

## Cancer mortality in workers exposed to dioxins. An international cohort study.

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### INTRODUCTION

Phenoxy herbicides are used extensively worldwide. Some of these herbicides (2,4,5-T and derivatives) have been banned in some countries because of contamination with polychlorinated dioxins including the most toxic dioxin congener, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Dioxins and related compounds such as furans and PCBs, are acutely toxic in all species examined and are among the most potent carcinogens in experimental animals <sup>1</sup>. In humans, exposure to chlorophenols and phenoxy herbicides contaminated with dioxins has been linked with excess overall cancer risk and excess risks from soft-tissue sarcoma, non-Hodgkin's lymphoma and other cancers but the evidence, particularly from case-control studies, is inconsistent.

The International Agency for Research on Cancer (IARC) maintains an international retrospective cohort study of subjects producing or spraying phenoxy herbicides. The study initially included workers from 10 countries. Results of the first follow-up of the international cohort <sup>2,3</sup>, and national cohorts <sup>4-8</sup> have been published. The IARC cohort has since been enlarged, incorporating herbicide production workers from 12 plants in the USA <sup>9</sup> and from four plants in Germany <sup>10-12</sup> and now includes nearly all the phenoxy herbicide production workers who have ever been studied. The mortality follow up has been updated for most cohorts. In parallel, dioxin levels have been determined in serum samples from workers in eight out of 12 countries included in the international cohort. In this paper we report the results on cancer mortality for the updated and enlarged IARC cohort.

# RISK I

## METHODS

### Subjects

Workers enrolled in the IARC cohort had been employed in plants producing phenoxy herbicides or chlorophenols, or in companies spraying phenoxy herbicides. In total, information was abstracted for 26,976 workers. We excluded 361 workers because of lack of information on date of birth (n=228), date of first employment (n=84) or other reasons (n=49), leaving 26,615 male and female workers. Of those workers, statistical analyses were limited to the 21,863 workers who had been exposed to any phenoxy herbicide or chlorophenol. The cohort includes workers ever employed in production or spraying, except in cohorts from New Zealand in which a minimum employment period of 1 month was specified, Australia (minimum period of 1 year), Canada (6 months), and Germany (1 month in three cohorts, 3 months in one cohort). The follow-up period varied by country and overall extended from 1945 to 1992. During this period, 970 subjects (4.4%) were lost to follow-up or emigrated. In no cohort were more than 10% of subjects lost to follow-up or emigrated.

### Exposure assessment

Exposure was reconstructed using individual job records, company exposure questionnaires developed specifically for the study and in some cohorts measurements of TCDD and other dioxin and furan congeners in serum. Information was retrieved for all jobs held by the workers during the study period. Exposure information was retrieved from each plant using an extended questionnaire<sup>13)</sup>. Additional detailed industrial hygiene investigations were conducted in the US and German cohorts.

All workers exposed to phenoxy herbicide or chlorophenol were classified to three distinct categories: those exposed to TCDD or higher chlorinated dioxins (n = 13,831); those not exposed to TCDD or higher chlorinated dioxins (n = 7,553); and those of unknown exposure to TCDD or higher chlorinated dioxins (n = 479). The latter category includes all workers in one British cohort for which production history, particularly for 2,4,5-T, was incomplete. Exposure to TCDD and higher chlorinated congeners was defined on the basis of measurements of TCDD in serum of workers, information on production volumes of phenoxy herbicides in each plant and other information on dioxin levels in the industrial environment and industrial products. Workers were classified as exposed to TCDD or higher chlorinated dioxins if employed in specific jobs/departments of plants with documented large scale (more than 10 tons per year) production, formulation or spraying of 2,4,5-T, 2,4,5-TCP, PCP or TeCP. Workers were classified as exposed only if they had been employed during the period of production of these chemicals in the plant.

### Statistical analysis

The person-years method was used to derive standardised mortality ratios (SMRs) with 95% confidence intervals (CI) based on the Poisson distribution. Poisson regression analysis was used in internal comparisons of workers according to exposure to TCDD or higher chlorinated congeners. Duration of exposure was treated as a time related variable and refers to exposure to specific chemicals (or groups of chemicals), and not to the total employment period of a worker in a plant.

## RESULTS

Workers exposed to any phenoxy herbicide or chlorophenol

In the total cohort of workers exposed to phenoxy herbicides or chlorophenols (n=21,863), all-cause mortality was slightly lower than expected from national mortality rates in both men (4,026 deaths, SMR = 0.97, CI 0.94-1.00) and women (133 deaths, SMR = 0.98, CI 0.82-1.17). This was mainly because of low mortality from circulatory and respiratory diseases. Excess mortality was observed from accidents in both men (SMR = 1.09) and women (SMR = 1.50) and also from ill-defined causes. A small statistically significant excess mortality from all neoplasms was observed in men (1083 deaths, SMR = 1.07, CI 1.01-1.13), but not in women (44 deaths, SMR = 0.93, CI 0.68-1.25). A two-fold excess mortality was observed from soft-tissue sarcoma (9 deaths, SMR = 2.0, CI 0.91-3.79), while only a slight excess was observed from non-Hodgkin's lymphoma (34 deaths, SMR = 1.27, CI 0.88-1.78).

Workers exposed to TCDD or higher chlorinated dioxins

Among the subgroup of 13,831 workers exposed to phenoxy herbicides contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) or higher chlorinated dioxins, excess mortality was observed for all malignant neoplasms (710 deaths, SMR = 1.12, CI 1.04-1.21) and soft tissue sarcoma (6 deaths, SMR 2.03, CI 0.75-4.43), while mortality from non-Hodgkin's lymphoma was only marginally elevated (24 deaths, SMR 1.34, CI 0.89-2.06); statistically significant excess mortality was observed for respiratory neoplasms (249 deaths, SMR 1.17, CI 1.03-1.33), kidney cancer (26 deaths, SMR 1.60, CI 1.05-2.35) and breast cancer (11 deaths, SMR 2.22, CI 1.11-3.98).

Mortality from all neoplasms increased slightly with time since first to dioxins (394 deaths, SMR = 1.20, CI 1.09-1.33, at 20 or more years since first exposure) while there was no consistent pattern of risk by calendar period or duration of exposure. Mortality from non-Hodgkin's lymphoma increased with time since first exposure (14 deaths, SMR = 1.63, CI 0.89-2.73, at 20 or more years since first exposure). The highest risks were observed among workers with less than one year duration of exposure (11 deaths, SMR = 2.43, CI 1.25-4.46), among production workers and in workers first employed before 1965. All deaths from soft-tissue sarcoma occurred 10 or more years after first exposure. The risk was higher among subjects with a long duration of exposure and in those first employed before 1965, and was fairly similar in production workers and sprayers. Six additional cases of soft tissue sarcoma were registered among workers who were either alive at the end of follow-up, had died from another disease, or had died from sarcoma but were coded on the death certificate under a site code other than the specific rubric "Sarcomas of connective and other soft tissue" (International Classification of Diseases, 9th Revision, code 171). Mortality from lung cancer was not associated with any of the time related exposure variables. The increased mortality from breast cancer (9 deaths, SMR = 2.16, CI 0.99-4.1) was confined to female workers in one plant in Germany<sup>10,11</sup>.

Workers minimally or non-exposed to TCDD or higher chlorinated dioxins

In the subgroup of 7,553 workers exposed to phenoxy herbicides without, or with minimal contamination by TCDD or higher dioxins, mortality from all neoplasms (398 deaths, SMR = 0.96, CI 0.87-1.06), soft tissue sarcoma (2 deaths, SMR = 1.35, CI 0.16-4.88), non-Hodgkin's lymphoma (9 deaths, SMR = 1.00, CI 0.46-1.90) and respiratory cancer (159 deaths, SMR = 1.05, CI 0.90-1.23) was around that expected. For none of these neoplasms was a consistent trend in risk observed by time since first exposure, duration of exposure or calendar period of first exposure.

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## Internal comparisons by exposure to TCDD

In a Poisson regression analysis adjusting for age, sex, calendar period, country, latency, duration of exposure and employment status, workers exposed to TCDD or higher dioxins had an increased risk of mortality from all neoplasms (rate ratio =1.34, 95% confidence interval 0.92-1.94), compared to workers of the same international cohort with no or minimal exposure to TCDD or higher chlorinated dioxins.

## CONCLUSIONS

The IARC international cohort includes now nearly all the phenoxy herbicide production workers who have ever been studied. These findings of the joint analysis of data from 12 participating countries indicate that exposure to herbicides contaminated with dioxins may be associated with a slight increase in overall cancer risk and with large increases in specific cancers.

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