, DOI: 10.1080/026520300283379

To link to this article: https://doi.org/10.1080/026520300283379

Food Additives and Contaminants, 2000, Vol. 17, No. 4, 303–316

Human health effects after exposure to 2,3,7,8-TCDD

Marie Haring Sweeney†* and Paolo Mocarelli‡
† National Institute for Occupational Safety and Health, Education and Information Division, Mailstop C-32, 4676 Columbia Parkway, Cincinatti, OH 45226-1988, USA; ‡ University Hospital Desio (Milano), Faculty of Medicin and Surgery, Via Benefattori Ospedale, I-20033 Desio, Milano, Italy

In 1949, the first descriptions of human exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD)-contaminated chemicals were reported after a trichlorophenol reactor explosion in Nitro, West Virginia, USA. Reported non-cancer health effects included a range of conditions affecting most systems. Additional reports of the health consequences of exposure continued through the remainder of the century. The majority of effects have been reported among highly exposed groups including occupational populations, such as chemical production workers, pesticide applicators, and individuals who handled or were exposed to materials treated with 2,3,7,8-TCDD-contaminated pesticides, and among residents of communities contaminated with tainted waste oil (Missouri, USA) and industrial e uent (Seveso, Italy). For only six exposed populations were biological measurements of 2,3,7,8-TCDD-contaminated collected and used to examine the relationship between non-cancer health effects and exposure. Of the many non-cancer health effects thought to be associated with 2,3,7,8-TCDD exposure, only chloracne, elevations in GGT and triglyceride levels, and alterations in FSH and LH were related to serum 2,3,7,8-TCDD levels. Mortality from cardiovascular diseases also appeared to be elevated among cohorts of exposed chemical workers and Seveso residents. Continued surveillance of the health of exposed populations will be useful in identifying the long-term effects of both high and low 2,3,7,8-TCDD exposure.

Keywords: cardiovascular disease, chloracne, hormonal alterations, immune effects, liver effects, neurological effects

* To whom correspondence should be addressed. e-mail: mhs2@cdc.gov

Introduction

Human exposure to 2,3,7,8-TCDD has been associated with non-cancer effects in most systems. The majority of effects have been reported among occupationally exposed groups, such as chemical production workers, pesticide users, and individuals who handled or were exposed to materials treated with 2,3,7,8-TCDD-contaminated pesticides, and among residents of communities contaminated with tainted waste oil (Missouri, USA) and industrial e uent (Seveso, Italy).

These effects represent a complex network of responses ranging from changes in hepatic enzyme levels, which, based on current evidence, do not appear to be related to clinical disease, to observable alterations in the character and physiology of the sebaceous gland, as in chloracne (Taylor 1979, Calvert *et al.* 1992). This paper describes by system the non-cancer effects associated with exposure to 2,3,7,8-TCDD. It is important to recognize that the observed effects are not independent events but rather may be one outcome in a series of interrelated outcomes, some of which we may be incapable of measuring with the present technology or which we currently do not recognize as an outcome of exposure to 2,3,7,8-TCDD.

Studies of exposed populations with biological measurements of 2,3,7,8-TCDD

Among the many populations studied to examine the relationship between non-cancer health effects and exposure to 2,3,7,8-TCDD contaminated chemicals, biological measures of exposure were collected for only six: chemical workers in the US (Piacitelli *et al.* 1992) and Germany (Ott *et al.* 1994); Air Force Ranch Hands (Roegner *et al.* 1991, Grubbs *et al.* 1995); Army Vietnam Veterans (Centers for Disease Control Vietnam Experience Study 1988a, b); and, residents of Missouri, USA

Table 1. 2,3,7,8-TCDD levels measured in exposed populations.

Author (country)	Population Exposed/ unexposed	Medium	Exposed				Unexposed		
			N	Level (pg/g)	Range (pg/g)	Half-life estimated (years)	*N*	Level (pg/g)	Range
Piacitelle *et al.* (1992)	TCP-production	Serum[a]	237	220[b]	ND–3400	ND–33 000	79	7	ND–26
Ott *et al.* (1994) (Germany)	TCP-production workers	Serum[a]	138	15.4[c]	< 1–553	20–1279 (no chloracne) 493–2955 (severe chloracne)	161	3.0 pg/g	0.6–9.1
Webb *et al.* (1989) (USA)	Missouri residents	Adipose tissue	16 13 12	< 20 ≥ 20–60 > 60	not stated	Not estimated	None	—	—
Mocarelli *et al.* (1991) (Italy) Needham *et al.* (1998)	Seveso residents	Serum[a]	426	—	ND–56 000	7.2–9.7	—	—	—
Roegner *et al.* (1991) (USA)	US Air Force Ranch Hands, 1987 exam	Serum[a]	866	12.8	ND–618	79	804	4.2	ND–54.8 pg/g
CDC Veterans Health Study (1988)	US Army Ground Personnel	Serum[a]	646	4.1[d]	SD ≥ 2.3	Not estimated	97	4.2[d]	SD ≥ 2.6

[a] Lipid adjusted.
[b] Arithmetic mean.
[c] Geometric mean.
[d] Median.
ND: Non-detectable; SD: Standard Deviation.

(Webb *et al.* 1989) and Seveso, Italy (Mocarelli *et al.* 1991). Descriptions of the study designs and populations have been detailed previously. A summary of the serum levels determined in each study group is included in table 1. In this discussion, more detailed analysis is restricted to these studies; however, where appropriate other studies will be included in the text.

Dermatological effects: chloracne and other dermatological conditions

The most widely recognized dermal effect of exposure to 2,3,7,8-TCDD-contaminated substances is chloracne. This acne-like condition is reported to have occurred with and without other effects in at least a few workers after all reported accidents at TCP production facilities (Ashe and Suskind 1950, Suskind *et al.* 1953, Goldman 1972, May 1973, Zober *et al.* 1990), among individuals involved in daily production of 2,3,7,8-TCDD-contaminated products (Bleiberg *et al.* 1964, Poland *et al.* 1971, Pazderova-Vejlupkova *et al.* 1981, Moses *et al.* 1984, Suskind and Hertzberg 1984, Moses and Prioleau 1985, Bond *et al.* 1989), among three laboratory workers exposed to pure 2,3,7,8-TCDD (Oliver 1975), and among at least 193 (0.6%) Seveso residents, mostly children (Caramaschi *et al.* 1981, Ideo *et al.* 1985, Mocarelli *et al.* 1986, Assennato *et al.* 1989). Chloracne was not found among Missouri residents (Hoffman *et al.* 1986, Webb *et al.* 1989) examined 10 years after exposure or among Ranch Hand personnel (Lathrop

et al. 1984, Roegner *et al.* 1991). In US Army Vietnam veterans, chloracne-like skin lesions were rarely observed on examination (0.9% in Vietnam veterans versus 0.8% in non-Vietnam veterans, OR = 1.4, 95% CI: 0.7–2.9) (Centers for Disease Control Vietnam Experience Study 1988a). Among Seveso residents, the condition disappeared after discontinuation of exposure (Assennato *et al.* 1989) despite high serum 2,3,7,8-TCDD levels (Mocarelli *et al.* 1991). But for a few TCP workers, the chloracne remained for many years (Suskind and Hertzberg 1984, Moses and Prioleau 1985).

Levels of 2,3,7,8-TCDD and HxCDD were measured in chloracne cases of Seveso residents (Mocarelli *et al.* 1991) and German chemical workers, respectively (Beck *et al.* 1989, Ott *et al.* 1993). Mocarelli *et al.* (1991) described chloracne in persons from Zone A who had very high serum 2,3,7,8-TCDD levels ranging from 820 to 56 000 pg/g measured within 1 year of the reactor release. The study also included other individuals from Zone A, but without chloracne, who had serum 2,3,7,8-TCDD levels that ranged from 1770 to 10 400 pg/g. With the exception of one person with chloracne who was 16 years old at the time of the accident, all of the cases were in children under age 11. Those without chloracne, for the most part, were over age 30. It is not clear whether the children were more susceptible to the chloranegenic effects or whether they had greater exposure to 2,3,7,8-TCDD-contaminated soil or airborne e uent.

Adipose tissue levels of 2,3,7,8-TCDD and HxCDD measured in adult chloracne cases of German chemical production workers suggest that these cases may have been a function of the combined exposure, making it difficult to isolate the contribution of the different chlorinated compounds (Beck *et al.* 1989). At the time of diagnosis, all cases had estimated adipose levels of greater than 200 pg/g 2,3,7,8-TCDD and in excess of 2000 pg/g lipid HxCDD. Estimated levels were based on the half-life extrapolation of the adipose tissue level measured in 1986 to the date of last occupational exposure, which may have occurred between 1949 and 1984. Similarly, Ott *et al.* (1993) found that 80% of the severe chloracne cases had estimated (back-calculated) levels of 250 pg/g. Yet, 26% of non-chloracne cases had estimated 2,3,7,8-TCDD concentrations of 250 pg/g.

Data from studies of Seveso residents conducted from 1982 to 1985 indicate that, despite high serum 2,3,7,8-TCDD levels, the chloracne resolved in all but one person by 1983 (Assennato *et al.* 1989). The fact that the cases of chloracne in Seveso residents resolved within 10 years may explain why no chloracne was observed in the Ranch Hand group although some serum 2,3,7,8-TCDD levels exceeded 600 pg/g in 1988 (Roegner *et al.* 1991) and may have been as high as 2400 pg/g at the time of last occupational exposure, assuming 21 years since last exposure and a 7-year half-life. Nevertheless, residual chloracne was observed 30 years after first exposure among workers from Nitro, West Virginia (Suskind and Hertzberg 1984) which may suggest that chronic high exposure to 2,3,7,8-TCDD or exposures higher than experienced by the Ranch Hands may account for long-term persistence of chloracne.

Dermal effects other than chloracne attributed to 2,3,7,8-TCDD exposure include symptoms and conditions that were reported much less frequently than chloracne but appeared in several groups subsequent to acute and continuous exposure to 2,3,7,8-TCDD-contaminated TCP and 2,4,5T. These conditions include red and irritated eyes, conjunctivitis, and blepharitis (inflammation of the eyelids) (Ashe and Suskind 1950, Baader and Bauer 1951), eyelid cysts (Suskind *et al.* 1953, Kimmig and Schulz 1957a,b, Poland *et al.* 1971, Reggiani 1980, Moses *et al.* 1984, Suskind and Hertzberg 1984), hyperpigmentation and hirsutism (also known as hypertrichosis or abnormal distribution of hair) (Ashe and Suskind 1950, Suskind *et al.* 1953, Bauer *et al.* 1961, Bleiberg *et al.* 1964, Poland *et al.* 1971, Goldman 1972, Oliver 1975), actinic elastosis (Suskind and Hertzberg 1984) and Peyronie's disease (Suskind and Hertzberg 1984).

Gastrointestinal effects

Liver size

Among exposed human populations, liver size was reportedly increased among two TCP production workers in West Virginia within a few months after a TCP reactor explosion (Ashe and Suskind 1950, Suskind *et al.* 1953) and among 'several' production workers in Czechoslovakia exposed to TCP, the butyl ester of 2,4,5-T, and sodium pentachlorophenol (Jirasek *et al.* 1974). Temporary liver enlargement was observed in five of 22 Seveso residents who had severe chloracne (Reggiani 1980). The hepatomegaly lasted

'several' months without concomitant elevation in hepatic enzymes. No evidence of liver enlargements was observed in cross-sectional medical studies of TCP production workers (Bond *et al.* 1983, Moses *et al.* 1984, Suskind and Hertzberg 1984, Calvert *et al.* 1992), Vietnam veterans (Centers for Disease Control Vietnam Experience Study 1988a, Roegner *et al.* 1991), and Missouri residents (Hoffman *et al.* 1986, Webb 1989). Additionally, no dose–response relationship was observed between serum levels of 2,3,7,8-TCDD and physical findings of an enlarged liver for the 1987 or 1992 examinations of Ranch Hands (≤ 10 pg/g 2,3,7,8-TCDD, RR ≤ 0.39, 95% CI: 0.11–1.33; 15-≤ 33.3 pg/g 2,3,7,8-TCDD, RR ≤ 1.47, 95% CI: 0.57–3.79; > 33.3 pg/g 2,3,7,8-TCDD, RR ≤ 1.6.9, 95% CI: 0.60–4.75) (Roegner *et al.* 1991) (background: RR ≤ 0.51 95% CI: 0.19, 1.38; low: RR ≤ 0.26, 95% CI: 0.06, 1.09; high: RR ≤ 1.02, 95% CI: 0.43, 2.44) (Grubbs *et al.* 1995) or the NIOSH study of TCP productions workers (two workers; four referents; OR ≤ 0.46, 95% CI: 0.09, 2.43) (Calvert *et al.* 1992).

Liver enzymes

The studies of Seveso children experienced a slight increase in gamma glutamyl transferase (GGT) levels occurring shortly after the reactor release and then a gradual decline to normal levels within 5 years. In one of the earliest studies of Seveso children with ($N \leq$ 141) and without chloracne ($N \leq$ 138), 2.8% of the children with chloracne had out-of-range GGT levels, but none of the children without chloracne had an out-of-range level ($p < 0.001$) (Caramaschi *et al.* 1981). These results were echoed in a study of children from Zones A, B, and R of Seveso, in which enzyme levels were measured yearly between June 1977 and June 1982 (Mocarelli *et al.* 1986). GGT levels were elevated in children of Zone A, particularly in boys, during the first 2 years after the explosion (1977: exposed ≤ 9.73 U/l; unexposed ≤ 7.28 U/l; $p < 0.01$; 1978: exposed ≤ 9.88 U/l; unexposed ≤ 8.26 U/l; $p < 0.05$) (Mocarelli *et al.* 1986). Levels in girls during the same years were elevated but did not achieve statistical significance. For the next 4 years of the study, GGT levels remained elevated in boys and girls from Zone A compared with unexposed children, but the values declined with time.

GGT was elevated among TCP production workers from plants in Great Britain and West Virginia, Missouri, and New Jersey up to 30 years after last occupational exposure to 2,3,7,8-TCDD-contaminated chemicals (May 1982, Martin 1984, Moses *et al.* 1984, Calvert *et al.* 1992). Among TCP production workers from the Missouri and New Jersey plants (Calvert *et al.* 1992), the mean GGT level and the proportion of workers with out-of-range levels were statistically significantly elevated (workers, mean GGT ≤ 58.5 U/l; unexposed referents, mean GGT ≤ 47.4 U/l, $p < 0.03$; workers, 11% abnormal; referents, 5% abnormal, OR ≤ 2.27, 95% CI: 1.17–4.39). Based on the logistic regression, the increases in GGT were limited to workers with high serum 2,3,7,8-TCDD levels (> 100 pg/g) and extremely high lifetime alcohol consumption (> 30 alcohol years) (alcohol year ≤ 1 alcoholic beverage/day for 1 year). The contribution of other potentially confounding exposures that may have affected GGT levels was not explored in this study. Other studies of TCP production workers in Michigan, West Virginia or the BASF accident cohort did not report elevations in GGT levels (Bond *et al.* 1983, Suskind and Hertzberg 1984, Ott *et al.* 1994).

Both the Vietnam Experience Study and the US Air Force Ranch Hand Study found statistically significant elevations in GGT levels (Centres for Disease Control Vietnam Experience Study 1988a, Roegner *et al.* 1991). In Army Vietnam veterans, mean GGT levels were 43.2 U/l compared with 41.1 U/l in non-Vietnam veterans (OR for out-of-range value ≤ 1.3, 95% CI: 1.0–1.8) (Centres for Disease Control Vietnam Experience Study 1988a). In the 1987 follow-up study, the comparison of the adjusted mean GGT level in the comparison group and in each of the three Ranch Hand groups defined by 2,3,7,8-TCDD level found statistically significant increases in the Ranch Hand population (≤ 10 pg/g 2,3,7,8-TCDD, $p < 0.017$; 15-≤ 33.3 pg/g 2,3,7,8-TCDD, $p < 0.043$; > 33.3 pg/g 2,3,7,8-TCDD, $p < 0.001$) (Roegner *et al.* 1991). In the 1992 follow up, significant increases were noted in Ranch Hands classified as either Low or High exposure (Grubbs *et al.* 1995).

AST and ALT

Elevations in serum ALT and AST appear to be transient effects of acute exposure to 2,3,7,8-TCDD. Case reports note that some populations have increased serum ALT levels shortly after exposure (Seveso children, British and Czechoslovakian TCP production workers) (May 1973, Jirasek *et al.* 1974, Caramaschi *et al.* 1981, Mocarelli *et al.* 1986).

Whereas epidemiological studies conducted 10–30 years after last exposure reported no effects in exposed workers, Vietnam veterans and Missouri residents compared with unexposed control groups (May 1982, Bond *et al.* 1983, Martin 1984, Suskind and Hertzberg 1984, Hoffman *et al.* 1986, Centres for Disease Control Vietnam Experience Study 1988a, Webb *et al.* 1989, Roegner *et al.* 1991, Calvert *et al.* 1992, Ott *et al.* 1994, Grubbs *et al.* 1995), or workers with and without chloracne (Moses *et al.* 1984). Normal levels of AST (AST = 10.6 U/l) were found in workers who volunteered to participate in a medical study conducted concurrently with their employment in a New Jersey chemical facility producing TCP and 2,4,5,-T (Poland *et al.* 1971). This was the same plant included in a later cross-sectional medical study of workers that found, in 1988, a high mean serum 2,3,7,8-TCDD level for the group (220 pg/g) but no elevations in AST or ALT (Calvert *et al.* 1992, Fingerhut *et al.* 1991a). Similarly, no increases in AST were noted in the BASF accident cohort (Ott *et al.* 1994).

During the first year after the TCP reactor release only ALT was statistically significantly elevated in children with chloracne (Caramaschi *et al.* 1981). In a larger study, Mocarelli *et al.* (1986) tested liver enzyme levels yearly from 1977 to 1982 in male and female children from Seveso and from the unexposed surrounding area. In the 1977, 1979, 1980, and 1981 test series ALT, but not AST, was statistically significantly ($p < 0.05$) elevated among male children in Seveso compared with unexposed comparisons. Female children had normal levels compared with controls for all years. In 1982, ALT levels in the exposed boys returned to normal.

None of the studies reporting elevations in ALT or AST identified clinical evidence of liver disease in the study populations. Therefore, in the absence of reports of hepatic or non-hepatic diseases related to changes in ALT or AST levels among exposed individuals, it is possible that the increases in ALT and AST are related to high-level, acute exposure to 2,3,7,8-TCDD-contaminated chemicals and that, barring additional exposure, the enzyme levels decrease with time.

D-Glucaric acid

Ideo and colleagues (1985) measured urinary D-glucaric acid in adults and children from all zones of Seveso and from nearby uncontaminated towns. Of adults tested in 1978, D-glucaric acid excretion was significantly elevated in adults residing in Seveso, Italy, at the time of the reactor explosion compared with residents of unexposed communities (Seveso = 27.1 μmol/g of creatinine vs unexposed = 19.8 μmol/g of creatinine, $p < 0.05$). No further studies of adults have been published. A series of studies evaluated D-glucaric acid excretion in Seveso children (Ideo *et al.* 1985). In 1976, the levels in children from Zone A with chloracne (39 μmol/g of creatinine) were significantly greater than in children without chloracne (20.5 μmol/g of creatinine). Additional studies, conducted until 1981, found significant yearly decreases in urinary D-glucaric acid excretion. By 1981, levels were within normal range.

Studies of Air Force Ranch Hands or TCP production workers did not find increases in D-glucaric acid excretion in exposed populations 10–37 years after last exposure to 2,3,7,8-TCDD-contaminated chemicals (Roegner *et al.* 1991, Calvert *et al.* 1992).

Porphyrin metabolism

Evidence of alterations in porphyrin metabolism among populations exposed to 2,3,7,8-TCDD is inconsistent. In 1964, 11 of 29 New Jersey workers TCP production workers with chloracne had porphyria cutanea tarda as a result of increased urinary uroporphyrins, coproporphyrins, and urobilinogen (Bleiberg *et al.* 1964). However, in follow up studies of subsets of the original population, only one individual of 73 tested had uroporphyrinuria in 1971 (Poland *et al.* 1971), and, in 1994, no difference was found between workers and an unexposed control group in the prevalence of PCT (OR = 0.93, 95% CI: 0.19, 4.54) (Calvert *et al.* 1994). Furthermore, in this study there were no differences in the risk between workers and the control group for an out-of-range uroporphyrin concentration or an out-of-range coproporphyrin concentration.

Lipid levels

Total cholesterol

In US TCP production workers, there was little difference between the adjusted mean total cholesterol

levels for workers (5.7 mmol/l) and referents (5.6 mmol/l) and no relation to increasing serum 2,3,7,8-TCDD levels (Calvert *et al.* 1996). The mean levels were adjusted for age, body mass index, age, and gender. Similarly, mean cholesterol levels were no different between workers in the BASF accident cohort (6.14 mmol/l) and the referent population (6.37 mmol/l) and were not related to current or log TCDD back-calculated levels (Ott *et al.* 1994). In addition, no significant differences were noted between the exposed and unexposed populations for HDL and LDL levels.

In general, cholesterol levels among exposed community residents were not increased. Neither children nor adults from Seveso were found to have elevated serum cholesterol levels compared with controls (Mocarelli *et al.* 1986, Assennato *et al.* 1989). Evaluated from 1976 through 1985, cholesterol levels in this population remained constant throughout the study period. Similarly, among Missouri residents, serum cholesterol was not related to residence in the Quail Run Mobile Home Park (Hoffman *et al.* 1986) or to adipose tissue 2,3,7,8-TCDD levels (Webb *et al.* 1989).

Among US Army veterans, there was no difference in total cholesterol levels between groups serving in Vietnam or other arenas (Centers for Disease Control Vietnam Experience Study 1988a). In contrast, there was a statistically significant positive relationship between Ranch Hands with serum 2,3,7,8-TCDD levels above 33.3 pg/g and total cholesterol in Air Force Ranch Hands (Roegner *et al.* 1991). The total cholesterol-HDL ratio was also highest in this serum 2,3,7,8-TCDD category. In the 1992 analysis, although cholesterol concentrations remained higher in the High Ranch Hand category compared with the Low, Background and Comparison group, the difference was not great enough to achieve statistical significance (Grubbs *et al.* 1995).

Triglycerides

Among workers in the NIOSH study there appeared to be a small rise in triglyceride levels with increasing serum 2,3,7,8-TCDD (Calvert *et al.* 1996). The mean adjusted triglyceride levels and the percent of abnormal triglyceride values increased with increasing serum 2,3,7,8-TCDD level (< 158 femtograms/litre [fg/l], mean = 1.04 mmol/l, % abnormal = 5.7; 158–520 fg/l, mean = 1.26 mmol/l, % abnormal = 6.1; 521–1515 fg/l, mean = 1.23 mmol/l, % abnormal = 6.1; 1516–19 717 fg/l, 1.35 mmol/l, % abnormal = 1.7, $p < 0.05$ compared with referents [1.15mmol/l]). Odds ratios and 95% confidence intervals for the quartiles are OR = 0.7 (95% CI: 0.2, 1.9), OR = 1.1 (95% CI: 0.4, 3.2), OR = 0.9 (95% CI: 0.3, 2.9), and OR = 1.7 (95% CI: 0.6, 4.6), respectively. The authors suggest that despite this small rise with 2,3,7,8-TCDD level, the influence of factors such as gender, body mass index, use of beta-blocker medication, and smoking had far greater effects on lipid concentration than did 2,3,7,8-TCDD level. Likewise, triglyceride levels in the BASF accident cohort were similar to those in the referent cohort and not related to 2,3,7,8-TCDD level (Ott *et al.* 1994). In the 1987 examination, mean adjusted triglyceride concentrations were statistically significantly higher among Ranch Hands whose serum 2,3,7,8-TCDD levels were above 15 pg/g of lipid (Roegner *et al.* 1991). In the 1991 examination, mean adjusted triglyceride concentrations only in the high group were significantly different from the comparison group (Grubbs *et al.* 1995).

Triglyceride levels were not elevated in Missouri (Hoffman *et al.* 1986, Webb *et al.* 1989) or Seveso residents (Mocarelli *et al.* 1986, Assennato *et al.* 1989) or in US Army Vietnam veterans (Centers for Disease Control Vietnam Experience Study 1988a).

Thyroid function

Only three studies of production workers examined thyroid function (Suskind and Hertzberg 1984, Ott *et al.* 1994, Calvert *et al.*, 1999). Suskind and Hertzberg (1984) performed T4 radioimmunoassay and thyroxine-binding globulin (TBG) tests and found no significant differences between exposed and unexposed workers. Quantitative results were not presented. Similarly, TSH, T4, and TBG levels were within normal range in the BASF accident workers and the means were not statistically different. However, TGB and T4 levels were positively related to 2,3,7,8-TCDD levels in regression analyses (Ott *et al.* 1994). Among US TCP workers, free thyroxine index and T4 were elevated compared with the unexposed referent population, although none of the differences were statistically significant, nor was there a dose-related trend (Calvert *et al.*, 1999). There were no differences in TSH levels between the exposed and

unexposed groups. The 1987 Ranch Hand study indicated a non-significant reduction of T3% uptake; T3% was not measured in the 1991 study. A slight increase in the mean level of thyroid-stimulating hormone (TSH) with increasing serum 2,3,7,8-TCDD level was noted in both 1987 and 1991; these results, however, did not reach statistical significance (Roegner *et al.* 1991, Grubbs *et al.* 1995). Among Army Vietnam veterans, mean TSH levels, but not mean free thyroxine index (FTI) levels, were statistically significantly higher than among non-Vietnam veterans, after adjustment for the six entry characteristics of age and year of enlistment, race, enlistment status, general technical test score, and primary military occupation (Centres for Disease Control Vietnam Experience Study 1988a). However, the percent of values that were out-of-reference range did not differ significantly for TSH (Vietnam veterans, 1.0%; non-Vietnam veterans, 0.6%, OR = 2.0, 95% CI: 0.9–4.3) and FTI (Vietnam veterans, 5.4%; non-Vietnam veterans, 4.6%, OR = 1.2, 95% CI: 0.9–1.5). The exposure levels were low, based on the sample for which 2,3,7,8-TCDD was measured.

Reproductive hormones

In linear regression analyses, serum 2,3,7,8-TCDD was positively and significantly related to serum concentration of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and inversely related to total testosterone after adjustment for potential confounders ($p < 0.05$) among TCP production workers (Egeland *et al.* 1994). The prevalence of abnormally low testosterone was two to four times higher among workers with serum 2,3,7,8-TCDD concentration of 20–75 pg/g (OR = 3.9, 95% CI: 1.3, 11.3), 76–243 pg/g (OR = 2.7, 95% CI: 0.9, 8.2), or = 244 pg/g (OR = 2.1, 95% CI: 0.8, 5.8) than among unexposed referents (4.8%) (mean serum 2,3,7,8-TCDD = 7 pg/g). Workers in these same serum 2,3,7,8-TCDD quartiles had a higher prevalence of abnormally high LH than workers with serum 2,3,7,8-TCDD levels of 244 pg/g to 3400 pg/g, but the differences between each serum 2,3,7,8-TCDD category and referents were not significant.

No association with serum 2,3,7,8-TCDD category was observed for testosterone, FSH, LH, testicular abnormalities or volume, or sperm count or abnormalities among Ranch Hand veterans and the comparison group (Henriksen *et al.* 1996). Similarly, no significant differences in mean levels of testosterone, FSH, and LH were noted between US Army veterans and non-Vietnam veterans (Centres for Disease Control Vietnam Experience Study 1988a).

Mocarelli *et al.* (1996) described a modification of sex ratio at birth with an excess of females over males in the period 1977–1984 in the most TCDD contaminated area in Seveso. Further analyses of these data are being conducted. More recently, an analysis of the relationship between paternal TCDD levels and the sex of offspring fathered by veterans of operation Ranch Hand found the percentages of female children in the background (< 10 pg/g) (51.9%), low (50.0%) and high (38.0%) exposure categories were similar to the percentage of female children in the comparison group (56.9%) (Michalek *et al.* 1998).

Diabetes

Cross-sectional studies of workers from Nitro, West Virginia (Moses *et al.* 1984, Suskind and Hertzberg 1984), found no difference in glucose levels between the exposed and control populations, although no quantitative values were presented in either study. Similarly, the adjusted odds ratio for out-of-range fasting glucose levels comparing US Army Vietnam veterans to non-Vietnam veterans was not statistically significant (OR = 1.0, 95% CI: 0.4–2.2) (Centres for Disease Control Vietnam Experience Study 1988a). But a comparison of the adjusted mean fasting glucose levels between the two groups was marginally significant (Vietnam veterans, 5.2 mmol/l; non-Vietnam veterans, 5.1 mmol/l, $p < 0.05$). In the BASF accident cohort, the mean fasting glucose levels were marginally elevated compared with the referent population and associated with concentrations of 2,3,7,8-TCDD ($p = 0.062$) at the time of the study but not the concentration estimated at the time of last exposure (back-extrapolated level) (Ott *et al.* 1994).

The proportion of Ranch Hands and unexposed comparisons with diabetes (defined as a medical record-verified history or diabetes of a 2-h postprandial serum glucose $\geqslant$ 200 mg/dl) were similar (Ranch Hands = 15%; RR = 1.08, 95% CI: 0.85, 1.37) (Grubbs *et al.* 1995). However, Ranch Hands with 2,3,7,8-TCDD concentrations $\geqslant$ 94 pg/g lipid mean fasting glucose levels were at increased risk

for diabetes (RR = 1.5, 95% CI: 1.2, 2.0) (Henriksen *et al.* 1997). Among US TCP production workers, the overall prevalence of diabetes mellitus was not significantly different between workers and referents nor was there a significant trend between prevalence of diabetes and increasing serum 2,3,7,8-TCDD concentration (Calvert *et al.*, 1999). However, diabetes was found in six of ten workers with serum 2,3,7,8-TCDD concentrations in excess of 1500 pg/g lipid.

In Seveso, 15 years after exposure (1976–1991), mortality from diabetes was elevated among female residents of Zone B (RR = 1.9, 95% CI: 1.2, 3.2) and Zone R (RR = 1.2, 95% CI: 1.0, 1.6). Only two cases of diabetes were observed in Zone A (Pesatori *et al.* 1998).

Immunological effects

Evaluation of the immunological status in exposed residential populations has not found a relationship between exposure and impaired status. Immunocompetence was tested twice in 44 children who were residents of the region of Seveso with the highest 2,3,7,8-TCDD contamination and in 43 age-matched children who did not reside in the contaminated area (Sirichia *et al.* 1982). Twenty of the exposed children had chloracne and 24 had no skin lesions. The tests included serum immunoglobulins, complement levels, lymphocyte subpopulations, and lymphocyte activity analysis. Some of the measures showed small differences between the two groups with slight increases in the exposed group.

In a study of Missouri residents, Webb *et al.* (1989) found no clinical evidence of immunosuppression in 40 individuals whose adipose 2,3,7,8-TCDD levels ranged from under 20 pg/g to over 430 pg/g (top of range not given). Tests included serum immunoglobulins, T-cell surface markers OKT3, OKT4, OKT8, OKT11, Leu11c, CD4/CD8 ratio, (CD4 = CD8)/CD3, and B1 and B2 cells. In logistic regression, significant ($p < 0.05$) relationships were noted for IgG, %CD3, %T11, %CD8, and %CD4 = LEU8 POS, controlling for age and sex.

Among participants in the BASF accident study cohort, with the exception of natural killer cells and helper-inducer cells, the proportions of some lymphocyte populations (B cells, T cells, T helper cells, T suppressor cells) were lower among workers, but the distribution of cells in referents and workers was equivalent (Ott *et al.* 1994). Levels for IgA, IgG, IgM, and complement C4 and C3 were slightly higher in workers than in the unexposed referent population. There also appeared to be slight dose-related increases in IgA, IgG, and complement C4 with 2,3,7,8-TCDD levels measured in October 1988 and February 1992. IgA and IgG were related to the half-life extrapolated 2,3,7,8-TCDD levels. It must be noted, however, that the statistically significant relationship between IgA and 2,3,7,8-TCDD is most probably due to a case of liver cirrhosis and the association with IgG due to a liver carcinoma.

The effect of past occupational exposure on immunological function was examined in 18 British workers who were evaluated 17 years after accidental industrial exposure to chemicals contaminated with 2,3,7,8-TCDD compared with unexposed controls matched for age, race, sex, smoking habit, alcohol consumption, and percent of ideal body weight (Jennings *et al.* 1988). There were no significant differences in the levels of immunoglobulins, T and B lymphocytes, responsiveness to phytohaemagglutinin A, and in the number of CD4 and CD8 counts. Three measures were found to be statistically significantly ($p < 0.05$) higher in workers than in controls: antinuclear antibodies (ANA) (8 workers vs 0 controls, $p < 0.01$) (when Hep2 cells were used as substrate but not when rat liver cells were used), immune complexes (workers = 11 vs 3 controls, $p < 0.05$), and natural killer cells (NK) (workers = $0.21 = 10^6$/l vs controls = $0.59 = 10^6$/l, $p < 0.002$) identified by the monoclonal antibody Leu-7. The authors could not explain the physiological basis of their findings and suggested that further research was needed.

No significant differences were noted among US Army ground troops and the comparison population in lymphocyte subset populations, T-cell populations, or serum immunoglobulins (Centres for Disease Control Vietnam Experience Study 1988a). Comprehensive immunological profiles were developed for each participant of the US Air Force Ranch Hand Study (Roegner *et al.* 1991). Significant positive associations were found only between IgA and serum 2,3,7,8-TCDD. The authors suggest that the rise in IgA is consistent with a subclinical inflammatory response, but the authors could not explain the source of the inflammatory response.

Neurological effects

Neurobehavioural assessments

Numerous case reports cite symptoms referable to the nervous system occurring after acute exposure among occupationally-exposed individuals (Ashe and Suskind 1950, Suskind *et al.* 1953, Goldman 1972, Creso *et al.* 1978), as well as chronic exposure to 2,3,7,8-TCDD-contaminated materials (Baader and Bauer 1951, Kimmig and Schulz 1957a,b, Bauer *et al.* 1961, Poland *et al.* 1971, Oliver 1975). Symptoms include headache (Ashe and Suskind 1950, Kimmig and Schulz 1957a,b, Bauer *et al.* 1961, Poland *et al.* 1971, Jirasek *et al.* 1974, Oliver 1975), insomnia (Ashe and Suskind 1950, Suskind *et al.* 1953, Kimmig and Schulz 1957a,b, Oliver 1975), nervousness or irritability (Ashe and Suskind 1950, Suskind *et al.* 1953, Bauer *et al.* 1961, Oliver 1975), depression and anxiety (Bauer *et al.* 1961, Jirasek *et al.* 1974), loss of libido, (Moses *et al.* 1984, Suskind and Hertzberg 1984) and encephalopathy (Kimmig and Schulz 1957a, Jirasek *et al.* 1974). Some reports indicate that symptoms referable to the CNS and PNS may persist in some exposed individuals for as long as 25 years (Ashe and Suskind 1950, Suskind *et al.* 1953, Poland *et al.* 1971, Jirasek *et al.* 1973, 1974, Creso *et al.* 1978).

A number of studies examined possible neurobehavioural effects among various exposed populations, however, there is little intrastudy consistency in the tests administered to study subjects. Thus, direct comparison of the results from the various studies is difficult.

The effects of exposure to 2,3,7,8-TCDD on measures of current symptoms of depression were evaluated (Alderfer *et al.* 1992) as part of the NIOSH cross-sectional medical study. Symptoms of depressed mood were measured by the Beck Depression Inventory and the depression subscale of the Self-Report Symptom Checklist-90-Revised (SCL-90-R). Neither serum 2,3,7,8-TCDD levels nor status as a worker was associated with depressed mood as assessed by either the Beck Depression Inventory or the SCL-90-R depression subscale (Alderfer *et al.* 1992). These findings are consistent with those of the US Air Force study (Roegner *et al.* 1991) of personnel who applied Agent Orange during the Vietnam war: serum 2,3,7,8-TCDD was not associated with the depression subscale score of the SCL-90-R after controlling for covariates.

In addition, in the Ranch Hand study there was no significant difference between groups or relationship with serum 2,3,7,8-TCDD levels on reported (and verified) data on lifetime psychological illness or sleep disorders or any SCL-90-R. Some of the MCMI parameters appeared to be related to serum 2,3,7,8-TCDD levels (significantly higher mean schizoid and schizotypal scores and significantly lower mean histrionic score in the group above 33.3 pg/g than in comparisons). However, these findings were inconsistent with similar variables in the SCL-90-R and the self-reported histories.

Among US Army Vietnam veterans there was a significantly greater prevalence of alcohol abuse or dependence (Vietnam veterans, 13.7%; non-Vietnam veterans, 9.2%; OR = 1.5, 95% CI: 1.2–1.8), depression (Vietnam veterans, 4.5%; non-Vietnam veterans, 3.2%; OR = 2.0, 95% CI: 1.4–2.9), and a higher prevalence of poor psychological status (Centers for Disease Control Vietnam Experience Study 1988b). The poor psychological status tended to be most prevalent in Vietnam veterans who were not white, who enlisted before their 19th birthday, and whose enlistment test scores fell below the group median.

Neurological status

Among New Jersey and Missouri TCP workers, no differences in neurological status or nerve function between workers or referents were detected, nor was there an apparent relationship with 2,3,7,8-TCDD concentration (Sweeney *et al.* 1993). Among Ranch Hands, the group with serum 2,3,7,8-TCDD concentrations above 33.3 pg/g tended to have a higher proportion of individuals with abnormal coordination than the comparisons (Ranch Hands, 2.7%; comparisons, 0.4%; adjusted RR = 18.3, $p < 0.001$) (Roegner *et al.* 1991). Overall neurologic status of US Army Vietnam veterans did not differ from that of non-Vietnam veterans (Vietnam veterans, 1.0%; non-Vietnam veterans, 0.8%; OR = 1.2, 95% CI: 0.6–2.3) (Centers for Disease Control Vietnam Experience Study 1988b). Only self-reported symptoms related to nerve disorders were significantly more prevalent among Vietnam veterans than non-

Vietnam veterans (Vietnam veterans, 8.2%; non-Vietnam veterans, 6.5%; OR = 1.2, 95% CI: 1.0–1.6).

Of the 200 workers at the Icmesa plant, approximately 4% (N = 8) were found to have damage to nerve fibres of multiple (unspecified) nerves, controlling for confounding factors such as alcohol abuse, diabetes, kidney disease, and neurotoxic medication use (Pocchiari *et al.* 1979). The report did not describe the extent of worker exposure to 2,3,7,8-TCDD nor the potential for exposure to other neurotoxins present at the worksite. Three workers were described as having polyneuropathies of the lower limbs.

In 1981, prevalence risk ratios (PRRs) for neuropathy were determined for 308 Seveso residents who exhibited clinical indication of 2,3,7,8-TCDD exposure, defined as the presence of elevated liver enzyme levels (GGT, ALT, AST) (which are also indicative of nonspecific insults to the liver) or chloracne, and for those who exhibited conditions that are risk factors for neuropathy, e.g. alcoholism, inflammatory disease, diabetes, or potential occupational exposure to neurotoxins (Filippini *et al.* 1981). Seveso residents who met the exposure definition had significantly greater prevalence of neuropathy than residents without either manifestation (PRR exposure = 2.8, 95% CI: 1.2–6.5; PRR for possible 2,3,7,8-TCDD-predisposing factors = 2.6, 95% CI: 1.2–5.6) (Filippini *et al.* 1981).

Residents of Seveso who developed chloracne after the reactor release (N = 193) were evaluated in a series of three follow-up screenings in 1982–1983, 1983–1984, and 1985 (Assennato *et al.* 1989). Compared with an unexposed control group, no increases were found in the prevalence of abnormal electrophysiological measures or in conduction velocities for each fibre from the 1982–1983 to 1985 studies.

Participants in the study of Missouri residents (Webb *et al.* 1989) were examined by a neurologist. The results were unremarkable. Of the 38 participants, two with levels above background had abnormal pin prick sensitivity (= 20 pg/g, N = 2; 20–60 pg/g, N = 1; = 60 pg/g, N = 1), three had abnormal vibration thresholds (= 20 pg/g, N = 2; 20–60 pg/g, N = 1; = 60 pg/g, N = 2), and four had abnormal reflexes (= 20 pg/g, N = 2; 20–60 pg/g, N = 2; = 60 pg/g, N = 2). The results of other components of the neurological examination were not reported and are assumed to be normal.

Circulatory system

Among TCP production workers, mortality from all diseases of the circulatory system was similar to mortality in the general population, as described by an SMR of 100, and in workers from The Netherlands (Plant A) (SMR = 98, 95% CI: 65–142) (Bueno de Mesquita *et al.* 1993), the United States (Nitro, West Virginia) (SMR = 90, 95% CI: 80–100) (Collins *et al.* 1993), and Great Britain (SMR = 116, 95% CI: 91–146) (Coggon *et al.* 1991). In two studies, mortality in workers with chloracne was not significantly different from that of the national comparison group (US workers, SMR = 93, 95% CI: 79–108; German workers, SMR = 121, 90% CI: 83–170) (Ott *et al.* 1987, Zober *et al.* 1990).

In a study of German chemical workers who manufactured 2,4,5-TCP, 2,4,5-T in addition to chemicals contaminated with higher chlorinated PCDDs and PCDFs (Flesch-Janys *et al.* 1995), mortality for all circulatory diseases was positively related to estimated TCDD levels and significantly related to estimated total TEQ concentrations above 39 ng/kg, lipid-adjusted. Lipid-adjusted 2,3,7,8-TCDD concentrations and total TEQ estimates for the cohort were based on PCDD and PCDF measurements of 190 male workers.

The SMR from ischaemic heart disease (IHD) was 102 (95% CI: 63–158) among Dutch chemical workers (Bueno de Mesquita *et al.* 1993) and 96 (95% CI: 51–164) in US workers (Midland, MI) (Bond *et al.* 1987) and was significantly increased among German chemical workers only in the highest 2,3,7,8-TCDD quintile (RR = 2.48, 95% CI 1.32–4.66) (Flesch-Janys *et al.* 1995). However, mortality from IHD was lower than expected (SMR = 82, 95% CI: 0.67–1.02) in a cohort of 1909 herbicide sprayers followed from 1972 through 1989 who applied a mixture of 2,4-D and 2,4,5-T for two weeks or longer anytime during the period 1951–1971 (Asp *et al.* 1994). Similar trends were observed for other diseases of the circulatory system.

In an analysis that included all diseases of the heart combined among 5200 US production workers, the SMR was 96 (95% CI: 87–106) (Fingerhut *et al.* 1991b). Cerebrovascular disease mortality was slightly elevated among Dutch TCP production workers (SMR = 117, 95% CI: 38–274) (Bueno de Mesquita *et al.* 1993) and increased by more than twofold in Michigan TCP production workers with

chloracne (SMR = 208, 95% CI: 57, 539) (Bond *et al.* 1987).

The SMR values for circulatory system diseases reported in the various mortality studies are close to 100, suggesting that the 'healthy worker effect' is not seen in these studies. Generally, because employed workers are healthier than the general population, the SMR for cardiovascular disease in employed populations tends to be lower than 100 (Fox and Collier 1976, McMichael 1976). The results in the Flesch-Janys paper underscore these findings (Flesch-Janys *et al.* 1995). The absence of a healthy worker effect, in light of the positive animal data, suggests that more detailed analyses should be conducted for cardiovascular outcomes in these populations.

Among 1261 Ranch Hand personnel, mortality from circulatory disease was non-significantly elevated (SMR = 110, 95% CI: 60–150) compared with that of a comparison population of 19 101 other Air Force veterans who were not exposed to herbicides (Michalek *et al.* 1990). These results were repeated in an updated mortality analysis (SMR = 105, 95% CI: 96–142) (Wolfe *et al.* 1994). Similar non-significant increases in the relative mortality ratio (RMR) were observed for circulatory diseases (RMR = 1.6, 95% CI: 0.8–3.2) in Australian Vietnam veterans (N = 19 205; 260 deaths) compared with 25 677 (263 deaths) non-Vietnam veterans who only served in Australia (Fett *et al.* 1987). In contrast, the unadjusted relative risk of 0.49 (95% CI: 0.25–0.99) for all circulatory diseases suggested a deficit of deaths from this cause among 9325 Vietnam Army veterans (246 deaths) compared with 8989 non-Vietnam veterans (200 deaths) (Centers for Disease Control Vietnam Experience Study 1988c).

Bertazzi and colleagues examined the mortality experience of Seveso residents aged 1–19 years (Bertazzi *et al.* 1992) and aged 20–74 years (Bertazzi *et al.* 1989) 10 years after the contamination of the town by 2,3,7,8-TCDD-contaminated effluent. In the younger population, two deaths from circulatory diseases occurred only in female residents (RR = 1.63, 95% CI: 0.3–8.1). In the older population, circulatory disease mortality of residents from Zone A (the most highly contaminated region) was elevated in both males (RR = 1.75, 95% CI: 1.0–3.2) and females (RR = 1.89, 95% CI: 0.8–4.2). In males, the highest death rate occurred during the first quinquennium, 1976–1981 (RR = 2.04, 95% CI: 1.0–4.2), and, in females, the highest death rate occurred during the second quinquennium,1982–1986. The authors suggest that the study was limited by the small number of subjects and the crude measure of 2,3,7,8-TCDD exposure. The authors could not attribute the increased mortality from circulatory disease to 2,3,7,8-TCDD exposure but suggested that the 'high stress and pollution' imposed on the residents of Zone A may have been a contributing factor. In the 15 year follow-up analysis, Pesatori *et al.* (1998) observed a three-fold increase in mortality from chronic ischaemic heart disease (RR = 3.0, 95% CI: 1.2–7.3) among males in Zone A, and a slight rise among men in Zone R (RR = 1.4, 95% CI: 1.1, 1.7), but not in Zone B, nor in female residents of any zone (Pesatori *et al.* 1998). Female residents were more likely to die from chronic rheumative heart disease or hypertensive related heart disease.

Pulmonary effects

Case reports have described temporary respiratory irritation (Zack and Suskind 1980) and tracheobronchitis (Goldman 1972) among chemical workers exposed to 2,3,7,8-TCDD-contaminated herbicides following industrial accidents. However, there is conflicting evidence from controlled epidemiological studies regarding an association between chronic respiratory system effects and human exposure to substances contaminated with 2,3,7,8-TCDD. A study of West Virginia (WV) workers involved in the production of TCP and 2,4,5T found a statistically significantly increased risk for an abnormal forced expiratory volume at 1 s (FEV_1) ($p < 0.01$), an abnormal forced vital capacity (FVC) ($p < 0.001$), and an abnormal FEV_1/FVC ratio ($p < 0.05$) among workers who were smoking at the time of the study (Suskind and Hertzberg 1984). For workers, the percent predicted spirometric parameters for FEV_1, FVC, and FEV_1/FVC were 99.4%, 92.7%, and 76.5% and for referents, 104.4%, 97.6%, and 79.9%, respectively. A study of TCP and 2,4,5-T production workers from Missouri (MO) and New Jersey (NJ) found no association between serum 2,3,7,8-TCDD concentrations and declines in ventilatory function (Calvert *et al.* 1991). The disparity in results may be related to differences in the ages of the comparison groups relative to the exposed study groups (WV 10 years; NJ&MO: 0.6 years) and the type of exposure (WV: 2,4,5-T acid dust; NJ&MO: 2,4,5,T acid liquid).

The Ranch Hand study found significant declines in the mean FEV_1 and the mean forced expiratory volume (FVC) for Ranch Hands with serum 2,3,7,8-TCDD levels above 33.3 pg/g (adjusted mean FEV_1 = 91.3%; mean FVC = 87.4) compared with a non-exposed comparison group (adjusted mean FEV_1 = 93.5%; mean FVC = 91.7) (Roegner *et al.* 1991). The 2,3,7,8-TCDD-related declines were small and were interpreted by the authors to be 'subtle' and 'not clinically significant'. As expected, smoking appeared to have the greater influence on lung function. In the follow up examination conducted in 1992, no consistent relationship was found between serum 2,3,7,8-TCDD concentrations and respiratory parameters (Grubbs *et al.* 1995).

Among Seveso residents, mortality from chronic obstructive pulmonary disease was statistically significantly increased among male residents of Zone A (RR = 3.7, 95% CI: 1.4, 9.9) and among female residents of Zone B (RR = 2.4, 95% CI: 1.1, 5.1) (Pesatori *et al.* 1998).

Renal effects

There is little evidence in the animal or human data to suggest that exposure to 2,3,7,8-TCDD is related to renal or bladder dysfunction. In a single case report, a child exposed to 2,3,7,8-TCDD after contact with soil sprayed with contaminated waste oil was diagnosed with focal pyelonephritis (Kimbrough *et al.* 1977). After diagnosis and treatment, the condition resolved with no reported recurrence. No major renal or bladder dysfunctions were noted among Air Force Ranch Hands (Lathrop *et al.* 1984, 1987, Roegner *et al.* 1991) or among TCP production workers from West Virginia (Suskind and Hertzberg 1984) or New Jersey (Poland *et al.* 1971).

References

Alderfer, R., Sweeney, M., Fingerhut, M., Hornung, R., Wille, K., and Fidler, A., 1992, Measures of depressed mood in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Chemosphere* , **25,** 247–250.

Ashe, W. F., and Suskind, R. R., 1950, Reports on chloracne cases, Monsanto Chemical Co., Nitro, West Virginia, October 1949 and April 1950. Cincinnati, OH, Department of Environmental Health, College of Medicine, University of Cincinnati (unpublished).

Asp, S., Riihimäki, V., Hernberg, S., and Pukkala, E., 1994, Mortality and cancer morbidity of Finnish chlorophenoxy herbicide applicators, an 18-year prospective follow-up. *American Journal of Industrial Medicine*, **26,** 243–253.

Assennato, G., Cervino, D., Emmet, E., Longo, G., and Merlo, F., 1989, Followup on subjects who developed chloracne following TCDD exposure of Seveso. *American Journal of Industrial Medicine*, **16,** 119–125.

Baader, E. W., and Bauer, H. J., 1951, Industrial intoxication due to pentachlorophenol. *Industrial Medicine and Surgery*, **20,** 286–290.

Bauer, H., Schulz, K., and Spiegelburg, W., 1961, Industrial poisoning in the manufacture of chlorophenol compounds. *Archiv für Gewerbepathologie und Gewerbehygiene*, **18,** 538–555.

Beck, H., Eckart, K., Mathar, W., and Wittkowski, R., 1989, Levels of PCDDs and PCDFs in adipose tissue of occupationally exposed workers. *Chemosphere* , **18,** 507–516.

Bertazzi, P. A., Zocchetti, C., Pesatori, A. C., Guercilena, S., Sanarico, M., and Radice, L., 1989, Ten-year mortality study of the population involved in the Seveso incident in 1976. *American Journal of Epidemiology*, **129,** 1187–1199.

Bertazzi, P. A., Zocchetti, C., Pesatori, A. C., Guercilena, S., Consonni, D., Tironi, A., and Landi, M. T., 1992, Mortality of a young population after accidental exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *International Journal of Epidemiology*, **21,** 118–123.

Bleiberg, J., Wallen, M., Brodkin, R., and Applebaum, I. L., 1964, Industrially acquired porphyria. *Archives of Dermatology*, **89,** 793–797.

Bond, G. G., Ott, M. G., Brenner, F. E., and Cook, R. R., 1983, Medical and morbidity surveillance findings among employees potentially exposed to TCDD. *British Journal of Industrial Medicine*, **40,** 318–324.

Bond, G. G., Cook, R. R., Brenner, F. E., and McLaren, E. A., 1987, Evaluation of mortality patterns among chemical workers with chloracne. *Chemosphere* , **16,** 2117–2121.

Bond, G. G., McLaren, E. A., Brenner, F. E., and Cook, R. A., 1989, Incidence of chloracne among chemical workers potentially exposed to chlorinated dioxins. *Journal of Occupational Medicine*, **31,** 771–774.

Bueno De Mesquita, H. B., Doornbos, G., Van Der Kuip, D. A. M., Kogevinas, M., and Winkelmann, R., 1993, Occupational exposure to phenoxy herbicides and chlorophenols and cancer mortality in The Netherlands. *American Journal of Industrial Medicine*, **23,** 289–300.

Calvert, G. M., Sweeney, M. H., Morris, J. A., Fingerhut, M. A., Hornung, R. W., and Halperin, W. E., 1991, Evaluation of chronic bronchitis, chronic obstructive pulmonary disease (COPD) and ventilatory function among workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). *American Review of Respiratory Disease*, **144,** 1302–1306.

Calvert, G. M., Hornung, R. W., Sweeney, M. H., Fingerhut, M. A., and Halperin, W. E., 1992, Hepatic and gastrointestinal effects in an occupational cohort exposed to 2,3,7,8-tetrachlorodibenzo-*para*-dioxin. *Journal of the American Medical Association*, **267,** 2209–2214.

Calvert, G. M., Sweeney, M. H., Fingerhut, M. A., Hornung, R. W., and Halperin, W. E., 1994, Evaluation of porphyria cutanea tarda in US workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *American Journal of Industrial Medicine*, **25,** 559–571.

Calvert, G. M., Wille, K. K., Sweeney, M. H., Fingerhut, M. A., and Halperin, W. E., 1996, Evaluation of serum lipid concentrations among US workers exposed to 2,3,7,8-tetrachloro-

dibenzo-*p*-dioxin. *Archives of Environmental Health*, **51,** 100–107.

Calvert, G. M., Sweeney, M. H., Deddens, J., and Wall, D. K., 1999, An evaluation of diabetes mellitus, serum glucose, and thyroid function among US workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Occupational Environmental Medicine*, **56,** 270–276.

Caramaschi, F., Del Caino, G., Favaretti, C., Giambelluca, S. E., Montesarchio, E., and Fara, G. M., 1981, Chloracne following environmental contamination by TCDD in Seveso, Italy. *International Journal of Epidemiology*, **10,** 135–143.

Centers For Disease Control Veterans Health Studies, 1988, Serum 2,3,7,8-tetrachlorodibenzo-*p*-dioxin levels in US Army Vietnamera veterans. *Journal of the American Medical Association* , **260,** 1249–1254.

Centers For Disease Control Vietnam Experience Study, 1988a, Health status of Vietnam veterans. II. Physical health. *Journal of the American Medical Association*, **259,** 2708–2714.

Centers For Disease Control Vietnam Experience Study, 1988b, Health status of Vietnam veterans. I. Psychosocial characteristics. *Journal of the American Medical Association*, **259,** 2701–2707.

Centers For Disease Control Vietnam Experience Study, 1988c, Postservice mortality among Vietnam veterans. *Journal of the American Medical Association*, **257,** 790–795.

Coggon, D., Pannett, B., and Winter, P., 1991, Mortality and incidence of cancer at four factories making phenoxy herbicides. *British Journal of Industrial Medicine*, **48,** 173–178.

Collins, J. J., Strauss, M. E., Levinkas, G. J., and Conner, P. R., 1993, The mortality experience of workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in a trichlorophenol process accident. *Epidemiology*, **4,** 7–13.

Creso, E., Demarino, V., Donatelli, L., and Pagini, G., 1978, Effette neuropsicofarmacologici deila TCDD. *Bollettino Societa Italiana Biologia Sperimentale*, **54,** 1592–1596.

Egeland, G. M., Sweeney, M. H., Fingerhut, M. A., Wille, K. K., Schnorr, T. M., and Halperin, W. E., 1994, Total serum testosterone and gonadotropins in workers exposed to dioxin. *American Journal of Epidemiology*, **139,** 272–281.

Fett, M. J., Adena, M. A., Cobbin, D. M., and Dunn, M., 1987, Mortality among Australian conscripts of the Vietnam conflict era. I. Causes of death. *American Journal of Epidemiology*, **125,** 878–884.

Filippini, G., Bordo, B., Crenna, P., Massetto, N., Musicco, M., and Boeri, R., 1981, Relationship between clinical and electrophysiological findings and indicators of heavy exposure to 2,3,7,8-tetrachlorodibenzodioxin. *Scandinavian Journal of Work Environment & Health*, **7,** 257–262.

Fingerhut, M. A., Halperin, W. E., Marlow, D. A., Piacitelli, L. A., Honchar, P. A., Sweeney, M. H., Greife, A. L., Dill, P. A., Steenland, K., and Suruda, A. J., 1991a, Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *New England Journal of Medicine*, **324,** 212–218.

Fingerhut, M. A., Halperin, W. E., Marlow, D. A., Piacitelli, L. A., Honchar, P. A., Sweeney, M. H., Greife, A. L., Dill, P. A., Steenland, K., and Suruda, A. J., 1991b, Mortality among US workers employed in the production of chemicals contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Cincinnati, OH, US Department of Health and Human Services, National Institute for Occupational Safety and Health, *National Technical Information Service* # *PB* **91**-125971.

Flesch-Janys, D., Berger, J., Gurn, P., Manz, A., Nagel, S., Waltsgott, H., and Dwyer, J. H., 1995, Exposure to polychlorinated dioxins and furans (PCDD/F) and mortality in a cohort of workers from a herbicide-producing plant in Hamburg, Federal Republic of Germany. *American Journal of Epidemiology*, **142,** 1165–1167.

Fox, A. J., and Collier, P. F., 1976, Low mortality rates in industrial cohort studies due to selection for work and survival in the industry. *British Journal of Preventive and Social Medicine*, **30,** 225–230.

Goldman, P. J., 1972, Critically acute chloracne caused by trichlorophenol decomposition products. *Arbeitsmedizin Sozialmedizin Arbeitshygiene,* **7,** 12–18.

Grubbs, W. D., Wolfe, W. H., Michalek, J. E., Williams, D. E., Lustik, M. B., Brockman, A. S., Henderson, S. C., Burnett, F. R., Land, R. J., Osborne, D. J., Rocconi, V. K., Schreiber, M. E., Miner, J. C., Henriksen, G. L., and Swaby, J. A., 1995, *Air Force Health Study, An epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides. Report number AL-TR-920 107.*

Henriksen, G. L., Michalek, J. E., Swaby, J. A., and Rahe, A. J., 1996, Serum dioxin, testosterone, and gonadotropins in veterans of Operation Ranch Hand. *Epidemiology*, **7,** 352–357.

Hoffman, R. E., and Stehr-Green, P. A., 1989, Localized contamination with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, the Missouri episode. *Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins, and Related Products,* edited by R. D. Kimbrough and A. A. Jensen (New York: Elsevier), pp. 471–483.

Hoffman, R. E., Stehr-Green, P. A., Webb, K. B., Evans, R. G., Knutsen, A. P., Schram, W. F., Staake, J. L., Gibson, B. B., and Steinberg, K. K., 1986, Health effects of longterm exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Journal of the American Medical Association*, **255,** 2031–2038.

Ideo, G., Ballati, G., Bellobuno, A., and Bissanti, L., 1985, Urinary D-glucaric excretion in the Seveso area, polluted by tetrachlorodibenzo-*p*-dioxin (TCDD), five years of experience. *Environmental Health Perspectives*, **60,** 151–157.

Jennings, A. M., Wild, G., Ward, J. D., and Milford Ward, A., 1988, Immunological abnormalities 17 years after accidental exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *British Journal of Industrial Medicine*, **45,** 701–704.

Jirasek, L., Kalensky, J., and Kulec, K., 1973, Chloracne and porphyria cutanea tarda in association with the production of herbicide. *Ceskoslovenska Dermatologie*, **48,** 306–317.

Jirasek, L., Kalensky, K., Kubec, K., Pazderova, J., and Lukas, E., 1974, Chronic poisoning by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Ceskoslovenska. Dermatologie*, **49,** 145–157.

Kimbrough, R. D., Carter, C. D., Liddle, J. A., and Cline, R. E., 1977, Epidemiology and pathology of a tetrachlorodibenzodioxin poisoning episode. *Archives of Environmental Health*, **32,** 77–85.

Kimmig, J., and Schulz, K. H., 1957a, Chlorinated aromatic cyclic ethers as the cause of socalled chloracne. *Naturwissenschaften*, **44,** 337–338.

Kimmig, J., and Schulz, K. H., 1957b, Occupational chloracne caused by aromatic cyclic ethers. *Dermatologica*, **115,** 540–546.

Lathrop, G. D., Wolfe, W. H., Albanese, R. A., and Moynihan, P. M., 1984, An epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides. Baseline morbidity study results. Brooks Air Force Base, TX, US Air Force School of Aerospace Medicine. Aerospace Medical Division (unpublished).

Martin, J. V., 1984, Lipid abnormalities in workers exposed to dioxin. *British Journal of Industrial Medicine*, **41,** 254–256.

May, G., 1973, Chloracne from the accidental production of tetrachlorodibenzodioxin. *British Journal of Industrial Medicine*, **30,** 276–283.

MAY, G., 1982, Tetrachlorodibenzodioxin, a survey of subjects ten years after exposure. *British Journal of Industrial Medicine*, **39,** 128–135.

MCMICHAEL, A. J., 1976, Standardized mortality ratios and the 'healthy worker effect', scratching beneath the surface. *Journal of Occupational Medicine*, **18,** 128–131.

MICHALEK, J. E., WOLFE, W. H., and MINER, J. C., 1990, Health status of Air Force veterans occupationally exposed to herbicides in Vietnam II. Mortality. *Journal of the American Medical Association*, **264,** 1832–1836.

MICHALEK, J. E., RAHE, A. J., and BOYLE, C. A., 1998, Paternal dioxin and the sex of children fathered by veterans of Operation Ranch Hand (letter to the editor). *Epidemiology*, **9,** 474–475.

MOCARELLI, P., MAROCCHI, A., BRAMBILLA, P., GERTHOUX, P. M., YOUNG, D. S., and MANTEL, N., 1986, Clinical laboratory manifestations of exposure to dioxin in children. A six year study of the effects of an environmental disaster near Seveso, Italy. *Journal of the American Medical Association*, **256,** 2687–2695.

MOCARELLI, P., NEEDHAM, L. L., MAROCCHI, A., PATTERSON, D. G., JR., BRAMBILLA, P., GERTHOUX, P. M., MEAZZA, L., and CARRERI, V., 1991, Serum concentrations of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and test results from selected residents of Seveso, Italy. *Journal of Toxicology and Environmental Health*, **32,** 357–366.

MOCARELLI, P., BRAMBILLA, P., GERTHOUX, P. M., PATTERON, D. G., and NEEDHAM, L. L., 1996, Change in sex ratio with exposure to dioxin. *Lancet* , 348–409.

MOSES, M., and PRIOLEAU, P. G., 1985, Cutaneous histologic findings in chemical workers with and without chloracne with past exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Journal of the American Academy of Dermatology*, **12,** 497–506.

MOSES, M., LILIS, R., CROW, K. D., THORNTON, J., FISCHBEIN, A., ANDERSON, H. A., and SELIKOFF, I. J., 1984, Health status of workers with past exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in the manufacture of 2,4,5-trichlorophenoxyacetic acid. Comparison of findings with and without chloracne. *American Journal of Industrial Medicine*, **5,** 161–182.

NEEDHAM, L. L., GERTHOUX, P. M., PATTERSON, D. G., JR., BRAMBILLA, P., TURNER, W. E., BERETTA, C., PIRKLE, J. L., COLOMBO, L., SAMPSON, E. J., TRAMACERE, P. L., SIGNORINI, S., MEAZZA, L., CARRERI, V., JACKSON, R. J., and MOCARELLI, P., 1997/1998, Serum dioxin levels in Seveso, Italy, population in 1976. *Teratogenesis, Carcinogenesis, and Mutagenesis* , **17,** 225–240.

OLIVER, R. M., 1975, Toxic effects of 2,3,7,8-tetrachlorodibenzo 1,4 dioxin in laboratory workers. *British Journal of Industrial Medicine*, **32,** 49–53.

OTT, M. G., OLSON, R. A., COOK, R. R., and BOND, G. G., 1987, Cohort mortality study of chemical workers with potential exposure to the higher chlorinated dioxins. *Journal of Occupational Medicine*, **29,** 422–429.

OTT, M. G., MESSERER, P., and ZOBER, A., 1993, Assessment of past occupational exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin using blood lipid analyses. *International Archives of Occupational and Environmental Health*, **65,** 1–8.

OTT, M. G., ZOBER, A., and GERMANN, C., 1994, Laboratory results for selected target organs in 138 individuals occupationally exposed to TCDD. *Chemosphere* , **29,** 2423–2437.

PAZDEROVA-VEJLUPKOVA, J., NEMCOVA, M., PICKOVA, J., JIRASEK, L., and LUKAS, E., 1981, The development and prognosis of chronic intoxication by tetrachlorodibenzo-*p*-dioxin in man. *Archives of Environmental Health*, **36,** 5–11.

PESATORI, A. C., ZOCCHETTI, C., GUERCILENA, S., CONSONNI, D., TURRINI, D., and BERTAZZRI, P. A., 1998, Dioxin exposure and nonmalignant health effects, a mortality study. *Occupational and Environmental Medicine*, **55,** 126–131.

PIACITELLI, L. A., SWEENEY, M. H., PATTERSON, D. G., TURNER, W. E., CONNALLY, L. B., WILLE, K. K., and TOMPKINS, B., 1992, Serum levels of 2,3,7,8-substituted PCDDs and PCDFs among workers exposed to 2,3,7,8-TCDD contaminated chemicals. *Chemosphere* , **25,** 251–254.

POCCHIARI, F., SILVANO, V., and ZAMPIERI, A., 1979, Human health effects from accidental release of tetrachlorodibenzo-*p*-dioxin (TCDD) at Seveso, Italy. *Annals of the New York Academy of Sciences*, **77,** 311–320.

POLAND, A. P., SMITH, D., METTER, G., and POSSICK, P., 1971, A health survey of workers in a 2,4-D and 2,4,5-T plant. *Archives of Environmental Health*, **22,** 316–327.

REGGIANI, G., 1980, Acute human exposure to TCDD in Seveso, Italy. *Journal of Toxicology and Environmental Health*, **6,** 27–43.

ROEGNER, R. H., GRUBBS, W. D., LUSTIK, M. B., BROCKMAN, A. S., HENDERSON, S. C., WILLIAMS, D. E., WOLFE, W. H., MICHALEK, J. E., and MINER, J. C., 1991, Air Force Health Study, an epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides. Serum dioxin analysis of 1987 examination results. National Technical Information Service # AD A-237-516 through AD A-237-524.

SIRICHIA, G., and THE GROUP FOR IMMUNOLOGICAL MONITORING, 1982, Exposure to TCDD, Immunologic effects. *Plans for Clinical and Epidemiological Follow-up after Area-wide Chemical Contamination, Proceedings of an international workshop,* edited by L. Dardanoni and R. W. Miller (Washington, DC: National Academy of Sciences), p. 234.

SUSKIND, R. R., and HERTZBERG, V. S., 1984, Human health effects of 2,4,5-T and its toxic contaminants. *Journal of the American Medical Association*, **251,** 2372–2380.

SUSKIND, R., CHOLAK, J., SCHATER, L. J., and YEAGER, D., 1953, Reports on clinical and environmental surveys at Monsanto Chemical Co., Nitro, West Virginia, 1953. Cincinnati, OH, Department of Environmental Health, University of Cincinnati (unpublished).

SWEENEY, M. H., FINGERHUT, M. A., AREZZO, J. C., HORNUNG, R. W., and CONNALLY, L. B., 1993, Peripheral neuropathy after occupational exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). *American Journal of Industrial Medicine*, **23,** 845–858.

TAYLOR, J. S., 1979, Environmental chloracne, update and overview. *Annals of the New York Academy of Sciences*, **320,** 295–407.

WEBB, K. B., EVANS, R. G., KNUDSEN, D. P., and ROODMAN, S., 1989, Medical evaluation of subjects with known body levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Journal of Toxicology and Environmental Health*, **28,** 183–193.

ZACK, J. A., and SUSKIND, R. R., 1980, The mortality experience of workers exposed to tetrachlorodibenzodioxin in a trichlorophenol process accident. *Journal of Occupational Medicine*, **22**, 11–14.

ZOBER, A., MESSERER, P., and HUBER, P., 1990, Thirty-four-year mortality follow-up of BASF employees exposed to 2,3,7,8-TCDD after the 1953 accident. *International Archives of Occupational and Environmental Health*, **62,** 139–157.