

Cohort studies of cancer risk among Danish workers exposed to TCE

Johnni Hansen

Inst. of Cancer Epidemiology, Danish Cancer Society

Copenhagen, Denmark



When an Entire Country Is a Cohort

Denmark has gathered more data on its citizens than any other country. Now scientists are pushing to make this vast array of statistics even more useful

For years, any woman who got an abortion had to accept more than the loss of her fetus: For some unknown reason, she also faced an elevated risk for breast cancer. At least that was what several small case-control studies had suggested before Mads Melbye, an epidemiologist at the Statens Serum Institute in Copenhagen, undertook the largest effort ever to explore the link. He and his colleagues obtained records on 400,000 women in Denmark's national Abortion Register, then checked how many of the same women were listed in the Danish Cancer Register. Their foray into the two databases led to a surprising result: As they reported in *The New England Journal of Medicine* in 1997,

digit personal identification number, called the CPR, that follows each Dane from cradle to grave. According to Melbye, "our registers allow for instant, large cohort studies that are impossible in most countries."

by th
hosp
datab
Denm
mark
its pr
cedu
unwi
S
to re
conc
denc
indiv
stitut



Central Person Registry

Establishment:	1968
Purpose:	Nationwide civil <i>administration</i>
Coverage:	“All”
Key information*:	CPR-no (incl. date of birth) Name Address Job title Place of birth Vital status Marital status Spouse Parents Children

Incl. Historical information



The Foundation of the Cancer Epidemiology in Denmark



The Danish Cancer Registry
Established in 1942



The Danish Cancer Society
started in 1928



**Dr. med. et h.c.
Johannes Clemmesen**



National Cancer Registry

Establishment:	1942
Completeness:	> 95%
Registration key:	CPR-no.
Tumor characteristics:	Diagnosis (ICD-7) Topography (ICD-O) Histology (ICD-O) Behavior Laterality Extent of tumor Basis of diagnosis Treatment Date of diagnosis Hospital department

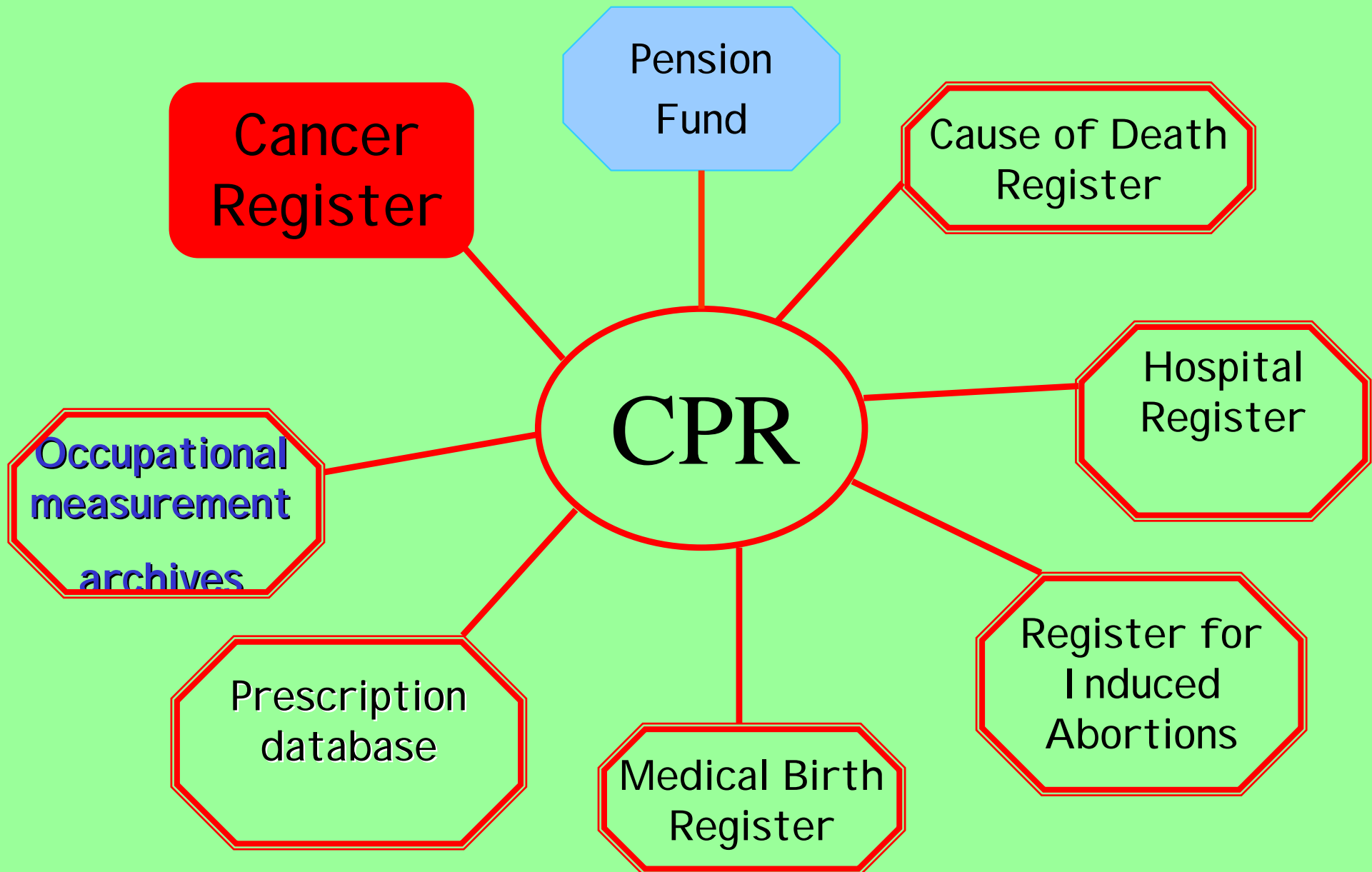


National Pension Fund

Establishment:	1964
Registration key:	CPR-no.
Employment characteristics:	Unique company no. Start of employment End of employment Industry code (ISIC/NACE)



Data linkage options



Occupation and cancer linkages in Denmark

Source

	Labour Inspection archives	CPR-Registry	Pension Fund Registry	CR
<i>CPR-no (birthday, sex, name)</i>	(+)	+	+	+
Company ID (and name)	+		+	
Dates of employment (start and end)	((+))		+	
Type of industry (ISIC, NACE)	+		+	
Job title (social class)	(+)	+		
Vital status		+		
Marital status		+		
Date of death, emmigration		+		
CPR-no. of children		+		
CPR-no. of parents		+		
Diagnosis (ICD-X)				+
Date of diagnosis				+
Measurements (air, blood, urine)	+			



Cohort studies of cancer risk among Danish workers exposed to TCE

Collaborators:

Ole Raaschou-Nielsen, Jørgen H Olsen
Inst. of Cancer Epidemiology, Danish Cancer Society

Jytte M. Christensen, Inger Johansen
National Inst. of Occup. Health, Denmark

Henrik H Kolstad
Department of Occup. Med. Aarhus Kommunehospital, Denmark

Joseph K. McLaughlin, Robert R Tarone, Loren Lipworth, William J. Blot
International Epidemiology Institute, USA



Cohort (I) based on urinary measurement (1947-89)

Cancer Incidence Among Danish Workers Exposed to Trichloroethylene

Johnni Hansen, PhD
Ole Raaschou-Nielsen, PhD
Jytte Molin Christensen, MDSc
Inger Johansen, Ms
Joseph K. McLaughlin, PhD
Loren Lipworth, ScD
William J. Blot, PhD
Jørgen H. Olsen, MDSc

Human evidence regarding the carcinogenicity of the animal carcinogen trichloroethylene (TCE) is limited. We evaluated cancer occurrence among 803 Danish workers exposed to TCE, using historical files of individual air and urinary measurements of TCE-exposure. The standardized incidence ratio (SIR) for cancer overall was close to unity for both men and women who were exposed to TCE. Men had significantly elevated SIRs for non-Hodgkin's lymphoma (SIR = 3.5; n = 8) and cancer of the esophagus (SIR = 4.2; n = 6). Among women, the SIR for cervical cancer was significantly increased (SIR = 3.8; n = 4). No clear dose-response relationship appeared for any of these cancers. We found no increased risk for kidney cancer. In summary, we found no overall increase in cancer risk among TCE-exposed workers in Denmark. For those cancer sites where excesses were noted, the small numbers of observed cases and the lack of dose-related effects hinder etiological conclusions. (J Occup Environ Med. 2001; 43:133-139)

Trichloroethylene (TCE) is among the most widely used chlorinated organic solvents and is mainly used for degreasing metal products before painting.¹ TCE is carcinogenic in long-term animal assays; tumors of the liver, kidney, and testis and lymphomas have been reported.¹⁻³ Epidemiological data are limited and inconsistent, although some studies suggest an association between TCE exposure and risk of cancers of the liver and biliary passages, non-Hodgkin's lymphoma, and leukemia.^{1,4,5} On the basis of experimental data and limited epidemiological evidence, the International Agency for Research on Cancer in 1995 classified TCE as a probable human carcinogen.¹ Since then, a potential association between occupational exposure to TCE and kidney cancer risk has been investigated, with conflicting results.^{4,6-12}

Most studies of cancer risk have been based on indirect assessment of TCE exposure, which may lead to the misclassification of exposure and a tendency to dilute the observation of a potential carcinogenic effect.¹³ Further, the largest studies^{4,6,7,14} concerned mortality rather than incidence rates. Death certificate data may have a higher proportion of misclassified diagnoses and may fail to identify cancers with very high survival rates.^{15,16} We conducted a cohort study in Denmark of cancer morbidity among workers with individual measurements of exposure to TCE.

From the Danish Cancer Society, Institute of Cancer Epidemiology (Dr Hansen, Dr Raaschou-Nielsen, Dr Olsen); and the National Institute of Occupational Health (Dr Christensen, Ms Johansen); Copenhagen, Denmark; the International Epidemiology Institute, Rockville, Md.; and the Department of Medicine, Vanderbilt University Medical Center, Vanderbilt-Ingram Cancer Center, Nashville, Tenn. (Dr McLaughlin, Dr Lipworth, Dr Blot).

Address correspondence to: Johnni Hansen, PhD, Danish Cancer Society, Institute of Cancer Epidemiology, Strandboulevarden 49, DK-2100 Copenhagen Ø, Denmark; e-mail johnni@cancer.dk.
Copyright © by American College of Occupational and Environmental Medicine



Hypothesis (I)

Occupational exposure to TCE increases the risk of:

- liver and biliary tract cancer
- non-Hodgkin's lymphoma
- kidney cancer

- cervical cancer
- lung cancer
- testicular cancer



Material and methods (I)

<u>Design:</u>	Cohort study, defined by TCE measurements
<u>Included persons:</u>	803 workers with individual measurement records (UTCA or breathing zone meas.)
<u>Exposure:</u>	Individual measurement Duration of employment (Pension Fund Data)
<u>Follow-up:</u>	April 1, 1968 or date of first measurement/employment
<u>Reference group:</u>	Standardized general Danish population



Exposure information from historical measurement files

Worker

Name

Birthday/ID-no

Address

Exposure condition

Type of production

Job tasks

Protective efforts

Measurement

Type

Date

Duration

Concentration

Company

Name, address

Type of industry

ID-no



Information on individual exposure to trichloroethylene

Type of measurement	Period	Companies	No. of samples
Urinary (trichloroacetic acid)	1947-89	275	2397
Breathing zone	1974-88	81	422

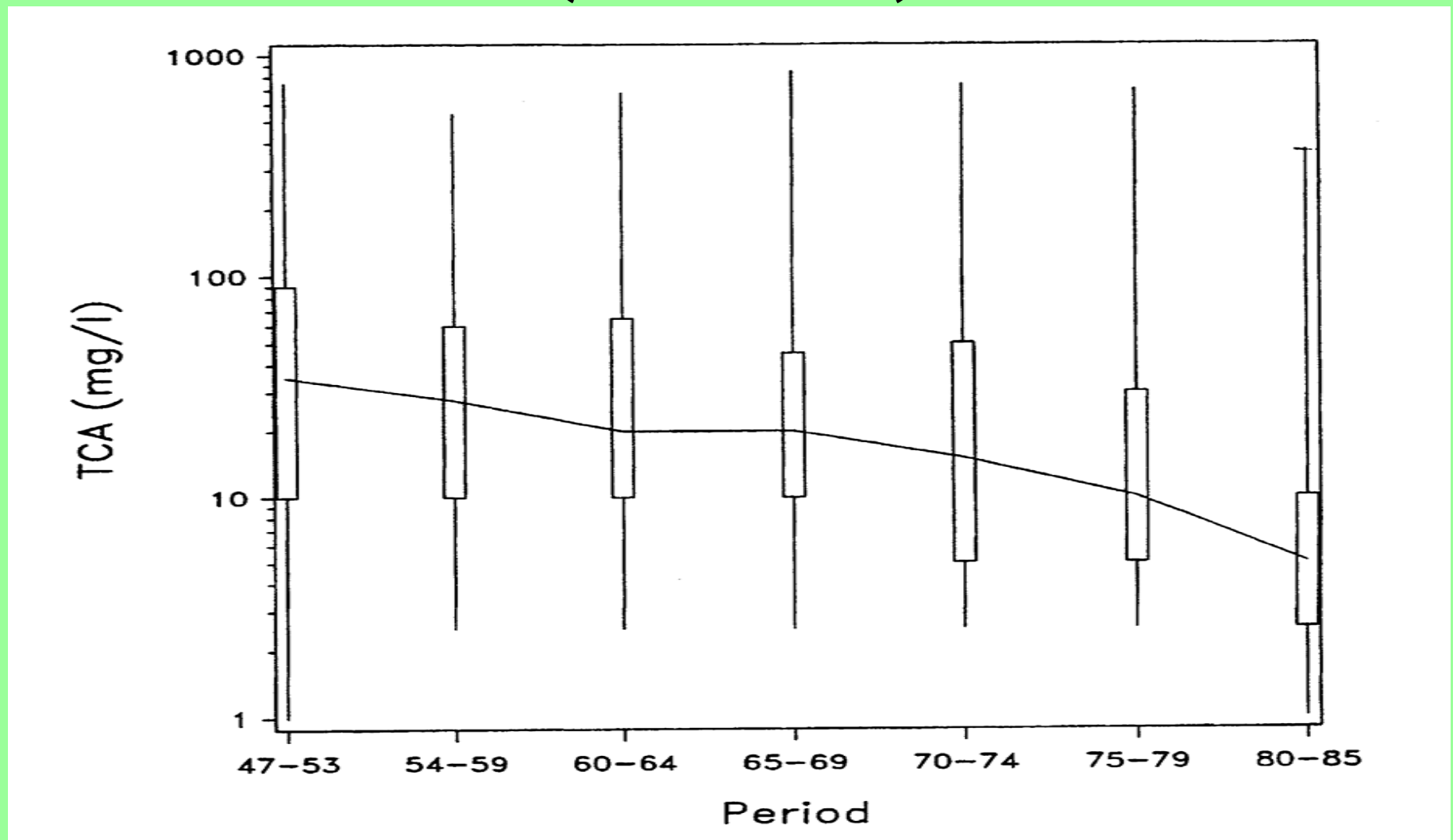


Characteristics of measurements for 803 TCE-exposed persons in the follow-up

Period of measurement	Urinary measurements (mg/l)			Air measurements (mg/m ³)		
	N	Mean	Median	N	Mean	Median
1947-64	401	62	25	0	-	-
1965-73	399	43	15	0	-	-
1974-79	562	30	10	18	372	138
1980-89	157	9	2	227	79	25
.....
1947-89	1519	40	15	245	101	28



Trichloroacetic acid (TCA) in urine of selected Danish workers (1947-85)



**Cancer incidence (1968-96) among 803* Danish workers
(m+w) exposed to trichloroethylene (1947-88)**

Site	Obs	Exp	SIR (95%CI)
Total	128	123.4	1.04 (0.87-1.23)
Liver, primary	2	1.2	1.7 (0.2-6.0)
Biliary tract	3	1.2	2.5 (0.5-7.3)
Kidney	4	3.7	1.1 (0.3-2.8)
Non-Hodgkin's	8	2.6	3.1 (1.3-6.1)
Cervix	4	1.1	3.8 (1.04-2.8)
Lung	17	1.8	0.8 (0.5-1.3)
Testis	1	1.4	0.7 (0.01-0.4)
Esophagus	6	1.5	4.0 (1.5-8.7)

m: men; w: women

*16,730 person-years; 18% women



Oesophagus cancer – histological distribution

	National* (N=2900)	TCE-cohort* (N=6)
Squamous cell	54%	17%
Adenocarcinomas	30%	83%
Other	16%	0%

*Men, born 1910-35, diagnosed 1980-96



Cancer incidence among 803 Danish workers exposed to TCA and exposure-related characteristics

Characteristics	NHL			Oesophagus		
	Obs	SIR	95%CI	Obs	SIR	95%CI
<i>Period of first employment</i>						
1947-64	4	3.5	0.9-8.9	2	2.6	0.3-9.5
1965-89	4	3.5	0.9-8.9	4	6.0	1.6-15
<i>Duration of employment (months)</i>						
unknown	2	3.7	0.4-13	0	-	-
<75*	2	2.5	0.3-9.2	2	4.4	0.5-16
>=75	4	4.2	1.1-11	4	6.6	1.8-17
<i>Cumulative exposure (months mg/m³)</i>						
unknown	2	3.6	0.4-13	0	-	-
<1080*	3	3.9	0.8-11	3	6.5	1.3-19
>=1080	3	3.1	0.6-9.1	3	4.2	1.5-9.2



Conclusions (I)

- No support for TCE-exposure and risk of lung, testis and kidney cancer
- Significantly increased risks of non-Hodgkin's lymphoma and cervical cancer
- Esophageal adenocarcinomas (surprisingly) increased
- No major known confounders for NHL and oesophageal adenocarcinomas
- (No dose-response relationship)
- Confounders can't be excluded
- A very small study. Larger studies is needed



Cohort based on companies with historical *use* of TCE



Cancer Risk among Workers at Danish Companies using Trichloroethylene: A Cohort Study

Ole Raaschou-Nielsen¹, Johnni Hansen¹, Joseph K. McLaughlin^{2,3}, Henrik Kolstad⁴, Jytte M. Christensen⁵, Robert E. Tarone², and Jørgen H. Olsen^{1,3}

¹ Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark.

² International Epidemiology Institute, Rockville, MD.

³ Department of Medicine, Vanderbilt University Medical School, Vanderbilt-Ingram Cancer Center, Nashville, TN.

⁴ Department of Occupational Medicine, Aarhus University Hospital, Aarhus, Denmark.

⁵ National Institute for Occupational Health, Copenhagen, Denmark.

Received for publication March 24, 2003; accepted for publication June 24, 2003.

Trichloroethylene is an animal carcinogen with limited evidence of carcinogenicity in humans. Cancer incidence between 1968 and 1997 was evaluated in a cohort of 40,049 blue-collar workers in 347 Danish companies with documented trichloroethylene use. Standardized incidence ratios for total cancer were 1.1 (95% confidence interval (CI): 1.04, 1.12) in men and 1.2 (95% CI: 1.14, 1.33) in women. For non-Hodgkin's lymphoma and renal cell carcinoma, the overall standardized incidence ratios were 1.2 (95% CI: 1.0, 1.5) and 1.2 (95% CI: 0.9, 1.5), respectively; standardized incidence ratios increased with duration of employment, and elevated standardized incidence ratios were limited to workers first employed before 1980 for non-Hodgkin's lymphoma and before 1970 for renal cell carcinoma. The standardized incidence ratio for esophageal adenocarcinoma was 1.8 (95% CI: 1.2, 2.7); the standardized incidence ratio was higher in companies with the highest probability of trichloroethylene exposure. In a subcohort of 14,360 presumably highly exposed workers, the standardized incidence ratios for non-Hodgkin's lymphoma, renal cell carcinoma, and esophageal adenocarcinoma were 1.5 (95% CI: 1.2, 2.0), 1.4 (95% CI: 1.0, 1.8), and 1.7 (95% CI: 0.9, 2.9), respectively. The present results and those of previous studies suggest that occupational exposure to trichloroethylene at past higher levels may be associated with elevated risk for non-Hodgkin's lymphoma. Associations between trichloroethylene exposure and other cancers are less consistent.

adenocarcinoma; biliary tract neoplasms; esophageal neoplasms; kidney neoplasms; liver neoplasms; lymphoma, non-Hodgkin; occupations; trichloroethylene

Abbreviation: CI, confidence interval.

Since the Second World War, trichloroethylene has been widely used in many industries, mainly because of its degreasing properties and nonflammable character. The risk of acute intoxication of workers exposed to high trichloroethylene concentrations has been known for decades (1), and exposure to trichloroethylene has been shown to induce cancer of the kidney, liver, lung, testis, and lymph nodes of experimental animals (2, 3). On the basis of experimental data and limited evidence from epidemiologic studies (primarily related to cancer of the liver and biliary tract and non-Hodgkin's lymphoma), the International Agency for

Research on Cancer in 1995 classified trichloroethylene as a probable human carcinogen (2). A more recent review reported the strongest epidemiologic evidence for cancer of the kidney and liver (4), but others have found the data for these cancers inconsistent, and the carcinogenicity of trichloroethylene in humans remains a matter of controversy (3, 5–9).

Previously, we reported a significantly increased risk of non-Hodgkin's lymphoma and esophageal adenocarcinoma among men and cervical cancer among women, nonsignificantly increased risk for cancer of the liver and biliary tract,



Hypothesis (II)

Occupational exposure to TCE increases the risk of:

- liver cancer
- biliary tract cancer
- non-Hodgkin's lymphoma
- renal cell cancer

- esophageal adenocarcinoma
- cervical cancer

- lung cancer
- testicular cancer



Material and methods (II)

<u>Design:</u>	Cohort study, defined by companies
<u>Included persons:</u>	Employees at 347 companies with historical <u>use</u> of TCE, linkage to Pension Fund data
<u>Exposure:</u>	> 3 month of employment (as a blue collar worker) in a “TCE-company” with < 200 employees
<u>Follow-up start:</u>	1968 or date of first employment
<u>Reference group:</u>	Standardized general population



Sources of exposure information (II)

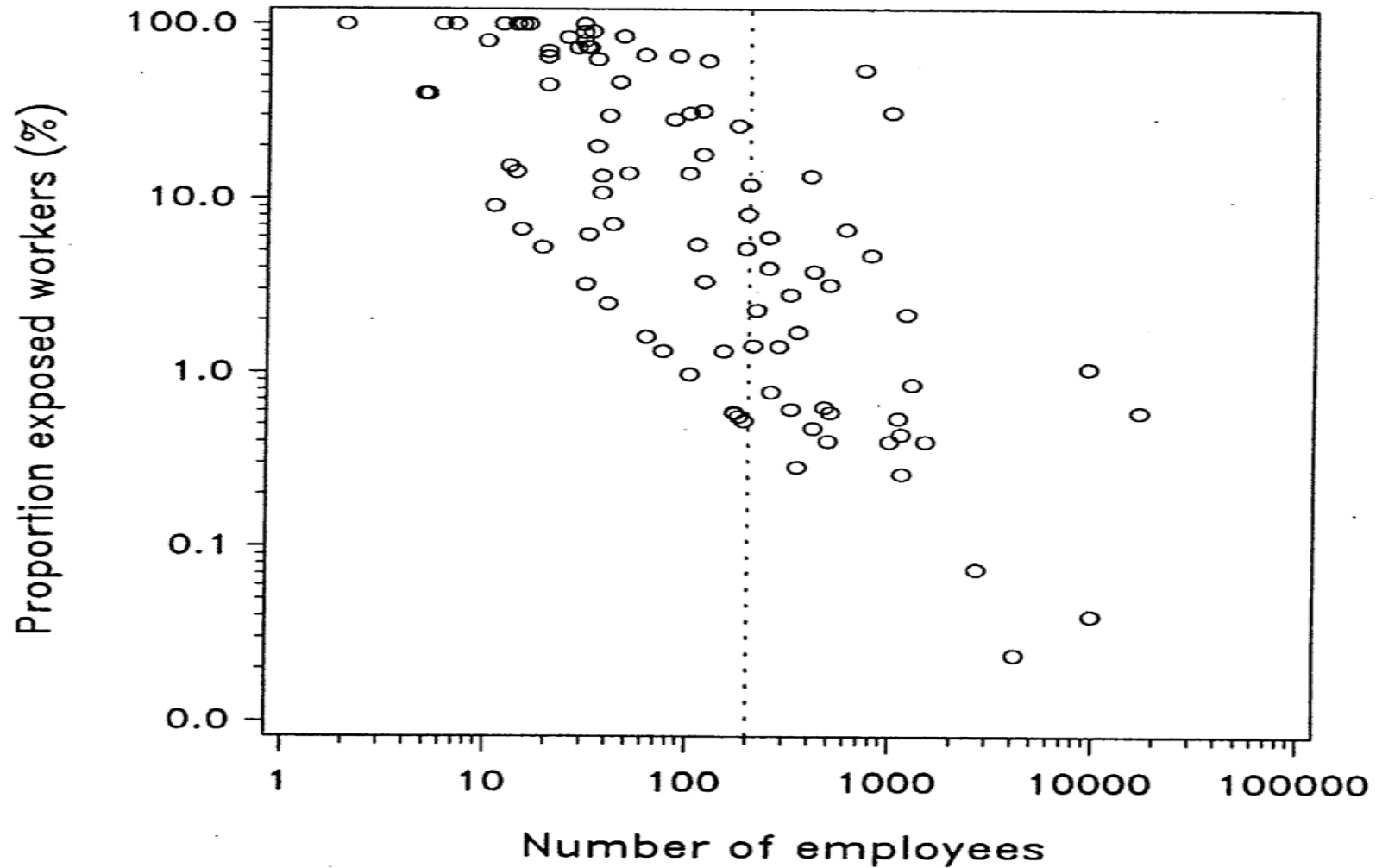
- Nationwide Product Registry Survey (1984)
- Dry cleaning survey (1987)
- Measurement files (1947-89)
- Dominant supplier of TCE in DK (1970-95)

In total 457 Danish *companies*

110 companies excluded: 347 companies



Number of company employees and proportion of workers exposed to organic solvents in Denmark



Selection of workers for final cohort

Employees at 347 companies:	152,726
- White collar workers	39,074
- Unknown collar	56,970
- Employment < 3 months	16,629
.....	
Final cohort	40,049
=====	



Cancer incidence (1968-96) among Danish *male* workers *potentially* exposed to TCE (1964-97)

Site	Obs	Exp	SIR (95%CI)
Total	2,620	2,434	1.08 (1.04-1.12)
Liver, primary	27	24.0	1.1 (0.7-1.6)
Biliary tract	14	12.5	1.1 (0.6-1.9)
Renal parenchyma	68	51.7	1.2 (0.9-1.5)
Non-Hodgkin's	83	67.6	1.2 (0.98-1.5)
Esophagus	40	35.5	1.1 (0.8-1.5)
* adenocarcinomas	23	12.7	1.8 (1.2-2.7)
Lung	559	402	1.4 (1.3-1.5)
Testis	93	81.3	1.1 (0.9-1.4)
Skin melanomas	56	0.7	0.7 (0.6-0.94)

*588,047 person-years



Cancer incidence (1968-96) among Danish *female* workers *potentially* exposed to TCE (1964-97)

Site	Obs	Exp	SIR (95%CI)
Total	624	507	1.2 (1.1-1.3)
Liver, primary	7	2.5	2.8 (1.1-5.8)
Biliary tract	9	3.2	2.8 (1.3-5.3)
Renal parenchyma	8	6.5	1.2 (0.5-2.4)
Non-Hodgkin's	13	9.5	1.4 (0.7-2.3)
Esophagus	2	2.0	2.0 (0.5-5.2)
* Adenocarcinomas	0	0.4	-
Cervix	62	33.5	1.9 (1.4-2.4)
Lung	73	39.0	1.9 (1.5-2.4)
Skin melanomas	16	20.9	0.8 (0.4-1.2)



Cancer incidence among Danish workers *potentially* exposed to TCE (1964-97)

Exposure and time indicators:

- Lag time: none; ≥ 20 years
- Duration of employment (years): < 1 ; 1-5; ≥ 5
- Year of first employment: < 1970 ; 1970-79; ≥ 1989
- Number of employees: < 50 ; 50-99; 100-200



Influence of different time and exposure indicators on the risk of *NHL* among TCE exposed Danish workers

Characteristic	Men			Women		
	Obs	SIR	95%CI	Obs	SIR	95%CI
<i>No lag time</i>	83	1.2	1.0-1.5	13	1.4	0.7-2.3
>= 20 years lag	31	1.3	0.9-1.7	3	1.9	0.8-3.9
<i>Duration of employment (years)</i>						
< 1	23	1.1	0.7-1.6	2	0.7	0.1-2.4
1-4.9	33	1.3	0.9-1.8	6	1.6	0.6-3.5
>= 5	27	1.4	0.9-2.0	5	1.8	0.6-4.3
<i>Year of first employment</i>						
Before 1970	38	1.4	0.4-13	6	1.5	0.6-3.4
1970-79	35	1.3	0.3-9.2	6	1.6	0.6-3.5
1980 and later	10	0.7	1.1-11	1	0.5	0.0-3.0
<i>No. of employee in company</i>						
1-50	13	0.9	0.5-1.6	2	1.1	0.1-4.1
50-99	23	1.3	0.9-2.0	3	1.6	0.3-4.6
100-200	47	1.3	0.9-1.7	3	1.4	0.6-2.7



Influence of different time and exposure indicators on OR of *renal cell cancer* among TCE exposed DK workers

Characteristic	Men			Women		
	Obs	SIR	95%CI	Obs	SIR	95%CI
<i>No lag time</i>	68	1.2	0.9-1.5	8	1.2	0.7-2.3
>= 20 years lag	25	1.3	0.8-1.9	3	1.3	0.8-3.9
<i>Duration of employment (years)</i>						
< 1	14	0.8	0.5-1.4	2	1.1	0.1-2.4
1-4.9	25	1.2	0.8-1.7	6	1.2	0.6-3.5
>= 5	29	1.6	1.1-2.3	5	1.5	0.6-4.3
<i>Year of first employment</i>						
Before 1970	44	1.7	0.2-2.3	6	1.9	0.6-3.4
1970-79	16	0.7	0.4-1.2	6	0.0	0.6-3.5
1980 and later	8	0.9	0.4-1.7	1	2.4	0.0-3.0
<i>No. of employee in company</i>						
1-50	8	0.7	0.3-1.4	0	0.0	0.0-2.6
50-99	23	1.6	1.0-2.4	2	1.7	0.2-6.1
100-200	37	1.2	0.8-1.6	6	1.5	0.5-3.2



Conclusions (II)

- No positive dose-response indication for increased risk of *female* liver and biliary tract cancer
- Support for association between past levels of TCE exposure and NHL. Confounders ?
- Association between TCE exposure and renal cell carcinoma. Confounders: tobacco smoking ?
- Confirmation of increased risk of esophageal adenocarcinomas – needs further research



Nordic cohort studies of exposure to TCE and risk of selected cancers

Study characteristics	No.	Liver and biliary tract		NHL	
		Obs	SIR	Obs	SIR
Urine and air monitoring, DK	803	5	2.1	8	3.1 ^p
Urine monitoring, Fin	3089	9	1.9	8	1.8
Urine monitoring, S (men)	1670	4	1.4	5	1.6

p < 0.05



Planned update of the three Nordic urinary measurement cohorts

	Present follow-up	Person years	Cancers	New update	Est. person years
Denmark	1968-96	16,730	128	+ 7 years	+ 5.000
Finland	1967-92	59,905	208	+ 11 years	+ 45.000
Sweden	1958-87	23,517	107	+ 15 years	+ 20.000
All		100,152	443		+ 70.000

