COHORT STUDIES OF OCCUPATIONALLY AND ENVIRONMENTALLY EXPOSED POPULATIONS

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Introduction

The association between exposure to dioxins, cancer and other health outcomes in humans has been examined in numerous epidemiological studies. Most are community based case-control studies on soft-tissue sarcoma and malignant lymphoma or studies on pesticide including phenoxy herbicides applicators. In most studies exposure to 2,3,7,8-TCDD has not been quantified and the data available indicates that levels of TCDD in most populations examined should be very low. This review is based on those human studies in which exposure to 2,3,7,8- TCDD or higher chlorinated PCDDs is documented, with particular emphasis in those studies with the highest exposure to TCDD. Typically this involves studies on workers exposed to phenoxy herbicides contaminated by 2,3,7,8-TCDD (particularly 2,4,5-T) or to other contaminated chemicals used in manufacturing processes (e.g., TCP), and also studies of the population accidentally exposed in Seveso.

Cancer

The epidemiological evidence from the most highly 2,3,7,8-TCDD-exposed cohorts studied produces the strongest evidence of increased risks for all cancer combined (Table 1), along with less strong evidence of increased risks for cancer of particular sites such as non-Hodgkin lymphoma, soft-tissue sarcoma and lung cancer. The relative risk for all cancer combined in the most highly exposed and longer-latency sub-cohorts is 1.4. While this relative risk is not likely to be explained by confounding, this possibility cannot be excluded.

In Seveso, an analysis of cancer mortality from 1976 to 1991 indicated an increased risk for gastrointestinal cancer and haematological neoplasms. No increase was seen for all cancer mortality nor for lung cancer in men or breast cancer in women.

Cardiovascular disease

In recent years dioxins have been linked with an excess risk for heart disease. Excess mortality from ischaemic heart disease has been found in several industrial cohorts (Table 2), and in the high exposure zone at Seveso. The US Air Force Ranch Hand personnel (non-flying) study was mostly negative with a an excess risk observed among personnel with the highest estimated TCDD exposure. No excess risk was observed in an analysis for cardiovascular morbidity in a subset of the NIOSH cohort.

Research priorities and conclusions

It took about 20 years of research and tens of epidemiological studies to reach some consensus concerning the carcinogenicity of dioxins and establish that dioxins are carcinogenic to humans (IARC 1997). Early community based (case-control) studies played a crucial role in setting up the issues. The turning point, however, considering the epidemiological evidence did not depend on the accumulation of such studies, but rather on the acceptance that large cohort studies of heavily exposed subjects were needed. Also that new analytical techniques allowing the detection of dioxin blood levels were necessary for the development of convincing exposure models. It is only the availability of several such studies with comparable protocols that allowed the identification of relatively low relative risks such as those found for all cancers in dioxin exposed persons.

It should be expected that similar problems of interpretation will be encountered in other areas of dioxin research such as effects of exposures in utero and early life, or hormonally mediated effects. The identification of relatively subtle effects in the general population (adults and infants) will require much larger studies than those available. The evaluation of such effects, for example the importance of dioxin like compounds in relation to hormonally mediated effects is particularly complicated given the relatively similar levels of exposure in the population of many industrialised countries.

Despite the availability of large cohorts with quantitative exposure data, the setting of tolerable daily intake for humans is still largely based on data from experimental animals. It should be borne in mind that the general population is exposed to 2-3 orders of magnitude lower levels of TCDD than those experienced by the equivalent lifetime dose in the industrial populations examined or the population of Seveso. To-date, the large epidemiological data sets available have been relatively poorly analysed concerning the quantitative aspects of the risk with the application, for example, of PBPK models.

In conclusion, results from cohort studies indicate an excess risk for mortality from cancer and ischaemic heart disease, particularly among the heaviset exposed workers. Results are still inconsistent concerning other health outcomes. Existing occupational cohorts may still help in examining specific research areas including the quantification of the risk. A number of new research issues, however, will necessitate the collection of extensive additional information and biological samples from existing cohorts or probably the conduct of new large studies in general population samples.

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Table 1. Cancer risk (standardised mortality ratios – SMR) in selected industrial cohorts with high exposure levels to PCDDs .

Reference	Observed deaths from all neoplasms	SMR	95% confidence interval
International cohort			
Kogevinas et al 1997 [a]	394	1.2	1.1-1.3
Industrial populations (high exposure sub-cohorts)			
Steenland et al 1999 [b]	40	1.6	1.2-1.8
Becher et al 1996 [c]	105	1.3	1.0-1.5
Hooiveld et al 1997 [d]	51	1.5	1.1-1.9
Ott & Zober 1996 (BASF accident) [e]	18	1.9	1.1-3.0

a Both sexes, >20 years latency.
b Follow-up of Fingerhut et al 1991. Men highest exposure septile.
c Men, (Boehringer Ingelheim, Bayer-Uerdingen cohort).
d Both sexes, Factory A.
e Men, chloracne subgroup, ≥20 years latency.

Table 2. Mortality from ischaemic heart disease in occupational cohorts and in Seveso

Reference	SMR	95% confidence interval
Vena et al 1998, international cohort	1.67	1.23-2.26
Hooiveld et al 1998, Dutch cohort	1.9	0.9-3.6
Flesch-Janys et al 1995, Boehringer cohort [a]	1.4	0.71-2.76
Michalek et al 1998, US Air Force, Ranch Hand [a]	1.5	1.0-2.2
Steenland et al 1999, NIOSH cohort [a]	1.75	1.07-2.87

[a] highest exposed group