META-ANALYSIS OF RISK ESTIMATES FOR LYMPHATIC AND HEMATOPOIETIC ORGAN CANCERS INVOLVING DIOXINS

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Introduction

PCDDs (polychlorinated dibenzo-p-dioxins) and PCDFs (polychlorinated dibenzofurans) are POPs (persistent organic pollutants) which are by-products of combustion and industrial processes, whereas PCBs (polychlorinated biphenyls) are industrial chemicals that have been used as plasticizers, organic diluents and dielectric fluids (1, 2). Several studies reported that these chemicals can cause serious health effects such as cancer, immune disorder and cardiovascular disease (3-5). In 1997, the International Agency for Research on Cancer (IARC) classified that 2,3,7,8-TCDD (2,3,7,8-tetrachlorodibenzo-para-dioxinormaldehyde) is carcinogenic for humans based on limited human epidemiologic data, sufficient animal data and biological mechanic information. Several studies have supported the effect of dioxins in carcinogenesis. In animal study, it was reported that 2,3,7,8-TCDD induced tumors in several organs such as liver, breast, prostate and pancreas (6). Kogevinas published that cancer mortality increased in workers exposed to 2,3,7,8-TCDD or more highly chlorinated dioxins (7). It was also reported that in race- and sex-specific analysis, white males had increased non-Hodgkin lymphoma mortality and males of other races had increased leukemia mortality (8). However, dioxins are incapable of increase all kinds of cancer incidence and mortality. Also, there are contributed epidemiologic evidences in different cancers. The purpose of this study is to examine mortality of lymphatic and hematopoietic cancers associated with population exposed to dioxins through meta-analysis.

Materials and methods

Based on PubMed MEDLINE database searches from inception until March 2012, we obtained epidemiologic papers related to cancer mortality due to dioxin exposure and used the key word "dioxin AND (cancer OR tumor) AND (cohort OR case-control OR RCT OR epidemiology)". We included epidemiologic studies in the order of the criteria: in English; original epidemiologic data on mortality; the associations between dioxin exposure and lymphatic and hematopoietic cancer including hodgkin's disease, non-hodgkin's lymphoma, multiple myeloma and leukemia; measures with SMR (standardized mortality ratio) and 95% CIs (confidence interval), or values in cells of a 2 X 2 table. We converted SMR to RR (relative risk) and carried out random effects meta-analyses using RevMan 5.1.

Results and discussion

In total, 9 studies remained for final analysis, based on information from 366 studies (Fig. 1). A total of 41782 participants exposed to high level dioxins according to work in plants that produced chemicals contaminated with dioxins and livelihood in contaminated zones were included. Table 1 presents the distribution of their major characteristics. These provide results for lymphatic and hematopoietic cancers which consist of hodgkin's disease, non-hodgkin's lymphoma, multi myeloma and leukemia. We estimated the methodologic quality of studies included in the final analysis based on the Newcastle-Ottawa scale assessing the quality of cohort studies (Table 2). The average quality score was 7.2. The high-quality studies (score of $\geq$ 7) included eight, whereas the low-quality study (score of < 7) was only one. It didn't impact this study.

As shown in figure 2, the overall exposure to dioxins was statistically significantly associated with the mortality of lymphatic and hematopoietic cancers in a random-effects model meta-analysis (RR=1.28; 95% CI, 1.06 to 1.54). However, Kogevinas 1997 was too high because of 41% weight of analysis. We tried to re-analyse all studies except Kogevinas 1997 and obtained similar result (RR=1.39; 95% CI, 1.09 to 1.78). After classifying lymphatic and hematopoietic cancers in four subgroup cancers such as hodgkin's disease, non-hodgkin's lymphoma, multi myeloma and leukemia, table 3 shows that there is significant association between participants exposed to dioxins and mortality of non-hodgkin's lymphoma (RR=1.43; 95% CI, 1.03 to 1.98).

The findings from this metal-analysis indicate that high level exposure of dioxins is associated with mortality of lymphatic and hematopoietic cancers. In subgroup cancer, a significant positive association was observed for non-hodgkin's lymphoma.

Fig 1. Flow diagram for study identification process

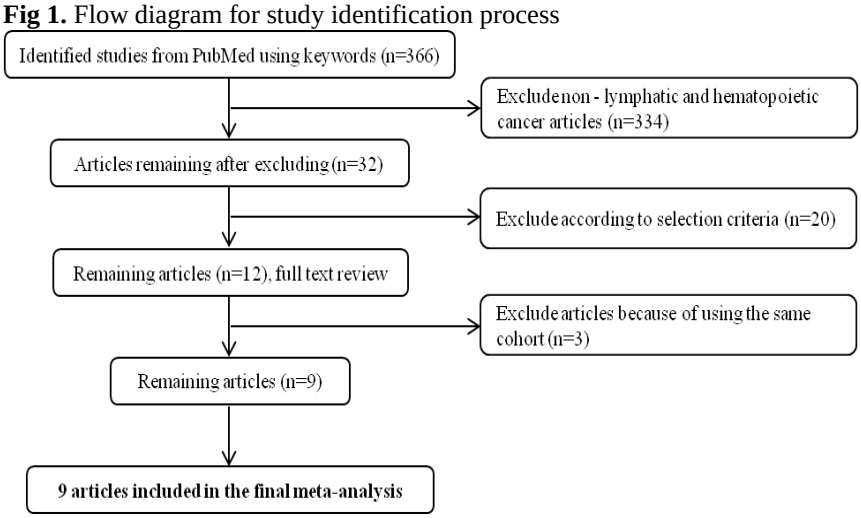


Table 1. Characteristics of each study (n=9)

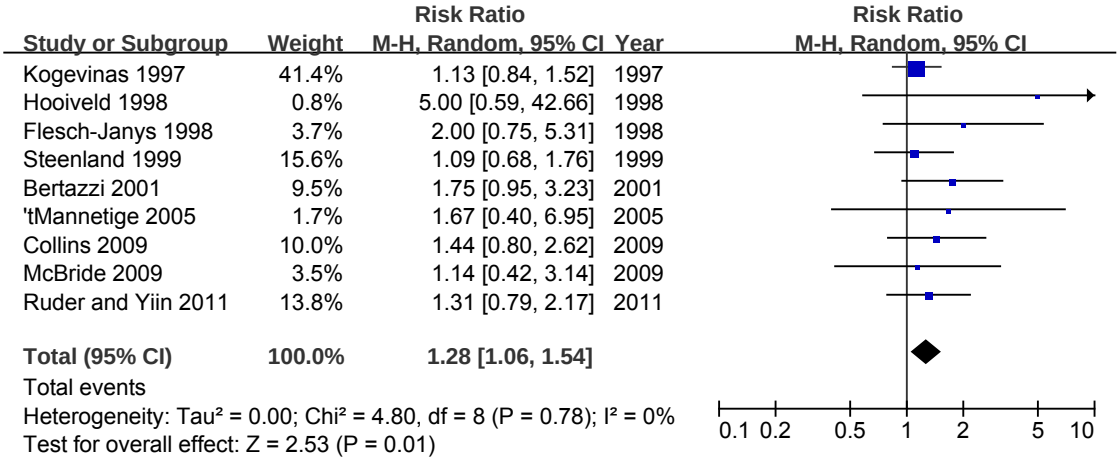
Study	Country/ Cohort	No. of subjects	Study period (follow-up)	Occupational setting	Exposure assessment	Major chemicals
Kogevinas (1997)	IARC cohorts (12 countries)	21863	1939-92 (1992)	Phenoxy herbicide manufactures	Job records, company exposure questionnaires, and serum and adipose tissue dioxin levels	Phenoxy herbicides, chlorophenos, and dioxins
Flesch-Janys (1998)	Germany	1189	1952-92 (1992)	Boehringer lngleheim phenoxy herbicide plant	Blood levels of 275 workers and working histories	Phenoy herbicides, and dioxins
Hooiveld (1998)	Netherlands	1167	1955-85 (1991)	Phenoxy herbicide manufactures	Serum TCDD levels of 50 and extensive company questionnaire	Phenoxy herbicides, clorophenols, TCDD, and PCDD
Steenland (1999)	USA	5132	1942-84 (1993)	12 plants that produced chemicals contaminated with TCDD	Job-exposure matrix of the basis on quantitative exposure score; 1)the concentration of TCDD(ug/g) present in process materials, 2)the fraction of the day the worker worked on the specific process, 3)a qualitative contact level (0.01-1.5)	TCDD
Bertazzi (2001)	Italy	278114	1976-96 (1996)	Residents of three dioxin-contaminated zones with decreasing mean soil levels (A, B, and R) and the surrounding non-contaminated zone	TCDD concentrations in soil; zone A (15.5-580.4 ug/m^2), zone B (1.7-4.3 ug/m^2), and zone R (0.9-1.4 ug/m^2)	TCDD
'tMannetije (2005)	New Zealand	1512	1969-2000 (2000)	Pheoxy herbicide producers and sprayers exposed to dioxins	Individual employment records included department and dates of employment	Phenoxy herbicide, and TCDD
Collins	USA	1615	1942-	Worker exposed to	Serum TCDD levels and	Trichlorophenol, and

(2009)			2003 (2003)	dioxins in trichlorophenol production	worker's job history	TCDD
McBride (2009)	New Zealand	1754	1969-2003 (2004)	Agrochemical manufacturing site	Work history records	Trichlorophenol, trichlorophenoxyacetic acid, and TCDD
Ruder and Yiin (2011)	USA	2122	1936-2006 (2005)	Pentachlorophenol production workers	Dioxin registry masterfile and work histories	Pentachlorophenol, trichlorophenol, and TCDD

Table 2. Methodological quality of studies based on the Newcastle-Ottawa scale for assessing the quality of cohort studies

Study	Selection				Comparability	Outcome			Total (0-9)
	Represen-tativeness of the exposed cohort	Selection of the nonexpo-sed cohort	Ascertai-nment of exposure	Outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assess-ment of outcome	Follow-up long enough form outcome to occur	Adequacy of follow-up of cohorts	
Kogevinas (1997)	1	1	0	0	2	1	1	1	7
Flesch-Janys (1998)	1	1	1	0	2	1	1	0	7
Hooiveld (1998)	1	1	1	0	2	1	1	0	7
Steenland (1999)	1	1	1	0	2	1	1	1	8
Bertazzi (2001)	1	1	1	0	2	1	1	1	8
'tMannetije (2005)	1	1	0	0	2	1	1	1	7
Collins (2009)	1	1	1	0	2	1	1	1	8
McBride (2009)	1	1	0	0	2	1	1	0	6
Ruder and Yiin (2011)	1	1	0	0	2	1	1	1	7

Fig 2. Overall exposure of dioxins and mortality of lymphatic and hematopoietic cancers in random effects model



Abbreviations: M-H: Mantel-Haenszel estimation method; CI: confidence interval

Table 3. Results for mortality of lymphatic and hematopoietic cancers

Mortality outcome	Summary RR	95% CI of RR	Heterogeneity, p value
Lymphatic and hematopoietic	1.28	1.06 to 1.58	0.78
Hodgkin's disease	1.14	0.64 to 2.05	0.91
Non-Hodgkin's lymphoma	1.43	1.03 to 1.98	0.86
Multiple myeloma	1.52	0.97 to 2.38	0.96
Leukemia	1.10	0.81 to 1.51	0.90

Abbreviations: RR: relative risk; CI: confidence interval

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References:

1. Safe SH. (1986) *Annu Rev Pharmacol Toxicol*. 26: 371-99
2. Cleverly D, Ferrario J, Byrne C, Riggs K, Joseph D, Hartford P. (2007) *Environ Sci Technol*. 41(5): 1537-44
3. International Agency for Research on Cancer. (1997) *IARC Monogr Eval Carcinog Risks Hum*. 69: 1-631
4. Kogevinas M. (2001) *Hum Reprod Update*. 7(3): 331-9
5. Humblet O, Birnbaum L, Rimm E, Mittleman MA, Hauser R. (2008) *Environ Health Perspect*. 116(11): 1443-8
6. National Toxicology Program. (2006) *Nati Toxicol Program Tech Rep Ser*. (526): 1-180
7. Kogevinas M, Becher H, Benn T, Bertazzi PA, Boffetta P, Bueno-de-Mesquita HB, Coggon D, Colin D, Flesch-Janys D, Fingerhut M, Green L, Kauppinen T, Littorin M, Lynge E, Mathews JD, Neuberger M, Pearce N, Saracci R. (1997) *Am J Epidemiol*. 145(12): 1061-75
8. Ruder AM, Yiin JH. (2011) *Chemosphere*. 83(6): 851-61
9. Flesch-Janys D, Steindorf K, Gurn P, Becher H. (1998) *Environ Health Perspect*. 106 Suppl 2: 655-62
10. Hooiveld M, Heederik DJ, Kogevinas M, Boffetta P, Needham LL, Patterson DG Jr, Bueno-de-Mesquita HB. (1998) *Am J Epidemiol*. 147(9): 891-901
11. Steenland K, Piacitelli L, Deddens J, Fingerhut M, Chang LI. (1999) *J Nati Cancer Inst*. 91(9): 779-86
12. Bertazzi PA, Consonni D, Bachetti S, Rubagotti M, Baccarelli A, Zocchetti C, Pesatori AC. (2001) *Am J Epidemiol*. 153(11): 1031-44
13. 't Mannetje A, McLean D, Cheng S, Boffetta P, Colin D, Pearce N. (2005) *Occup Environ Med*. 62(1): 34-40
14. Collins JJ, Bodner K, Aylward LL, Wilken M, Bodnar CM. (2009) *Am J Epidemiol*. 170(4): 501-6
15. McBride DI, Burns CJ, Herbison GP, Humphry NF, Bodner K, Collins JJ. (2009) *Occup Med (Lond)*. 59(4): 255-63