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Mortality risk among workers with exposure to dioxins

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Background	In several studies, dioxin exposure has been associated with increased risk from several causes of death.
Aims	To compare the mortality experience of workers exposed to dioxins during trichlorophenol (TCP) and pentachlorophenol (PCP) production to that of the general population and to examine mortality risk by estimated exposure levels.
Methods	A retrospective cohort study which followed up workers' vital status from 1940 to 2011, with serum surveys to support estimation of historical dioxin exposure levels.
Results	Among the 2192 study subjects, there were nine deaths in TCP workers from acute non-lymphatic leukaemia [standardized mortality ratio (SMR) = 2.88, 95% confidence interval (CI) 1.32–5.47], four mesothelioma deaths (SMR = 5.12, 95% CI 1.39–13.10) and four soft tissue sarcoma (STS) deaths (SMR = 3.08, 95% CI 0.84–7.87). In PCP workers, there were eight deaths from non-Hodgkin's lymphoma (SMR = 1.92, 95% CI 0.83–3.79), 150 from ischaemic heart disease (SMR = 1.20, 95% CI 1.01–7.89) and five from stomach ulcers (SMR = 3.38, 95% CI 1.10–7.89). There were no trends of increased mortality with increased dioxin exposure except for STS and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin levels. This finding for STS should be interpreted with caution due to the small number of deaths and the uncertainty in diagnosis and nosology.
Conclusions	While some causes of death were greater than expected, this study provides little evidence of increased risk when dioxin exposures are considered.
Key words	Bio-monitoring; cancer; dioxin; exposure estimation.

Introduction

There are seven polychlorinated dibenzo-*p*-dioxin constituents, including 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin (PeCDD), 1,2,3,4,7,8-hexachlorodibenzo-*p*-dioxin (1,4-HxCDD), 1,2,3,6,7,8-hexachlorodibenzo-*p*-dioxin (1,6-HxCDD), 1,2,3,7,8,9-hexachlorodibenzo-*p*-dioxin (1,9-HxCDD), 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin (HpCDD) and octachlorodibenzo-*p*-dioxin (OCDD) which can activate the aryl hydrocarbon receptor. These dioxins are considered toxic by the World Health Organization (WHO), which has assigned toxic equivalency factors (TEFs) that express the potency of each constituent relative to TCDD [1]. The toxicity of a mixture of dioxins and dioxin-like compounds can be expressed in a single number, the toxic equivalency (TEQ).

TCDD is classified by the International Agency for Research on Cancer (IARC) as a known human carcinogen based on animal and human studies and mechanistic information [2,3]. According to IARC, the epidemiological evidence was strongest for all cancers combined, with positive associations in some studies for lung cancer, non-Hodgkin's lymphoma and soft tissue sarcoma (STS). Some non-cancer effects such as type 2 diabetes and ischaemic heart disease have also been associated with TCDD exposures [4,5]. There is currently too little human and experimental data for IARC to classify the other dioxins as to their carcinogenicity [2].

Methods

This was a retrospective cohort study established in 1982 at a large chemical plant in Midland, MI. Commercial production of many chemicals occurred at this site,

including trichlorophenol (TCP) manufactured from 1942 to 1979, 2,4,5-T (subsequently referred to as TCP department) from 1948 to 1982 and pentachlorophenol (PCP) from the 1930s until 1980. Work history records, automated in 1982, were used to identify workers who had potential dioxin exposure in either the TCP or PCP departments at any time from 1 January 1937 to the end of 1982 when dioxin exposures from production ceased at this site. Periodic vital status follow-up of these workers has continued from 1979 to the present. Person-years at risk were accumulated from the date at which a TCP or PCP department assignment first appeared in the job history and continued to the date of death or to the end of follow-up, 31 December 2011. Death certificates were obtained from the states in which the employees died and coded to the International Classification of Disease (ICD) revision in effect at the time of death. This study was subject to oversight by an institutional review board. Informed consent was obtained from all study participants involved in the serum dioxin collection by a signed form approved by the institution review board.

Dioxin exposures at this site were relatively high: 12% of the TCP workers and 20% of the PCP workers developed chloracne, a hallmark of high dioxin exposure [6]. A total of 431 serum dioxin levels were collected in studies beginning in 2004 on a random sample of the TCP and PCP workers able to report for phlebotomy. Because of the different process chemistry, workers manufacturing TCP typically have higher serum dioxin levels of TCDD and PCP workers typically higher levels of 1,4-HxCDD, 1,6-HxCDD, 1,9-HxCDD, HpCDD and OCDD [7]. The mean TCDD concentrations found in these serum studies in TCP workers was 16 parts per trillion (ppt) and for workers in the PCP departments the means were 20 ppt for 1,4-HxCDD, 151 ppt for 1,6-HxCDD, 20 ppt for 1,9-HxCDD, 193 ppt for HpCDD and 2594 ppt for OCDD. These means were well above community levels and levels of non-exposed workers at the chemical plant [7]. We used the measured serum dioxin levels from the sample to produce a model estimating historical levels for each of the six dioxins in the TCP or PCP departments for all 2192 workers, as described in detail elsewhere [8,9].

Serum lipid concentration versus time profiles associated with occupational exposure for TCDD, summed HxCDD constituents, HpCDD and OCDD were previously estimated for each member of these cohorts [8,9]. We omitted the remaining dioxins, furans and PCBs in the TEQ calculation because these were only measured at background concentrations in the workers. We relied upon measured concentrations of the work-related chemicals to develop an exposure matrix by job for TCP and PCP departments. We integrated a simple pharmacokinetic model with the work history information detailing duration of exposed jobs for each worker. We estimated the average dioxin dose associated with jobs in each group after accounting for the presence of background exposures, as estimated from the residual serum dioxin concentrations in the sampled individuals. A pharmacokinetic model applied job-specific dose rates from the sampled workers to the work history of each member of the study group to estimate time-dependent serum concentration profiles for each dioxin congener.

For the current analyses and updates, the concentration versus time profile for each worker surviving at the end of the previous follow-up and for each chemical was extended from the end of the previous study period to the date of death or through the end of follow-up, 31 December 2011, whichever came first. The concentrations at the end of the previous follow-up were extended using the median concentration-based apparent half-lives of elimination observed in a subsample of this cohort with serial serum concentration measures available, as reported in Aylward *et al*. [10]. The half-lives used were 6.5, 10.1, 7.0 and 7.8 years for TCDD, summed HxCDD, HpCDD and OCDD, respectively. The highest TCDD historical exposure was estimated as 8848 ppt and the highest OCDD level was 365 299 ppt. Serum lipid TEQ was calculated at each time point as the sum of the TEF-adjusted concentrations of these congeners.

The modelled time-dependent 'area under the curve' for each dioxin or dioxin sum was calculated from the concentration versus time curves and used to represent the cumulative workplace dioxin exposures above background at any point in the worker's life after the time of first exposure. This cumulated area under the curve provides a biologically based metric of exposure because it takes into account both accumulation and elimination of dioxins in the body.

In external mortality comparisons, standardized mortality ratios (SMRs) for cause-specific mortality of the workers compared with the US population were calculated using OCMAP [11]. For causes of death where specific codes were not available for the entire follow-up period, we limited the calculation to the years when the ICD coded these deaths. Analyses were stratified: (i) by PCP and/or TCP department assignments; (ii) by three categories of cumulative dioxin exposure for TCDD, HxCDD, HpCDD, OCDD and the TEQ and (iii) by latency of ≥20 years. To examine internal trends, we employed a proportional hazards regression model with SAS PROC PHREG treating serum dioxin level as a continuous linear predictor [12]. We calculated hazard ratio per unit change in exposure and a 95% confidence limit for each model. The time variable for the proportional hazards model was age, and all models included hire year and year of birth. Exposure was treated as a time-dependent variable. The causes of death for exposure response analyses were selected based on findings from previous studies and results of the current study.

Results

There were 2192 workers who had potential dioxin exposure. Of these 1419 workers were exposed only in the TCP manufacturing process, 577 exposed only in the PCP manufacturing process and 196 who worked in both processes. Complete vital status follow-up was achieved, and death certificates of all but one of the 1198 decedents were obtained. The single exception was for a person known to have died overseas during military service. The mean age at start of follow-up was 29.8 years, and the mean duration of follow-up was 40.4 years. Of the 1198 total deaths [SMR = 0.95, 95% confidence interval (CI) 0.90–1.01], 326 were cancers (SMR = 0.98, 95% CI 0.88–1.10) (Table 1). SMRs for all causes of deaths, all cancers combined, and most specific causes of death were similar for TCP and PCP workers.

Among 1615 TCP workers, there were fewer deaths than expected from the cancers of a priori interest, including all cancers combined (SMR = 0.98, 95% CI 0.86–1.11) and lung cancers (SMR = 0.86, 95% CI 0.67–1.08). Deaths from non-Hodgkin's lymphoma only slightly exceeded the expected number (SMR 1.08, 95% CI 0.52–1.99). There were more deaths than expected for STS (SMR = 3.08, 95% CI 0.84–7.87). We also observed more non-lymphatic leukaemia (SMR = 2.88, 95% CI 1.32–5.47) and mesothelioma (SMR = 5.12, 95% CI 1.39–13.10) than expected.

Among 773 PCP workers, the observed numbers of deaths essentially matched expected numbers for all cancers combined (SMR = 1.04, 95% CI 0.86–1.24) and lung cancers (SMR = 1.02, 95% CI 0.73–1.40). SMRs were increased for non-Hodgkin's lymphoma (SMR = 1.92, 95% CI 0.83–3.79), STS (SMR = 1.73, 95% CI 0.04–9.62); ischemic heart disease (SMR = 1.20, 95% CI 1.01–1.41), ulcer of the stomach and duodenum (SMR = 3.38, 95% CI 1.10–7.89) and mesothelioma (SMR = 3.56, 95% CI 0.09–19.84). However, the increased SMRs for STS and mesothelioma were each based on just one observed death. Analysis of latency (data not shown) made little impact on the findings for any cause of death.

Table 2 describes the risk for diseases of *a priori* interest for dioxin exposure levels of each constituent and TEQ. The only cause of death that showed even the slightest increasing trend with cumulative exposure for both external and internal analyses was STS, with increasing trends for TCDD and the TEQ. The hazard ratio for TCDD was 1.06 (95% CI 1.02–1.09). Hazard ratios for all other causes of death were consistent with no increased risk related to increasing estimated exposure level. For non-Hodgkin's lymphoma, SMRs increased with increasing cumulative exposure categories of HpCDD and OCDD, but the trends were not statistically significant for the external and internal analyses. We also observed increasing SMRs with increasing cumulative exposure to OCDD for ulcers of the stomach and duodenum, but no trends were observed in the internal analysis.

Discussion

While some causes of death were greater than expected, there is little evidence that dioxin exposure levels were related to the increase in deaths. Among this investigation's several strengths it included the largest single-plant group of TCP and/or PCP workers of all dioxin studies. It followed this cohort for the longest period (up to 75 years) of any other dioxin study. No workers were lost to follow-up. Quantitative exposure measures were based on detailed work history information combined with the largest serum dioxin evaluation ever conducted on industrial workers. This study group is the first to use serum measurements to estimate levels for the dioxins found in PCP. Extensive industrial hygiene monitoring and cases of chloracne, a hallmark of high dioxin exposure, also served to validate the elevated serum dioxin levels. Furthermore, we used WHO's TEQ to summarize the estimated potency of the dioxin congeners to determine if a mixture of dioxins was associated with increased risk of death.

Limitations of this study include its relatively small size (<2200 workers), which undermines examination of rare causes of death. Also, even exposure estimates based on present day serum dioxin levels are likely to be subject to some misclassification when exposure extrapolation extends back several decades. On the other hand, exposure estimation from our modelling approach is expected to be more valid than the duration of exposure measures commonly used in many other dioxin studies.

Previous studies of workers with TCDD exposures have identified increased rates of all cancers combined, lung cancer, non-Hodgkin's lymphoma, STS and ischaemic heart disease [2,3]. We observed no association with any dioxin exposure and increasing overall rates or trends with levels for all cancers combined or cancers of the lung. The six previous studies that based their exposure assessment on serum dioxin evaluation were inconsistent regarding the specific cancers with increased risk. Three of these six studies report increased risk from all cancers combined related to TCDD levels. However, in these three studies, the other cancers associated with TCDD varied. Ott and Zober [13] noted digestive cancers, Steenland *et al.* [4] cited lung cancer and Flesch-Janys *et al.* [14] do not mention other TCDD–cancer associations. The studies of Ketchum and Michalek and Boers *et al.* found no increase overall in all cancers combined [15–17]. McBride *et al.* [17] did find slightly more cancers than expected, but the risk was not related to TCDD levels.

Although we observed more non-Hodgkin's lymphoma deaths than expected among PCP workers, there

Table 1. SMRs and 95% CIs for selected causes of death for workers with TCP and/or PCP exposure

Death category (ICD-10 code)[a]	All TCP/PCP workers		All TCP workers (includes 196 workers who also had PCP exposure)		All PCP workers (includes 196 workers who also had TCP exposure)	
	Deaths	SMR (95% CI)	Deaths	SMR (95% CI)	Deaths	SMR (95% CI)
All causes (A00–Y89)	1198	0.95 (0.90–1.01)	866	0.95 (0.88–1.01)	446	1.00 (0.91–1.10)
All cancers (C00–C97)	326	0.98 (0.88–1.10)	239	0.98 (0.86–1.11)	119	1.04 (0.86–1.24)
Oesophagus (C15)	13	1.32 (0.71–2.26)	8	1.09 (0.47–2.14)	5	1.52 (0.49–3.54)
Stomach (C16)	14	1.40 (0.77–2.35)	11	1.58 (0.79–2.83)	5	1.30 (0.42–3.04)
Large intestine (C18)	31	1.13 (0.77–1.61)	22	1.11 (0.69–1.67)	12	1.23 (0.64–2.15)
Rectum (C20–C21)	4	0.68 (0.18–1.73)	3	0.72 (0.15–2.11)	1	0.44 (0.01–2.48)
Biliary passages and liver (C22, C24)	4	0.46 (0.13–1.18)	4	0.62 (0.17–1.58)	0	0.00 (0.0–1.25)
Pancreas (C25)	10	0.58 (0.28–1.07)	7	0.55 (0.22–1.14)	6	1.00 (0.37–2.18)
Other digestive cancers (C17, C19, C23, C26, C48)	4	1.37 (0.37–3.51)	4	1.91 (0.52–4.89)	1	0.94 (0.02–5.25)
Respiratory system (C30–C39)	110	0.94 (0.77–1.13)	77	0.88 (0.69–1.10)	42	1.05 (0.76–1.42)
Bronchus, trachea, lung (C33–C34)	103	0.92 (0.75–1.11)	72	0.86 (0.67–1.08)	39	1.02 (0.73–1.40)
Prostate (C61)	31	1.07 (0.72–1.51)	21	1.01 (0.62–1.54)	11	1.05 (0.53–1.87)
Testes and other male genital	1	1.05 (0.03–5.85)	1	1.43 (0.04–7.96)	0	0.00 (0.0–10.99)
Kidney (C64–C65)	8	0.93 (0.40–1.84)	4	0.63 (0.17–1.61)	4	1.37 (0.37–3.51)
Bladder and other urinary (C66–C68)	12	1.21 (0.63–2.11)	9	1.26 (0.57–2.38)	4	1.13 (0.31–2.90)
Malignant melanoma (C43)	2	0.36 (0.04–1.30)	2	0.47 (0.06–1.71)	1	0.56 (0.01–3.09)
Central nervous system (C70–C72)	3	0.35 (0.07–1.03)	3	0.47 (0.10–1.38)	1	0.35 (0.01–1.93)
Hodgkin's disease	2	1.17 (0.14–4.22)	2	1.61 (0.20–5.85)	0	0.00 (0.0–5.87)
Non-Hodgkin's lymphoma (C82, C83.0–C83.8, C84, C85.1–C85.9)[b]	17	1.38 (0.80–2.20)	10	1.08 (0.52–1.99)	8	1.92 (0.83–3.79)
Leukaemia and leukaemia (C91–C95)	18	1.39 (0.82–2.19)	17	1.78 (1.04–2.85)	3	0.67 (0.14–1.96)
Total lymphoid leukaemia (C91–C95)[c]	5	1.48 (0.48–3.45)	5	1.99 (0.64–4.64)	1	0.87 (0.02–4.87)
Total myeloid leukaemia (C92)[c]	11	2.02 (1.01–3.61)	10	2.42 (1.16–4.46)	2	1.12 (0.14–4.03)
Acute non-lymphatic leukaemia (92.0, 93.0, 94.0)[c]	10	2.43 (1.16–4.47)	9	2.88 (1.32–5.47)	2	1.49 (0.18–5.38)
All other leukaemia (C93–C95)[c]	2	0.70 (0.09–2.54)	2	0.94 (0.11–3.39)	0	0.00 (0.0–3.89)
STS	4	2.31 (0.63–5.91)	4	3.08 (0.84–7.87)	1	1.73 (0.04–9.62)
Mesothelioma[d]	5	5.07 (1.65–11.84)	4	5.12 (1.39–13.10)	1	3.56 (0.09–19.84)
Diabetes mellitus (E10–E14)	27	0.97 (0.64–1.42)	19	0.92 (0.55–1.43)	9	0.97 (0.44–1.84)
All diseases of the nervous system (G00–G99)	21	0.74 (0.46–1.13)	17	0.79 (0.46–1.26)	7	0.79 (0.32–1.63)
Cerebrovascular disease (I60–I69)	68	1.03 (0.80–1.30)	49	1.07 (0.79–1.41)	27	1.07 (0.70–1.55)
Ischemic heart disease (I20–I25)	371	1.10 (0.99–1.22)	256	1.07 (0.95–1.21)	150	1.20 (1.01–1.41)
Non-malignant respiratory disease (J00–J99)	101	0.90 (0.73–1.09)	75	0.92 (0.72–1.15)	35	0.89 (0.62–1.23)
Ulcer of stomach and duodenum (K25–K27)	6	1.61 (0.59–3.50)	2	0.78 (0.10–2.82)	5	3.38 (1.10–7.89)
Cirrhosis of liver (K70–K74)	16	66.2 (0.38–1.08)	8	0.44 (0.19–87.2)	8	0.97 (0.42–1.91)
Accidents (V01–X59)	56	1.06 (0.80–1.37)	40	1.02 (0.73–1.38)	22	1.21 (0.76–1.82)
Missing certificates	1		1		0	
Persons	2192		1615		773	
Person-years	88 523		65 886		30 482	

[a]Deaths were coded to the ICD revision in force at time of death.
[b]These comparison rates were only available since 1960.
[c]Disease classifications not introduced until the 8th Revision of the ICD.
[d]Disease classifications not introduced until the 10th Revision of the ICD.

was no trend with exposure level for any dioxin. Findings for non-Hodgkin's lymphoma have been inconsistent in other studies of PCP workers.

STS refers to a somewhat arbitrary collection of tumours that are subject to misclassification when ascertained from death certificates. ICD coding rules use morphology, tumour behaviour and anatomic sites of the tumour origin such that a STS that originates in a visceral organ is coded to that organ and not to the STS category. Within the four STS deaths in our study, three were originally classified as malignant fibrous histiocytomas and one was an angiosarcoma of the scalp. These deaths occurred in 1975, 1983, 1997 and 1998. In a previous study, two of these deaths were subject to tissue review,

Table 2. SMR or hazard ratio with 95% CI for selected causes of death by dioxin congener related to TCP and/or PCP exposures or TEQ

Cause of death	Congener or TEQ[a]	External analysis by exposure categories				Internal analysis linear trend on continuous exposure[c]	
		Low SMR (95% CI)	Moderate SMR (95% CI)	High SMR (95% CI)	Trend *P* value	Coefficient estimate (SE)	Hazard ratio (95% CI)
All cancers	TCDD	0.88 (0.72–1.07)	1.06 (0.87–1.27)	1.02 (0.84–1.24)	0.500	−0.000131 (0.00500)	0.99987 (0.99012–1.00972)
	HxCDD[b]	0.91 (0.74–1.10)	1.04 (0.86–1.25)	1.01 (0.82–1.22)	0.673	0.00185 (0.00345)	1.00185 (0.99510–1.00865)
	HpCDD	0.95 (0.83–1.09)	1.05 (0.80–1.35)	1.03 (0.78–1.33)	0.665	0.000085 (0.000126)	1.00009 (0.99984–1.00033)
	OCDD	0.93 (0.77–1.13)	1.10 (0.92–1.31)	0.91 (0.73–1.11)	0.395	0.000032 (0.000051)	1.00003 (0.99993–1.00013)
	TEQ	1.01 (0.83–1.21)	0.90 (074–1.09)	1.05 (0.86–1.27)	0.513	0.00116 (0.00434)	1.00116 (0.99268–1.00971)
Lung cancer	TCDD	0.84 (0.59–1.17)	1.20 (0.88–1.62)	0.69 (0.45–1.03)	0.163	−0.000487 (0.00885)	0.99951 (0.98233–1.01700)
	HxCDD[b]	0.88 (0.62–1.22)	1.06 (0.76–1.44)	0.79 (0.51–1.15)	0.425	0.00333 (0.00597)	1.00334 (0.99166–1.01514)
	HpCDD	0.86 (0.66–1.10)	1.02 (0.62–1.58)	1.02 (0.62–1.60)	0.568	0.000069 (0.000242)	1.00007 (0.99959–1.00054)
	OCDD	0.82 (0.57–1.16)	1.02 (0.73–1.39)	0.90 (0.61–1.28)	0.944	0.000041 (0.000093)	1.00004 (0.99986–1.00022)
	TEQ	0.94 (0.66–1.30)	1.00 (0.71–1.37)	0.79 (0.52–1.14)	0.366	0.000833 (0.00776)	1.00083 (0.98573–1.01617)
Non-Hodgkin's lymphoma	TCDD	1.28 (0.47–2.78)	1.75 (0.70–3.60)	1.09 (0.30–2.80)	0.630	−0.00201 (0.02365)	0.99799 (0.95279–1.04534)
	HxCDD[b]	1.30 (0.48–2.83)	1.43 (0.53–3.11)	1.41 (0.46–3.28)	0.958	0.01333 (0.00846)	1.01342 (0.99675–1.03036)
	HpCDD	1.10 (0.50–2.08)	1.39 (0.29–4.07)	2.51 (0.82–5.86)	0.132	0.000325 (0.000384)	1.00032 (0.99957–1.00108)
	OCDD	1.11 (0.36–2.58)	1.42 (0.52–3.09)	1.66 (0.61–3.61)	0.534	0.000167 (0.000145)	1.00017 (0.99988–1.00045)
	TEQ	1.35 (0.49–2.93)	1.17 (0.38–2.74)	1.65 (0.61–3.59)	0.596	0.00758 (0.01668)	1.00761 (0.97520–1.04109)
Acute non-lymphatic leukaemia	TCDD	1.91 (0.39–5.59)	2.27 (0.47–6.62)	3.27 (0.89–8.36)	0.441	−0.07990 (0.12635)	0.92321 (0.72069–1.18263)
	HxCDD[b]	3.86 (1.42–8.41)	1.43 (0.17–5.16)	1.72 (0.21–6.20)	0.451	−0.06480 (0.10439)	0.93725 (0.76384–1.15004)
	HpCDD	2.88 (1.24–5.68)	0.00 (0.00–5.16)	3.19 (0.39–11.52)	0.696	−0.000198 (0.00129)	0.99980 (0.99728–1.00233)
	OCDD	3.91 (1.44–8.51)	1.41 (0.17–5.10)	1.71 (0.21–6.19)	0.474	−0.000292 (0.000825)	0.99971 (0.99809–1.00132)
	TEQ	2.66 (0.72–6.81)	2.12 (0.44–6.21)	2.50 (0.52–7.29)	0.994	−0.05799 (0.08085)	0.94366 (0.80537–1.10569)
STS	TCDD	1.45 (0.04–8.09)	1.78 (0.04–9.91)	4.15 (0.50–14.99)	0.320	0.05494 (0.01827)	1.05648 (1.01932–1.09499)
	HxCDD[b]	2.92 (0.35–10.54)	0.00 (0.00–6.30)	4.34 (0.53–15.66)	0.395	−0.02577 (0.07650)	0.97456 (0.83886–1.13221)
	HpCDD	2.59 (0.54–7.58)	0.00 (0.00–11.97)	3.73 (0.09–20.76)	0.691	−0.00548 (0.01209)	0.99453 (0.97125–1.01838)
	OCDD	3.01 (0.36–10.86)	1.70 (0.04–9.49	2.08 (0.05–11.59)	0.882	−0.00112 (0.00266)	0.99888 (0.99369–1.00410)
	TEQ	1.51 (0.04–8.42)	1.69 (0.04–9.44)	4.16 (0.50–15.02)	0.320	0.05251 (0.01928)	1.05391 (1.01483–1.09450)
Mesothelioma	TCDD	7.70 (1.59–22.52)	0.00 (0.00–11.35)	7.37 (0.89–26.62)	0.766	−0.09529 (0.18845)	0.90911 (0.62836–1.31530)
	HxCDD[b]	7.80 (1.61–22.80)	0.00 (0.00–10.41)	8.10 (0.98–29.28)	0.375	−0.14971 (0.22218)	0.86096 (0.55701–1.33077)
	HpCDD	5.68 (1.55–14.53)	0.00 (0.00–22.47)	8.57 (0.21–47.73)	0.508	−0.00303 (0.00930)	0.99697 (0.97897–1.01531)
	OCDD	7.63 (1.57–22.30)	2.82 (0.07–15.72)	4.20 (0.11–23.41)	0.949	−0.00182 (0.00464)	0.99818 (0.98915–1.00730)
	TEQ	5.27 (0.64–19.04)	2.87 (0.07–15.97)	7.77 (0.94–28.07)	0.661	−0.10592 (0.17376)	0.89950 (0.63987–1.26446)
Ischaemic heart disease	TCDD	1.12 (0.93–1.33)	0.99 (0.81–1.19)	1.20 (1.01–1.42)	0.273	0.000909 (0.00473)	1.00091 (0.99167–1.01023)
	HxCDD[b]	1.05 (0.86–1.26)	1.18 (0.99–1.40)	1.08 (0.90–1.28)	0.839	−0.000053 (0.00312)	0.99995 (0.99385–1.00608)
	HpCDD	1.04 (0.91–1.19)	1.33 (1.05–1.66)	1.10 (0.86–1.38)	0.960	−0.000105 (0.000134)	0.99990 (0.99963–1.00016)
	OCDD	1.00 (0.82–1.21)	1.22 (1.03–1.44)	1.07 (0.89–1.28)	0.784	−0.000027 (0.000051)	0.99997 (0.99987–1.00007)
	TEQ	1.09 (0.90–1.31)	1.05 (0.87–1.25)	1.17 (0.98–1.38)	0.462	−0.000571 (0.00424)	0.99943 (0.99116–1.00777)
Ulcer of stomach and duodenum	TCDD	3.11 (0.85–7.97)	0.82 (0.02–4.59)	0.81 (0.02–4.52)	0.317	−0.08637 (0.16934)	0.91725 (0.65818–1.27830)
	HxCDD[b]	0.00 (0.00–3.05)	3.27 (0.89–8.36)	1.54 (0.19–5.56)	0.895[d]	−0.04050 (0.06358)	0.96031 (0.84780–1.08775)
	HpCDD	0.44 (0.01–2.46)	4.66 (0.96–13.62)	2.42 (0.29–8.75)	0.408[d]	−0.00371 (0.00476)	0.99630 (0.98705–1.00564)
	OCDD	0.00 (0.00–3.24)	1.56 (0.19–5.66)	3.04 (0.83–7.79)	0.097	−0.000945 (0.00135)	0.99906 (0.99642–1.00170)
	TEQ	0.86 (0.02–4.80)	2.33 (0.48–6.80)	1.56 (0.19–5.63)	0.934	−0.12150 (0.14269)	0.88559 (0.66954–1.17136)

[a]Exposure categories (low, moderate, high; ppt-months): TCDD 0–249.9, 250–1499.9, 1500–112 272; HxCDD 0–349.9, 350–2499.9, 2500–182 922; HpCDD 0–0, 0.01–39 999.9, 40 000–4 986 908; OCDD 0–3999.9, 4000–49 999.9, 50 000–11 415 063; TEQ 0–449.9, 450–2499.9, 2500–113 415.

[b]Sum of 1,4-HxCDD, 1,6-HxCDD and 1,9-HxCDD.

[c]All proportional hazards models represent a 1-ppt-year increase and include the dioxin congener along with year of birth and year of hire as predictive variables with the dioxin.

[d]Significant lack of linear fit for HxCDD and HpCDD ($P < 0.05$). For HpCDD, significant heterogeneity ($P < 0.05$). No other causes or congeners showed significant lack of fit or significant heterogeneity.

and one was found not to be STS [18]. The misclassified death occurred in the highest TCDD category. While it is unlikely that misclassification of this disease occurs differentially in the referent and the exposed populations, reclassification of one or two deaths could dramatically impact exposure response trends for uncommon causes of death. To avoid bias, our analysis did not consider this misclassification. Among the four workers who died of STS, all four were TCP workers and one was also a PCP worker. The small number of STS deaths in our study, the potential for misdiagnosis, the uncertainty of coding, the diversity of histological types, the known misclassification and the lack of similar findings in other studies of dioxin-exposed workers cast doubt on the role of dioxin exposure as a causal aetiology for this tumour category.

Deaths from ischaemic heart disease, mesothelioma and acute non-lymphatic leukaemia also exceeded expected numbers, but the risk was not associated with

level of dioxin exposure. In the case of mesothelioma, other exposures at the plants may be to blame. TCP and PCP production occurred in autoclaves that might have been insulated with asbestos [19]. In addition, workers might have held jobs with asbestos exposure earlier or later in their careers. Although the risk of acute non-lymphatic leukaemia is increased with exposure to high levels of benzene, a recent study of benzene-exposed workers at this plant found no increased risk of this leukaemia [20]. This cancer was not elevated in other studies.

IARC has suggested that dioxin has a 'pluripotential' mode of action increasing all cancers combined in the absence of consistent findings for any specific cancer site [2]. A posited causal relationship for all cancers combined in the absence of a consistent finding for any specific cancer site is unique in occupational epidemiology studies. Some have argued that dioxin may be a late-stage carcinogen producing excess cancers at many organ sites. While this hypothesis may explain the increased risk with all cancers combined, it does not explain the lack of consistency of specific cancer site findings across studies. All late-stage carcinogens cause one or more specific cancers [21]. Cancer bioassays of laboratory rodents demonstrate dioxin's clear target organ specificity, with liver, lung and oral mucosa cancers being elevated following high levels of TCDD exposure [22,23]. Another explanation is that a variety of non-dioxin exposures are increasing risk from diverse and inconsistent cancer sites across studies. This hypothesis has only been rarely studied in industrial workers exposed to dioxins. The excess of mesothelioma in this cohort of dioxin-exposed workers might indicate that other workplace exposures contribute to the all cancer excess seen in some studies. There appears to be little consistency in disease outcomes across the dioxin studies of TCP or PCP workers.

Key points

- Our study included the largest single-plant group of trichlorophenol and/or pentachlorophenol workers of all dioxin studies and followed the cohort for a longer period (up to 75 years) than any other study of dioxins.
- These workers had dioxin levels well above past background levels.
- This study provides little evidence of increased risk of death from exposure to any of the dioxins present in trichlorophenol and pentachlorophenol.

Conflicts of interest

All authors, except J.J.C. and L.L.A., were employees of The Dow Chemical Company at the time of the study, whose company provided full funding. K.M.B. is now retired from Dow but occasionally performs contract work for Dow. The other Dow authors receive a salary and may receive shares of stock each year. J.J.C. retired from Dow in 2014. J.J.C. and L.L.A. did the work on the study by an unrestricted grant.

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Shaking All Over

As a medical student I remember very clearly a visiting American research doctor who on his first day introduced himself to me by firmly shaking my hand and telling me his name. Strange to think this now but then it was unusual, particularly from more senior doctors, and it left a lasting impression. Over the years my handshaking practice has developed to the point where I always shake hands with my patients, both at the beginning of the consultation and usually at the end. The patient who won't or 'can't' shake hands provides useful clinical information but that is another story.

What does a handshake mean? They are a form of greeting, or parting or seal an agreement. Many years ago in a *BMJ* personal view, Edwards spoke about contact with patients. He felt that consultations which ended in a handshake indicated that the patient was saying 'Thank you'.

When I had the privilege of working in France, I soon realized it was the land of the handshake. At work, it was obligatory to shake everybody you met by the hand. Working in an open plan office with 46 other people meant that turning up for work could be a major ordeal. Forty-seven people each shaking hands with each other means over 1000 handshakes first thing in the morning or about one person hour. More strange was the fact that it was definitely taboo to shake the same person's hand twice in one day. The French have an impressive ability to remember names and exactly which hands they had already shaken. More than once, miserable English man that I am, I offered a hand to be turned down with the words 'Non, deja vu'.

With time I adopted strategies to cope with all this repetitive upper limb activity. It became extremely time-efficient to arrive in the office as early as possible so that rather than making the rounds of your colleagues, they visited me at my desk.

In the factory the handshaking continued. Workers would spot you from the other side of the building and cross the shop floor simply to say 'Bonjour, ca va?' and shake you by the hand. There were also interesting variants of the practice: the *Mechanics* or *Dirty-hand-handshake* consists of shaking the proffered wrist rather than the hand; the *Right-hand-occupied-handshake*, e.g. on the telephone, involves shaking the upside down left hand; and the *Postprandial handshake*, which never occurs before lunchtime so they are more certain that you have washed your hands.

Does such frequent epidermal contact spread microbes? After all the French are great kissers as well. Perhaps the exchange of skin flora on a friendly basis helps build immunity? Some of my more squeamish expatriate colleagues believed that the shaking of hands was responsible for the increase in upper respiratory tract infection they experienced when working abroad. However, whatever the loss of productivity and resultant upper limb disorder and minor infection, I have to say I found all that civility rather nice.

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