THIRD FOLLOW-UP OF A DUTCH COHORT STUDY ON THE EFFECTS OF OCCUPATIONAL EXPOSURE TO CHLOROPHENOXY HERBICIDES, CHLOROPHENOLS AND CONTAMINANTS

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Introduction

Chlorophenoxy herbicides have been used worldwide since the 1940s as defoliants, wood preservatives and for weed control. Mixtures of 2,4,5-T and 2,4-D were also used during the Vietnam War as Agent Orange or Agent Purple for defoliation and crop destruction. Chlorophenoxy herbicides may be contaminated with polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) during production (1, 2).
In the early eighties, a retrospective cohort study was conducted in two factories (referred to as factory A and B) producing several chlorophenoxy herbicides, chlorophenols and other pesticides (3, 4).
The first follow-up, which included both factories, lasted from 1955-1985 for factory A and from 1965-1986 for factory B. This follow-up showed an increased risk of mortality from all cancers (RR=1.7) and respiratory cancer, though none of the results were significant (3).
The second follow-up was conducted in 1991 and added an additional 6 years of follow-up. The second follow-up was conducted only for factory A. Increased risks were reported for mortality from all cancers (RR=4.1, significant), respiratory cancer (RR=7.5, significant), non-Hodgkin's lymphoma (RR=1.7) and ischemic heart disease (RR=1.8) (4).
The purpose of the current third follow-up is, to study in both factories cause-specific mortality among workers occupationally exposed to chlorophenoxy herbicides, chlorophenols, and contaminants.

Materials and Methods

The study population was defined as all persons working during 1955-1985 at factory A, or during 1965-1986 at factory B. In factory A the main product was 2,4,5-T, although other pesticides were also synthesized and formulated. During production of 2,4,5-T, contamination with TCDD is possible. In march 1963, an uncontrolled reaction occurred in the autoclave where at that time 2,4,5-TCP was synthesized. In the explosion that followed, the compounds including TCDD were released in the factory hall.
In factory B the main products were 2,4-D, MCPP and MCPA. 2,4-D may be contaminated with dioxins, but not with TCDD.
The third follow-up has been extended to include an additional 15-16 years of follow-up until December 2006. Information on vital status was obtained from municipal records. Cause-specific mortality was updated through linkage to death certificates at the Central Bureau of Statistics in the Netherlands.
Individual exposure status was based on detailed occupational history, including periods of employment in different departments and positions held. In addition, exposure during the clean-up after the accident in factory A was taken into account. 538 workers were classified as exposed to chlorophenoxy herbicides and 477 workers as non-exposed for factory A. For factory B a total of 407 workers were classified as exposed to chlorophenoxy herbicides and 624 workers as non-exposed.
Due to small number of females in the cohort, they have been excluded from analysis, as well as all deaths occurring within 1 year since first employment.

Cox proportional hazard models were used, including attained age as the time-scale. Since exposed workers started to work earlier than non-exposed in factory A, analysis have been corrected for year of first employment (first employment before or after 1965), to account for potential confounding.

Results

At the end of follow-up in 2006, 1413 workers were alive, 56 workers were lost-to-follow-up and 35 workers had emigrated. A total of 542 workers had died 340 workers from factory A and 202 workers from factory B (see table 1).
The final analysis included 2046 workers contributing a total of 64,824 person years. Population characteristics are shown in table 1. In factory A, exposed workers were on average older, were employed earlier and worked longer than non-exposed workers. Although exposed workers in factory B were employed considerably longer than non-exposed workers, there were no differences in year of first employment or age at first employment between exposed and non-exposed workers.

Table 1: Population characteristics for exposed and non-exposed male workers from factory A and factory B, the Netherlands 1955-2006

	Factory A				**Factory B**			
	Exposed		**Non-exposed**		**Exposed**		**Non-exposed**	
	No	%	No	%	No	%	No	%
No of workers	538	53.0	477	47.0	407	39.5	624	60.5
Person years at risk	18,778		14,627		12,880		18,539	
Mean age at entry (sd)*	32.5		29.6		31.7		30.2	
	(0.41)		(0.39)		(0.48)		(0.35)	
Vital status								
Alive	277	51.5	351	73.6	306	75.2	479	76.8
Deceased	234	43.5	106	22.2	90	22.1	112	18.0
Lost to follow up	21	3.9	13	2.7	5	1.2	17	2.7
Emigrated	6	1.1	7	1.5	6	1.5	16	2.6
Age at first employment (years)								
< 25	154	28.6	170	35.6	141	34.6	182	29.2
25-34	204	37.9	202	42.4	143	35.1	263	42.1
35-44	128	23.8	71	14.9	81	19.9	131	21.0
> 45	52	9.6	34	7.1	42	10.3	48	7.7
Year of first employment								
Before 1955	55	10.2	20	4.2	-	-	1	0.2
1955-1964	302	56.1	99	20.8	67	16.5	46	7.4
1965-1974	145	27.0	171	35.9	205	50.4	309	49.5
1975 and later	36	6.7	187	39.2	135	33.2	268	43.0
Duration of employment (years)								
0 – 5	302	56.1	305	63.9	102	25.1	294	47.1
5 +	236	43.9	172	36.1	305	74.9	330	52.9

* Standard error

Hazard ratios by cause of death for workers exposed to chlorophenoxy herbicides are presented in table 2. For analysis an internal control group has been used. Slightly increased hazard ratios were found for all cancers in both factories that were borderline significant for factory B. Previously reported increased risks for respiratory cancers, non-Hodgkin's lymphoma and ischemic heart disease in factory A, could not be confirmed in the present analysis.

Table 2: Hazard ratios by cause of death for male workers exposed to chlorophenoxy herbicides compared to non-exposed male workers, the Netherlands 1955-2006

	Factory A			Factory B		
Causes of death (ICD 10th revision)	**Exp / non-exp**	**HR[1 #]**	**95% CI[2]**	**Exp / non-exp**	**HR[1]**	**95% CI[2]**
All causes (A00-Y89)	234/106	1.16	0.91-1.47	90/112	1.02	0.77-1.34
All cancers (C00-D48)	81/31	1.31	0.86-2.01	44/36	1.54	1.00-2.37
Respiratory cancers (C33-C39)	21/8	1.11	0.49-2.52	12/12	1.22	0.56-2.66
Trachea, bronchus and lung (C33-C34)	20/7	1.15	0.48-2.77	12/12	1.22	0.56-2.66
Lymphatic cancers (C81-C96)	11/7	0.89	0.31-2.61	3/3	1.52	0.31-7.45
Non–Hodgkin's lymphoma (C82-C83, C85)	4/3	0.92	0.19-4.47	1/0	Inf[3]	
Leukaemia (C91-C95)	2/3	0.28	0.03-2.61	2/2	1.53	0.22-10.82
Diseases of circulatory system (I00-I99)	77/37	1.07	0.70-1.62	31/37	1.06	0.66-1.70
Ischemic heart diseases (I20-I25)	43/18	1.15	0.66-1.98	18/15	1.56	0.79-3.11

[1] *Hazard ratio (HR) adjusted for age*
[#] *Hazard ratios for factory A are adjusted for year of first employment*
[2] *95 % confidence interval*
[3] *Results hazard ratio are infinitively large*

Discussion

The third-follow of the Dutch cohort on the effects of occupational exposure to chlorophenoxy, chlorophenols and contaminants added 201 cases (for factory A) to the study thereby significantly increasing the power of the previous follow-up. Interestingly, previously reported increased risks for respiratory cancer, non-Hodgkin's lymphoma and ischemic heart disease could not be confirmed in the present analysis. This is likely due to the small number of cases in the second follow-up, leading to imprecise risk estimates. Future analyses should focus on the incorporation of quantitative measures of dioxins in this population.

References

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