Preliminary results of the second follow-up of a Dutch cohort of workers occupationally exposed to phenoxy herbicides, chlorophenols and contaminants

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Introduction

We conducted a retrospective cohort study in two chemical factories involved in synthesis and formulation of phenoxy herbicides [1], which forms the Dutch contribution to the IARC international study of workers exposed to phenoxy herbicides, chlorophenols and contaminants [2]. The purpose of the current analysis was to provide an updated assessment of mortality, especially from cancer, for the period 1955-1991. In addition, more elaborate proxies of exposure were used in the statistical analysis than before. These exposure proxies were based on modelled 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) levels in serum, available for a subset of the cohort.

Materials and methods

Population

The study-cohort incorporates information from two companies, designated by the letters A and B, involved in the synthesis and formulation of chlorophenoxy herbicides. The study population was defined as all persons working in the factories during the period 1955-1985 (factory A) or 1965-1986 (factory B). A total of 2,310 workers was enrolled in the cohort. Twelve subjects were excluded, because of missing date of birth (n=10), missing date on first employment (n=1) or missing date of follow-up (n=1), leaving 2,298 subjects (2,107 males and 191 females).

Exposure assessment

For each individual, the definition of exposure status was based on a detailed occupational history, including periods of employment in different departments and positions held, as well as exposure to the accident that had occurred in 1963 at factory A. Subjects were classified as exposed 1) if they worked in any of the following departments: synthesis,

finishing, formulation, packing, maintenance/repair, laboratory, chemical effluent/waste, cleaning, shipping-transport, plant supervision; 2) if they were exposed as a result of the accident; or 3) if they were exposed by proximity (working in any department not listed above but entering a department, defined as exposed, at least once a week on a regular basis). All other workers were classified as non-exposed to the compounds of interest. For exposed, a distinction was made whether or not they had ever worked on departments of main production (synthesis, finishing, formulation, packing, chemical effluent/waste or other production department).

Serum measurements

Serum TCDD levels were measured in 1993 in a sample of 50 surviving cohort members from factory A. They had to be first employed before 1975 and had at least one year of employment. For exposed male workers, who were not exposed due to the accident, distinction was made for department (ever and never worked in main production). Controls were selected among the non-exposed workers, individually matched for age, sex, date of first employment and length of employment. Furthermore, some male workers exposed due to the accident and some female exposed workers were selected.
Blood samples were collected according to standard protocol and analyzed for polychlorinated dioxins, furans and biphenyls by high resolution gas-chromatography at the Centers for Disease Control in Atlanta, USA [3].

Statistical methods

For exposed workers, measured TCDD levels were back-extrapolated to the time of assumed maximum exposure (TCDD-max), using first-order kinetics and a half-life estimate of 7.1 years [4]. Lag is defined as years since last accident related exposure for workers exposed in the 1963 accident, or years since last exposure for other exposed workers. For non-exposed workers, TCDD-max was equal to measured TCDD level. Simple regression models were analyzed with ln(TCDD-max) as dependent variable and exposure during the accident (yes/no), duration of employment in departments of main production (years), and period of first exposure (before/after 1970 (1/0)) as explanatory variables. The obtained regression equation was used to predict TCDD exposure levels for all cohort members from factory A.
Standardized mortality ratios (SMRs) were calculated by the person-years method, using age-, year-, and gender-specific national mortality rates. Internal comparisons between exposed and non-exposed workers as well as between three categories of predicted TCDD exposure levels were analyzed by Poisson regression.

Results

At the end of the second follow-up 1,944 subjects (85%) were known to be alive, 262 (11%) had died, 74 (3%) had emigrated, and 18 (1%) were lost to follow-up. 981 Subjects were classified as being exposed to the compounds of interest (963 males and 18 females) and 1,283 were non-exposed (1,110 male and 173 female workers). For 34 male workers there was no information available to define their exposure status and they were classified as 'unknown exposure'.

Table 1. Mortality of male workers exposed to phenoxy herbicides, chlorophenols and contaminants, from factory A (549 subjects) and factory B (414 subjects)

	Factory A			Factory B		
Cause of Death	Obs	SMR	(95% CI)	Obs	SMR	(95% CI)
All causes	139	129	(109-153)	31	83	(56-118)
Cancer	51	146	(109-192)	10	82	(39-151)
Lung cancer	14	100	(55-168)	1	21	(1-117)
Bladder cancer	4	370	(101-947)	0	0	
Kidney cancer	4	406	(110-1039)	0	0	
NHL	3	375	(77-1095)	1	309	(8-1721)
STS	0	0		0	0	

Serum measurements

Serum TCDD levels on a lipid-adjusted basis were available for 48 subjects. The Geometric Mean (GM) concentration for non-exposed workers (5.7 ppt) was significantly lower than for all exposed workers (GM=25.6 ppt). However, the levels in men who never had worked in main production (GM=5.5 ppt) and women (GM=6.4 ppt) were within the same range as for non-exposed workers, while levels in men who worked in main production were higher (GM=22.9 ppt). The mean TCDD level in subjects exposed as a result of the accident (GM=87.2 ppt) was clearly and statistically significant higher than for all other exposed workers (GM=8.7 ppt; t=-6.37; $p<0.001$). Among workers exposed due to the accident, subjects with a history of chloracne had a higher mean TCDD level (GM=97.3 ppt) than subjects without chloracne (GM=42.9 ppt), and subjects who ever had worked in main production had a higher mean level (GM=145.2 ppt) than subjects who never had worked there (GM=55.8 ppt).

Regression analysis was performed for back-calculated, log transformed TCDD levels. The adjusted R^2 was high (86%). The estimated parameters were 1.95 (standard error (se)=0.21; p=0.001) for the intercept, 2.07 (se=0.40; p=0.001) for exposure (0/1) due to the accident, +0.16 (se=0.05; p=0.029) for each year working in main production departments, and +2.85 (se=0.36; p=0.001) for first exposure before 1970. With the regression equations and information on job history, ln(TCDD-max) was predicted for all exposed and non-exposed workers from factory A.

Mortality

Overall mortality among exposed males workers from both factories was higher than expected from national death rates (SMR=117; CI=100-136). Table 1 shows the number of deaths and calculated SMRs for selected causes of death. The majority of deaths (82%) occurred in factory A. Total mortality (SMR=129; CI=109-153) and cancer mortality (SMR=146; CI=109-192) were statistically significant increased, due to increased risks for workers who were first exposed 20 or more years ago (SMR=160; CI=110-225). There were no cases of soft-tissue sarcoma (STS). The risk for non-Hodgkin's lymphoma (NHL) was elevated, but statistically not significant. We found increased risks for bladder cancer (SMR=370; CI=101-947) and kidney cancer (SMR=406; CI=110-1039). For

Table 2. Relative risks with 95% confidence intervals for 549 exposed compared to 482 non-exposed male workers from factory A

Cause of Death	Obs exp/nonexp	RR	(95% CI)	RR*	(95% CI)
All causes	139/40	2.24	(1.57-3.18)	1.77	(1.24-2.53)
Cancer	51/7	4.69	(2.15-10.23)	3.94	(1.77-8.80)
Lung cancer	14/1	9.01	(1.21-67.29)	6.49	(0.85-49.38)
Urinary organs	8/0†	51.42	(0.11-∞)	44.43	(0.19-∞)
NHL	3/1	1.93	(0.20-18.50)	1.52	(0.15-15.12)
Circulatory system	45/16	1.81	(1.02-3.20)	1.42	(0.80-2.53)
IHD	33/10	2.12	(1.05-4.30)	1.80	(0.87-3.71)

* Adjusted for age at end of follow-up, calendar period, and time since first exposure/employment.

† Assumption of 0.1 observed death for non-exposed.

factory B, both total mortality (SMR=83; CI=56-118) and cancer mortality (SMR=82; CI=39-151) were slightly lower then expected.

Table 2 shows estimated relative risks (RRs) of exposed male workers from factory A compared to non-exposed workers for selected causes of death. Mortality due to all causes (RR=2.24), cancer (RR=4.69) and lung cancer (RR=9.01), diseases of the circulatory system (RR=1.81) and ischaemic heart disease (IHD; RR=2.12) were statistically significant higher among exposed workers. After adjusting for age, calendar year and time since first exposure, these risks were still increased, although in general somewhat less than before.

Table 3 shows estimated relative risks, using predicted TCDD levels as exposure proxy. The lowest category served as reference group and consisted of workers for whom none of the exposure variables had any effect (non-exposed workers plus all exposed workers who were first exposed after 1970 and never had work on departments of main production). Relative risks were comparable with those derived from the dichotomous exposure classification based on job histories. In general, relative risks were highest in the highest exposure group, indicating a dose-response relationship with TCDD exposure level.

Conclusions

Serum measurements of TCDD in a subset of cohort-members from factory A showed that the dichotomous exposure classification based on individual job histories was valid. Within the group of exposed, workers who never worked on any department of the main production and female workers had mean TCDD levels comparable to non-exposed workers. The mean TCDD level in workers exposed due to the 1963-accident was significantly higher than in other exposed workers.

Table 3. Relative risks with 95% confidence intervals for 3 categories of predicted ln(TCDD-max) level for 1,129 workers (male and female) from factory A

Cause of Death	Low* 1.95	Middle <1.95-4.80]		High <4.80-9.40]	
All causes	1.00	2.31	(1.59-3.37)	2.85	(1.98-4.09)
Cancer	1.00	3.40	(1.71-6.75)	3.96	(2.02-7.75)
Lung cancer	1.00	10.19	(1.27-81.82)	14.07	(1.82-108.67)
Urinary organs	1.00†	118.63	(0.28-∞)	17.55	(0.03-∞)
NHL	1.00	1.70	(0.11-26.9)	3.52	(0.33-38.03)
Circulatory system	1.00	1.89	(1.00-3.55)	2.44	(1.34-4.46)
IHD	1.00	2.04	(0.89-4.69)	3.70	(1.75-7.80)

* Reference category.
† Assumption of 0.1 observed death.

Statistically significant increased risks for total mortality, cancer mortality, bladder cancer and kidney cancer were observed for exposed male workers from factory A, compared to the general population. Workers from factory B showed no elevated risks.
Internal comparison between exposed and non-exposed male workers showed increased relative risks for total mortality, cancer mortality, lung cancer, NHL, and diseases of the circulatory system. Using predicted TCDD levels as exposure proxy, estimated relative risks were comparable with risks derived from the dichotomous exposure classification. In general, relative risks were highest in the highest exposure category, indicating a dose-response relationship with TCDD exposure level.

References

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