

# **Occupational determinants of pancreatic cancer**

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*To Olli, Jaakko and Alma*



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## ABSTRACT

**Objective and background.** Tobacco smoking, pancreatitis and diabetes mellitus are the only known causes of pancreatic cancer, leaving ample room for yet unidentified determinants. This is an empirical study on a Finnish data on occupational exposures and pancreatic cancer risk, and a non-Bayesian and a hierarchical Bayesian meta-analysis of data on occupational factors and pancreatic cancer.

**Methods.** The case-control study analyzed 595 incident cases of pancreatic cancer and 1,622 controls of stomach, colon, and rectum cancer, diagnosed 1984-1987 and known to be dead by 1990 in Finland. The next-of-kin responded to a mail questionnaire on job and medical histories and lifestyles. Meta-analysis of occupational risk factors of pancreatic cancer started off with 1,903 identified studies. The analyses were based on different subsets of that database. Five epidemiologists examined the reports and extracted the pertinent data using a standardized extraction form that covered 20 study descriptors and the relevant relative risk estimates. Random effects meta-analyses were applied for 23 chemical agents. In addition, hierarchical Bayesian models for meta-analysis were applied to the occupational data of 27 job titles using job exposure matrix as a link matrix and estimating the relative risks of pancreatic cancer associated with nine occupational agents.

**Results.** In the case-control study, logistic regressions revealed excess risks of pancreatic cancer associated with occupational exposures to ionizing radiation, nonchlorinated solvents, and pesticides. Chlorinated hydrocarbon solvents and related compounds, used mainly in metal degreasing and dry cleaning, are emerging as likely risk factors of pancreatic cancer in the non-Bayesian and the hierarchical Bayesian meta-analysis. Consistent excess risk was found for insecticides, and a high excess for nickel and nickel compounds in the random effects meta-analysis but not in the hierarchical Bayesian meta-analysis.

**Conclusions.** In this study occupational exposure to chlorinated hydrocarbon solvents and related compounds and insecticides increase risk of pancreatic cancer. Hierarchical Bayesian meta-analysis is applicable when studies addressing the agent(s) under study are lacking or very few, but several studies address job titles with potential exposure to these agents. A job-exposure matrix or a formal expert assessment system is necessary in this situation.



## LIST OF ORIGINAL COMMUNICATIONS

The thesis is based on the following original publications, which are referred to in the text by their Roman numerals:

- I Kauppinen T, Partanen T, Degerth R, Ojajarvi A. Pancreatic cancer and occupational exposures. *Epidemiology* 1995;6:498-502.
- II Ojajarvi IA., Partanen TJ, Ahlbom A, Boffetta P, Hakulinen T, Jourenkova N, Kauppinen TP, Kogevinas M, Porta M, Vainio HU, Weiderpass E, Wesseling CH. Occupational exposures and pancreatic cancer: a meta-analysis. *Occup Environ Med* 2000;57:316-24.
- III Ojajarvi A., Partanen T, Ahlbom A, Boffetta P, Hakulinen T, Jourenkova N, Kauppinen T, Kogevinas M, Vainio H, Weiderpass E, Wesseling C. Risk of pancreatic cancer in workers exposed to chlorinated hydrocarbon solvents and related compounds: a meta-analysis. *Am J Epidemiol* 2001;153:841-50.
- IV Ojajarvi A., Partanen T, Ahlbom A, Hakulinen T, Kauppinen T, Weiderpass E, Wesseling C. Estimating the relative risk of pancreatic cancer associated with exposure agents from job title data with hierarchical Bayesian meta-analysis. Submitted

## ABBREVIATIONS

AICR	American Institute of Cancer Research
ALHC	Aliphatic and alicyclic hydrocarbons
CKK	Chelocytoskinine-pancreazymin
CHC	Chlorinated hydrocarbon
CI	Confidence interval
CR	Chromium
CrI	Credible interval
DDD	Dichlorodiphenyldichloroethane
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
EEF	Etiological fraction among exposed
FINJEM	Finnish job exposure matrix
FUNG	Fungicides
HB	Hierarchical Bayesian
HMSO	Her Majesty's Stationery Office
HR	Hazard ratio
IH	Industrial hygienist
IARC	International Agency for Research on Cancer
INSC	Insecticides
JEM	Job exposure matrix
MCMC	Markov chain Monte Carlo
MOR	Mortality odds ratio
MRR	Meta-relative risk
NI	Nickel and nickel compounds
OR	Odds ratio
PAH	Polycyclic aromatic hydrocarbon
PCB	Polychlorinated biphenyl
PCMR	Proportional cancer mortality ratio
PEF	Population etiological fraction
PMR	Proportional mortality ratio
RE	Random effects
RR	Relative risk
SIL	Silica dust
SIR	Standardized incidence ratio
SMR	Standardized mortality ratio
TDE	Tetrachlorodiphenyletane
WOOD	Wood dust

## 1. INTRODUCTION

The pancreas is about 15 cm long organ and is located behind the stomach. It has two functions: to send insulin into the bloodstream to control the amount of sugar in the blood, and to send pancreatic juice into the intestine to help digest food. About 95% of all pancreatic cancers derive from the exocrine component, which transports the pancreatic juice. Endocrine tumors arising in islet cells constitute about 5% of all pancreatic cancers (Brennan et al., 1993).

According to Ferley et al. (2001) approximately 200,000 new cases of pancreatic cancer (International Classification of Diseases: code 157 in 9<sup>th</sup> revision and code C25 in 10<sup>th</sup> revision) were annually diagnosed worldwide in 2000. In Finland, the number was 878 in 2004 ([www.syoparekisteri.fi](http://www.syoparekisteri.fi)).

Results of the epidemiological studies of associations between risk of pancreatic cancer and occupational branches and job titles are heterogeneous and inconsistent, and exposures shared by high-risk jobs are hard to identify (Partanen et al., 1994; Ji et al., 1999; Kernan et al., 1999; Alguacil et al., 2000a; Alguacil et al., 2000b; Alguacil et al., 2003a). The population etiologic fraction of pancreatic cancer due to occupational exposures was estimated at 26% in Montreal, Canada (Siemiatycki et al., 1991). No single occupational exposure has been confirmed to increase the risk of pancreatic cancer with high probability. Most of the associations with single chemical agents emerged in one study only. The separation between spurious and causal associations presents serious difficulties.

This study investigated the relationship between occupational determinants and pancreatic cancer, first in the case-control study based on Finnish data, and secondly in meta-analyses of occupational agents and occupations by using random effects and hierarchical Bayesian models for meta-analysis. In the hierarchical Bayesian models, this study also evaluates the feasibility of use of a job-exposure matrix in meta-analysis.

## **2. A LITERATURE REVIEW**

### **2.1 Pancreatic cancer**

#### **2.1.1 Descriptive epidemiology of pancreatic cancer**

##### **Incidence and geographical distribution**

The populations of “developed” countries appear to carry a higher burden of pancreatic cancer than those of less developed countries. Regionally, the highest annual age-adjusted incidence rates per 100 000 person years in 2000 were estimated among black males in Connecticut, USA (14.7) and Michigan, Detroit, USA (13.7), and among males in Hungary (12.3) and Latvia (12.1) (Ferlay et al., 2001; Parkin et al., 2002). The lowest rates were reported among both genders for Western Africa, South Central Asia and Melanesia (Ferlay et al. 2001). No consistent urban-rural gradient is discernible (Parkin et al., 1993). Mortality rates follow closely incidence rates because of rapid fatality of pancreatic cancer.

##### **Time trends**

Incidence rates have been rising in developed countries since the 1960s and leveled or leveling off in populations such as those of the Nordic countries, Scotland, Northern Ireland (Coleman et al., 1993; Estève et al., 1993; Fernandez et al., 1994) and USA (Zheng et al., 1995). The increase may be attributable to increased sensitivity of modern preoperative diagnostic methods, to the higher accessibility of people to the health system, and to better registration procedures, but an actual increase in incidence appears to have taken place (Estève et al., 1993).

##### **Age and gender distribution**

Incidence and mortality rates increase steeply among people 40-70 years of age. Incidence of pancreatic cancer is higher among men than women. The average age-adjusted male-to-female ratio of pancreatic cancer incidence is about 1.5 for more developed countries and 1.4 for less developed countries (Ferlay et al., 2001). It was 1.46 in Finland in 2004 ([www.syoparekisteri.fi](http://www.syoparekisteri.fi)). The age-adjusted incidence ratio between more developed and less developed countries was 2.8 for men and 2.5 for women during the same time period (Ferlay et al., 2001).

##### **Socioeconomic status**

Pancreatic cancer is not consistently associated with socioeconomic status within national populations (Faggiano and Partanen 1997; Kogevinas et al., 1997b).

### **2.1.2 Determinants of pancreatic cancer**

Migrant studies suggest that environmental factors influence the risk of pancreatic cancer. Studies have been conducted on Italian migrants, on migrants from Europe to Australia and Israel, and from Mexico to Los Angeles. Pancreatic cancer rates have usually shifted from the level of the country of origin toward that of the host country (Geddes et al., 1993; Geddes et al., 1994).

Pancreatic cancer is strongly related to tobacco smoking, which carries an average of 2-3 fold relative risk that increases with the number of pack-years of smoking (Lund Nilssen and Vatten, 2000). The association between tobacco smoking and pancreatic cancer is weaker than that between tobacco smoking and lung cancer. Acute and chronic pancreatitis, type II diabetes and past gastric surgery have been associated with pancreatic cancer (Lowenfels et al., 1997; Gold and Goldin, 1998; Malka et al., 2002; Huxley et al. 2005). A number of dietary factors have been associated with pancreatic cancer (Gold and Goldin, 1998). Table 1 illustrates nonoccupational risk factors of pancreatic cancer.

Workplace exposures may be causally associated with pancreatic cancer (Weiderpass et al., 1998). Results of a large number of epidemiological studies that have linked industries and jobs with pancreatic cancer are heterogeneous and inconsistent. No single occupational agent has been confirmed to increase the risk of pancreatic cancer.

## A LITERATURE REVIEW

TABLE 1. Risk factors of pancreatic cancer.

	High risk	Moderate risk	Low risk
<b>General factors:</b>			
Age	Old	Middle	Young
Gender	Male		Female
Geographic location	Developed country		Developing country
<b>Lifestyle factors:</b>			
Smoking	Heavy	Light	No
Body mass index	Obese	High	Normal/Low
<b>Medical factors:</b>			
Type II diabetes duration	< 5yrs	> 4 yrs	No diabetes
Pancreatitis	Yes		No
Helicobacter	Yes		No
<b>Dietary factors:</b>			
Intake level of vegetables	Low		High
fruits	Low		High
fibers	Low		High
carbohydrates	High		Low
proteins	High		Low
<b>Other factors:</b>			
Family history	Yes		No

### Lifestyles

#### *Tobacco smoking*

Tobacco smoking is the single major substantiated cause of exocrine pancreatic cancer (Silverman et al., 1994). Results from over 30 studies are available. With the exception of the indeterminate results of three studies (La Vecchia et al., 1987; Pisani, 1994; Shibata et al., 1994), all are consistent with cigarette smoking as a cause of pancreatic cancer (Ishii et al., 1973; Williams and Horm, 1977; Jick and Dinan, 1981; Severson et al., 1982; Hsieh et al., 1986; Mack et al., 1986; Norell et al., 1986a; Wynder et al., 1986; Carstensen et al., 1987; Hiatt et al., 1988; Mills et al., 1988; Cuzick and Babiker, 1989; Ferraroni et

al., 1989; Olsen et al., 1989; Farrow and Davis, 1990; Tomioka et al., 1990; Baghurst et al., 1991; Howe et al., 1991; Ghadirian et al., 1991b; Bueno de Mesquita et al., 1991; Lyon et al., 1992; Friedman and van den Eeden, 1993; Zatonski et al., 1993; Zheng et al., 1993; Silverman et al., 1994; Ji et al., 1995; Fernandez et al., 1996; Fuchs et al. 1996; Harnack et al., 1997; Muscat et al., 1997; Partanen et al., 1997; Coughlin et al., 2000; Lund Nilsen and Vatten, 2000; Villeneuve et al., 2000; Chiu et al., 2001; Silverman, 2001; Stolzenberg-Solomon et al., 2001b; Inoue et al., 2003). A dose-response relationship with the number of cigarettes per day was observed in several studies (Farrow and Davis, 1990; Howe et al., 1991; Zheng et al., 1993; Muscat et al., 1997; Partanen et al., 1997; Coughlin et al., 2000; Lund Nilsen and Vatten, 2000; Chiu et al. 2001; Stolzenberg-Solomon et al., 2001b; Inoue et al., 2003). High daily doses of tobacco smoke have been associated with risk ratios of the order of 2-3, occasionally reaching values over 5. Several studies have found a positive dose-response association with the number of pack years of smoking and pancreatic cancer (Bueno de Mesquita et al., 1991; Fuch et al. 1996; Harnack et al., 1997; Lund Nilsen and Vatten, 2000; Villeneuve et al., 2000; Stolzenberg-Solomon et al., 2001b). In a cohort study among Finnish male smokers (Stolzenberg-Solomon et al., 2001b), over 49 pack-years of cigarette smoking, compared with less than 22 pack-years, was associated with pancreatic cancer incidence with hazard ratio (HR) 1.67; 95 % confidence interval (CI) 1.04-2.72; trend p 0.04. Two studies have found a strong increased association between smokeless tobacco use and risk of pancreatic cancer (Alguacil and Silverman, 2004; Boffetta et al., 2005). The estimated attributable risk from smoking (the proportion of pancreatic cancer caused by smoking) ranges between 26% and 52% in the United States (Moolgavkar and Stevens, 1981; Gold et al., 1985; Mack et al., 1986; Silverman et al., 1994); in northern Italy, it was 20% for men and 5% for women (Fernandez et al., 1996). Giving up smoking would substantially reduce the subsequent incidence of pancreatic cancer (Mulder et al., 2002).

### *Alcoholic beverages*

Several epidemiological studies, including 30 studies in the review study conducted by American Institute of Cancer Research (AICR) (1997) and a number of further studies (La Vecchia et al., 1987; Gorham et al., 1988; Ferraroni et al., 1989; Bouchardy et al., 1990; Partanen et al., 1997; Villeneuve et al., 2000; Silverman, 2001), found an association between alcohol consumption and risk of pancreatic cancer. Nine cohort studies yielded a consolidated risk ratio (RR) of 1.2 (95% CI 0.9-1.4) for heavy consumers (Velema et al., 1986). Silverman et al. (1995) found an increased risk among heavy alcohol drinkers in the United States, particularly among black non-smokers. However, 22 studies with a reasonable power to detect a positive association between alcohol consumption and risk of pancreatic cancer failed to do so (La Vecchia et al., 1987; Gorham et al., 1988; Ferraroni et al., 1989; Bouchardy et al., 1990; AICR, 1997). On occasion the excess may

## A LITERATURE REVIEW

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have been a result of confounding by tobacco smoking (Lyon et al., 1992). According to the review of AICR (1997) high alcohol consumption probably has no relationship with the risk of pancreatic cancer. Confounding by tobacco smoking is possible in studies that did not adjust for smoking.

### *Coffee consumption*

Seven studies reviewed by AICR (1997) and one further study (Gullo et al. 1995) found relative risks of pancreatic cancer of the order of 2-3 for those who drank 5 or more cups daily. A dose-response was found in some studies. Confounding from smoking may have been possible in some of the studies. Nineteen studies in the study of AICR (1997) and Elinder et al. (1981), Jick and Dinan (1981), Heuch et al. (1983), Whittemore et al. (1983), Stensvold and Jakobsen (1994), Partanen et al. (1995), and Villeneuve et al. (2000) failed to reproduce the coffee association. Coffee consumption may not have an independent effect but it is possible that coffee potentiates or decreases the effect of other risk factors, possibly depending on metabolizing phenotypes (Vineis, 1993). Confounding by tobacco smoking may be possible in studies without control of such potential confounding.

### *Diet*

Eighteen case-control studies (Falk et al., 1988; Raymond et al., 1987; Goto et al., 1990; Negri et al., 1991; AICR, 1997; Silverman et al. 1998; Stolzenberg-Solomon et al., 1999; Stolzenberg-Solomon et al., 2001b; Stolzenberg-Solomon et al., 2002a) and two prospective cohort studies (AICR, 1997) reported a decreased pancreatic cancer risk at high consumption levels of vegetables or fruit (Odds Ratios [ORs] ranged 0.3-0.9 and RRs 0.6-0.9). For meat and meat products; seven case-control studies (Goto et al., 1990; AICR, 1997) and three cohort studies (AICR, 1997) reported a positive association with pancreatic cancer. One case-control study (AICR, 1997) have reported a strong increase in the risk with a high consumption (smoking adjusted OR 2.5, 95%CI 1.2-5.1 for >10 vs <5 servings meat per week). Four case-control studies (AICR, 1997; Silverman et al., 1998) and one prospective cohort study (Michaud et al., 2003) failed to do so, and one case-control study (AICR, 1997) suggested protection by high lean pork meat intake (OR 0.6, 95% CI 0.3-1.2). The strength of the consolidated evidence on excess associated with meat consumption is only moderately convincing.

*Total energy, macronutrients and dietary fiber.* Most of the current evidence on pancreatic cancer and intake of total energy and macronutrients comes from a multicentric case-control study conducted in Adelaide, Australia; Toronto and Montreal, Canada; Opole, Poland; and the Netherlands (AICR, 1997). A pooled analysis revealed an increased risk at high levels of total energy intake (ORs 1.2, 1.2, 2.0 and 2.1;  $p > 0.0001$  for trend) and

at high intakes of total carbohydrates (OR 1.7, 95% CI 1.3-2.4 for the highest vs the lowest quartile)(AICR, 1997). An evidence of decrease in pancreatic cancer risk at high intakes of dietary fiber was revealed. The effects of total energy intake and macronutrients have been investigated in three case-control studies (AICR, 1997). A French study found an excess risk for high intake of total fat, but the finding was unadjusted for total energy intake (AICR, 1997). The western Washington, United States, and Athens, Greece, studies did not find associations for either total or saturated fat or total carbohydrates (AICR, 1997). For protein, nine case-control studies (including the multicentric study) failed to show a clear association with pancreatic cancer risk, while one study reported an excess at high intake levels (AICR, 1997).

*Micronutrients.* A negative association between pancreatic cancer risk and intake levels of vitamin C has been repeatedly reported (Falk et al., 1988; Howe et al., 1990; Ghadirian et al., 1991c; Zatonski et al., 1991; Kalapothaki et al., 1993). Associations with intake levels of carotenoids were generally weaker. One prospective cohort study on serum concentrations of carotenoids (Comstock et al., 1991) found a strong inverse association with serum levels of lycopene.

### *Obesity*

Six studies (Friedman and van den Eeden, 1993; Moller et al., 1994; Silverman et al., 1998; Michaud et al., 2001; Silverman, 2001; Pan et al., 2004; Fryzek et al., 2005) reported positive associations between obesity and pancreatic cancer risk, which were however not confirmed in other studies (Mack et al., 1986; Bueno de Mesquita et al., 1990; Howe et al., 1990; Ghadirian et al., 1991c; Bueno de Mesquita et al., 1992; Kalapothaki et al., 1993; Pezzilli et al., 2005). In a recent meta-analysis (Berrington de Gonzalez et al., 2003), including six case-control and eight cohort studies, the meta-relative risk (MRR) for pancreatic cancer per unit increase in body mass index (BMI) was estimated to be 1.02 (95% CI: 1.01-1.03).

### *Use of aspirin*

Two cohort studies found a decreased pancreatic cancer risk in aspirin users, while two case-control studies failed to confirm this association (Baron, 2004), one cohort study suggesting that the use of aspirin would increase the risk (Baron, 2004).

### **Medical conditions**

*Helicobacter pylori* have been sporadically associated with pancreatic cancer (Gold and Goldin, 1998; Stolzenberg-Solomon et al., 2001a). For two additional conditions, pancreatitis and type II diabetes mellitus, a fair number of studies are available (Gold and Goldin, 1998; Huxley et al., 2005).

### *Pancreatitis*

Pancreatitis, both chronic and acute, is frequently caused by heavy consumption of alcohol. Pancreatitis has been linked with pancreatic cancer (Ansari and Burch, 1968; Lowenfels, 1984; Velema et al., 1986; Gorham et al., 1988; Lowenfels, 1993; Fernandez et al., 1995, Malka et al., 2002). In a cohort study (Malka et al., 2002), the standardized incidence ratio (SIR) was 26.7 (95% CI 7.3-68.3). As this condition is rare, population etiologic fraction is low, estimated at 0.1-5 percent (Fernandez et al., 1995). Lowenfels et al (1997) have reported an increased risk in hereditary chronic pancreatitis.

### *Diabetes mellitus*

Huxley et al. (2005) updated a meta-analysis of pancreatic cancer and type II diabetes (Everhart and Wright, 1995). Ten out of 17 case-control studies and all 19 cohort studies found an association between pancreatic cancer and diabetes mellitus diagnosed at least one year before the diagnosis of pancreatic cancer. The meta-relative risk (MRR) was negatively associated with the duration of diabetes mellitus (MRRs 2.1, 1.5 and 1.5). Subjects who had had diabetes diagnosed less than five years had 50% higher MRR than five or longer diagnosed. Stolzenberg-Solomon et al. (2002b) reported a strong association between pancreatic cancer and self reported diabetes mellitus in a cohort study of Finnish male smokers.

### *Helicobacter pylori*

An association between helicobacter pylori and pancreatic cancer has been reported in few studies, but the evidence remains insufficient (Raderer et al., 1998; Stolzenberg-Solomon et al., 2001a; Manes et al., 2003).

## **Family history and genetic factors**

While two studies found familial clustering of pancreatic cancer, the data are inconsistent. Ghadirian et al. (1991a) reported that 7.8% of their pancreatic cancer patients had a family history of pancreatic cancer, compared with 0.6% in its matched controls in the Francophone community in Montreal, Canada. Another positive suggestion comes from Italy (La Vecchia et al., 1992). Lynch et al. (1992) reported a family cluster with pancreatic cancer through three generations. The genetic component in the familial aggregation of pancreatic cancer has been estimated at 2 % in northern Italy (Fernandez et al., 1996). Silverman (2001) found high elevated risks of pancreatic cancer for subjects with a family history of cancers of the pancreas, colon or ovary.

Hereditary chronic pancreatitis appears to be associated with pancreatic cancer (Tersmette et al., 2001; Malka et al., 2002). The role of genetic polymorphisms of metabolic enzymes in the modification of pancreatic cancer risk is not clear (Malats et al., 1997).

Pancreatic cancer has the highest frequency (75%-85%) of K-ras mutations among all human neoplasms. Environmental factors that have been associated with K-ras mutations in pancreatic cancer are alcohol consumption, tobacco smoking (Malats et al., 1997; Porta et al., 1999b), coffee drinking (Porta et al., 1999a; Porta et al., 1999b), and organochlorines (Porta et al., 1999c). In the first study on occupational exposures and K-ras mutations in pancreatic cancer Alguacil et al. (2002) found a strong association between K-ras mutations and organic solvents. Alguacil et al. (2003b) also observed an association between K-ras mutations and occupational exposure to dyes and organic pigments (OR 4.8), lead, polycyclic aromatic hydrocarbons (PAHs), benzo[a]pyrene, gasoline, nickel, inhalatory exposure to chromium, and sedentary work.

### **Occupational factors**

Some workplace exposures may increase the risk of pancreatic cancer. Results of a fair number of epidemiological studies that have linked industries and job titles with an excess of pancreatic cancer are heterogeneous and inconsistent, and exposures shared by alleged high-risk jobs are hard to identify.

### ***Job titles***

*Laundry and dry cleaning operators.* Partanen et al. (1994) found excess risk (OR 2.4, 95% CI 0.3-17) of pancreatic cancer among laundry and dry cleaners in a case-control study. Out of nine standardized incidence ratio (SIR) and standardized mortality ratio (SMR) studies, three (Lynge and Thygesen, 1990; Ruder et al., 1994; Ruder et al., 2001) found a high excess; four (Brown and Kaplan, 1987; Blair et al., 1990; Pukkala, 1995; Andersen et al., 1999) reported smaller excesses, while two (Norell et al., 1986b; Travier et al., 2003) failed to find an excess. Hrubec et al. (1992) observed a weak positive association in their cohort mortality study. Out of nine proportional mortality ratio (PMR) or mortality odds ratio (MOR) studies, four (Katz and Jowett, 1981; Dubrow, 1984; Petrone, 1988; Gallagher et al., 1989) found a weak positive association, while five (Duh and Asal, 1984; Nakamura, 1985; Olsen and Jensen, 1987; Milham, 1997; Walker et al., 1997) reported a negative association.

*Machine and automobile manufacture workers.* Alguacil et al. (2000b) found an excess risk (OR 3.4) of pancreatic cancer for Spanish machinery mechanics and fitters in a case-control study. Out of eight SMR studies, four (Eisen et al., 1992; Garabrant et al., 1988; Rotimi et al., 1993; Eisen et al., 2001) observed high excesses; two (Delzell et al., 1993; Beall et al., 1995) a low positive risk; while two (Costa et al., 1989; Rushton, 1993) failed to show an excess. Out of seven PMR/MOR-studies one (Vena et al., 1985) had a strong positive association; five (Chiazze et al., 1984; Dubrow, 1984; Mallin et al., 1986; Park et al., 1988; Silverstein et al., 1988) a weak positive; and one (Milham, 1997) a weak negative association.

*Printing workers.* Out of seven case-control studies five (Pietri et al., 1990; Siemiatycki et al., 1991; Ji et al., 1999; Kernan et al., 1999; Alguacil et al., 2003a) found high excesses for printing workers (OR ranged 1.2 - 5.2). Partanen et al. (1994) found a weak positive association, while the Bouchardy et al. study (2002) was nonpositive. In cohort studies, Coggon et al. (1986a) found a positive and Hrubec et al. (1992) a negative association. One (Minder and Beer-Porizek, 1992) of the seven SIR/SMR-studies found a high excess; four (Paganini-Hill et al., 1980; Malke and Gemne, 1987; Leon, 1994; Lynge et al., 1995) reported a smaller positive association with pancreatic cancer; while two (Michaels et al., 1991; Pukkala, 1995) were nonpositive. Out of the nine PMR/MOR-studies, Lloyd et al. (1977) found a high excess, while the remaining studies (Greene et al., 1979; Dubrow, 1984; Zoloth et al., 1986; Magnani et al., 1987; Olsen and Jensen, 1987; Gallagher et al., 1989; Costa et al., 1995; Milham, 1997) reported smaller excesses.

*Pulp and paper workers.* Four case-control study studies (Wingren et al., 1991; Partanen et al., 1994; Kernan et al., 1999; Alguacil et al., 2003a) reported moderately low excesses (OR 1.3 - 1.4), and one (Siemiatycki et al., 1991) a weak negative association for pulp and paper workers. Out of 12 SIR/SMR-studies, Pukkala (1995) reported a strong positive association; four studies (Norell et al., 1986b; Henneberger et al., 1989; Coggon et al., 1997; Rix et al., 1998) had a weaker positive; and seven (Robinson et al., 1986; Lanes et al., 1993; Sala-Serra et al., 1996; Wong et al., 1996; Band et al., 1997; Szadkowska-Stanczyk et al., 1997; Matanoski et al., 1998) a negative association. Out of the five PMR/MOR studies, Magnani et al. (1987) found a high excess, while in three studies (Milham and Demers, 1984; Schwartz, 1988; Milham, 1997) the excess was smaller, and two (Dubrow, 1984; Solet et al., 1989) reported deficits.

*Textile workers.* Out of eight case-control studies three (Partanen et al., 1994; Alguacil et al., 2000b; Zhang et al., 2005) found a high excess risk for pancreatic cancer (OR ranged 5.8 - 11.5) and the rest of studies (Pietri et al., 1990; Siemiatycki et al., 1991; Ji et al., 1999; Kernan et al., 1999; Boychardy et al., 2002) a smallest excess risk (OR ranged 1.1 - 1.9). Pukkala (1995) observed a positive association in a SIR-study and Delzell et al. (1989) a negative association in a SMR-study. Out of four PMR/MOR-studies two (Dubrow, 1984; Olsen and Jensen, 1987) found a positive association with pancreatic cancer and two (Delzell and Drufferman, 1983; Dubrow and Gute, 1988) failed to do it.

Job titles with reported excess risk of pancreatic cancer at least two epidemiological studies are listed in Table 2. Various chemical exposures have been and are present in these job titles.

### *Occupational agents*

No single occupational agent has been confirmed to increase the risk of pancreatic cancer with reasonable likelihood. The bulk of the occupational chemical agents that have been associated with excess risk in the epidemiological studies emerged in one study only, sug-

gesting that many of the associations may be artifacts from confounding or chance. If no additional information, e.g. from animal bioassays, is available, the distinction between spurious and causal associations presents formidable difficulties, given the general uncertainty about the causative agents involved in the development of pancreatic cancer. The pervasive lack of individual historical exposure data in epidemiological studies of cancers with long latency periods is an additional problem in the interpretation of the findings. Also, many reported “agents” have in fact been more or less heterogeneous groups of agents such as “pesticides” or “organic solvents”.

*Chlorinated hydrocarbon solvents* have been associated with high excess risk of pancreatic cancer in two case-control studies (Kernan et al., 1999; Hoppin et al., 2000), in which ORs were 2.9 and 4.2, respectively, and in three SIR/SMR-studies three (Benson and Teta, 1993; Yassi et al., 1994; Anttila et al., 1995), in which SIR/SMR ranged from 2.0 to 4.9. Lower excesses were found in two case-control studies (Greenland et al., 1994; Alguacil et al., 2000a), in five SIR/SMR-studies (Nakamura, 1983; Smulevich et al., 1988; Wong et al., 1991; Tomenson et al., 1997; Chang et al., 2003), and in two PMR-studies (Chiazze and Ference, 1981; Magnani et al., 1987). A weak negative association was reported in one case-control study (Siemiatycki et al., 1991), and in seven SIR/SMR-studies (Brown, 1987; Simonato et al., 1991; Spirtas et al., 1991; Sinks et al., 1992; Lanes et al., 1993; Axelson et al., 1994; Gibbs et al., 1996).

*Pesticides* have been associated with high risk of pancreatic cancer in five case-control-studies (Garabrant et al., 1993; Kernan et al., 1999; Alguacil et al., 2000a; Ji et al., 2001; Clary and Ritz, 2003), in one SMR-study (Beard et al., 2003), and in one RR-study (Cantor and Silberman, 1999). ORs ranged from 1.5 to 21.0, SMR was 1.9 and RR 2.7. Smaller excesses were found in one case-control study (Fryzek et al., 1997), in five SIR/SMR-studies (Swaen et al., 1992; Asp et al., 1994; Lee et al., 1996; Satihakumar et al., 1996; Hooiveld et al., 1998) and in one RR-study (Ramlow et al., 1996). Deficits were found in one case-control study (Siemiatycki et al., 1991), in five SIR/SMR-studies (Lynge, 1985; Coggon et al., 1986b; Ott et al., 1987; Brown et al., 1992; Kogevinas et al., 1997a) and in two PMR-studies (Magnani et al., 1987; Cocco et al., 1997).

*Polycyclic aromatic hydrocarbons* have been associated with high excess risk in one case-control study (Romudstad et al., 2000; OR 6.38, 95% CI 1.3-30.6 in the highest exposure category) and in one incidence study (Weiderpass et al., 2003), in which RR was 1.5. Two case-control studies (Siemiatycki et al., 1991; Alguacil et al., 2000a) and two SIR/SMR-studies (Cammарone et al., 1986; Moulin et al., 1989) reported smaller excesses.

Nine occupational agents have been associated with excess risk in more than two studies: pesticides in nine studies; chlorinated hydrocarbon solvents in six studies; asbestos and polycyclic aromatic hydrocarbons in four studies; chromium and chromium compounds, electromagnetic fields and low frequency electromagnetic fields in three studies; ionization radiation, and nickel and nickel compounds in two studies (Table 2).

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**TABLE 2.** Job titles and occupational agents with reported excess risks of pancreatic cancer at least two epidemiological studies.

### Job

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Administration, science, managers (Lin and Kessler, 1981; Falk et al., 1990; Siemiatycki et al., 1991; Partanen et al., 1994; Kernan et al., 1999; Alguacil et al., 2003a)

Aluminium reduction, aluminium workers (Rockette and Arena, 1983; Mur et al., 1987; Carta et al., 1992)

Auto mechanics; gas station and garage workers (Lin and Kessler, 1981; Hansen, 1989)

Chemical workers (Mancuso and El Attar, 1966; Hanis et al., 1982; Bond et al., 1985; Hirayama, 1989)

Chemists (Li et al., 1969; Cordier, 1990; Cordier et al., 1995; Milham, 1997)

Cooks (Siemiatycki et al., 1991; Andersen et al., 1999; Alguacil et al., 2003a)

Electrical and electronic workers (Andersen et al., 1999; Alguacil et al., 2003a)

Foodstuff workers (Magnani et al., 1987; Carstensen et al., 1990; Siemiatycki et al., 1991; Andersen et al., 1999; Alguacil et al., 2003a)

Farmers (Burmeister, 1981; Blair et al., 1993; Cerhan, 1998; Alguacil et al., 2000b; Lee et al., 2002)

Hairdressers, barbers (Pukkala, 1995; Lamba et al., 2001)

Laundry and dry cleaning operators (Lynge and Thyngensen, 1990; Ruder et al., 1994; Andersen et al., 1999; Ruder et al., 2001)

Leather and footwear workers (Decoufle et al., 1977; Edling et al., 1986; Constantini et al., 1989; Siemiatycki et al., 1991)

Machine and automobile manufacture workers (Vena et al., 1985; Mallin et al., 1986; Silverstein et al., 1988; Alguacil et al., 2000b; Eisen et al., 2001)

Maintenance personnel, charworkers (Siemiatycki et al., 1991; Andersen et al., 1999; Bouchardy et al., 2002; Alguacil et al., 2003a)

Motor vehicle drivers (Andersen et al., 1999; Bouchardy et al., 2002; Alguacil et al., 2003a)

Painters, lacquerers (Pukkala, 1995; Alguacil et al., 2000b; Brown et al., 2002)

Printing workers (Decoufle et al., 1977; Lloyd et al., 1977; Zoloth et al., 1986; Magnani et al., 1987; Mallin et al., 1989; Siemiatycki et al., 1991; Leon 1994; Alguacil et al., 2003a)

Pulp and paper workers (Bross et al., 1978; Magnani et al., 1987; Henneberger 1989; Wingren et al., 1991; Pukkala 1995; Wild et al., 1998)

Refinery workers (Gallagher et al., 1989; Pickle and Gottlieb 1980; Thomas et al., 1980; Siemiatycki et al., 1991; Shallenberger et al., 1992; Dement et al., 1998; Kernan et al., 1999)

Rubber industry workers (Monson and Fine 1978; Delzell et al., 1981; Szeszenia Dabrowska et al., 1991; Solovena 1992)

Seafarers, sailors, seamen (Andersen et al., 1999; Saarni et al., 2002)

Textile workers (Bross et al., 1978; Olsen and Jensen 1987; Partanen et al., 1994; Ji 1999; Alguacil et al., 2000b; Zhang et al., 2005)

Woodworkers (Kawachi et al., 1989; Bouchardy et al., 2002)

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### Agent

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Asbestos (Selikoff and Seidman 1981; Seidman, 1986; Szeszenia Dabrowska et al., 1988; Falk et al., 1990)

Chlorinated hydrocarbon solvents (Hearne et al., 1990; Benson and Teta, 1993; Yassi et al., 1994;

Anttila et al., 1995; Kernan et al., 1999; Hoppin et al., 2000)  
Chromium and chromium compounds (Franchini et al., 1983; Magnani et al., 1987; Weiderpass et al., 2003)  
Electromagnetic fields (Tynes et al., 1992; Ji et al., 1999; Weiderpass et al., 2003)  
Ionizing radiation (Polednak et al., 1983; Magnani et al., 1987)  
Low frequency electromagnetic fields (Tynes et al., 1992; Ji et al., 1999; Weiderpass et al., 2003)  
Nickel and nickel compounds (Siemiatycki et al., 1991; Weiderpass et al., 2003)  
Pesticides (Alavanja et al., 1990; Garabrant et al., 1992; Garabrant et al., 1993; Forastiere et al., 1993;  
Cantor and Silberman, 1999; Alguacil et al., 2000a; Ji et al., 2001; Clary and Ritz, 2003; Beard et al., 2003)  
Polycyclic aromatic hydrocarbons (Siemiatycki et al., 1991; Romundstad et al., 2000a;  
Romundstad et al., 2000b; Weiderpass et al., 2003)

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## 2.2 Job-exposure matrix

Job-exposure matrices (JEMs) were developed to translate job titles to occupational agents occurring in different jobs. A number of occupational studies based on individual data have applied JEMs, especially when individual exposure assessment was impossible. A Finnish JEM (FINJEM) has been developed at the Finnish Institute of Occupational Health (Kauppinen et al., 1998). Three dimensions of FINJEM are job titles, agents, and calendar period. Exposure has been characterized by the proportion of exposed and the mean level of exposure in each job title (Pukkala et al., 2005). Thus, a pancreatic cancer case-control study based on Spanish data (Alguacil et al., 2000a) applied FINJEM. JEMs have been used in several large register-based studies in which exposure assessment at the individual level is not available. Four register-based studies of various cancers (Vasama-Neuvonen et al., 1999; Weiderpass et al., 2003; Guo et al., 2004a; Guo et al., 2004b; Pukkala et al., 2005) applied FINJEM. FINJEM was used also in a pooled study of 11 West European case-control studies of bladder cancer and job titles (Kogevinas et al., 2003), translating job titles to occupational agents at the study level. Hierarchical Bayesian methods and JEM have been applied on individual job title data using logistic regression models in one study (Gilks and Richardson, 1992). Their results from three models, two logistic regression models and one Bayesian logistic regression model, showed that the Bayesian model overestimated results whereas ecological or aggregated bias on average weaken the relative risks.

## 2.3 Meta-analysis in occupational cancer epidemiology

McElvenny et al. (2004) reviewed meta-analyses of occupational epidemiology. They identified 64 study reports (excluding Studies II and III) published during the period from

1975 to October 2001. Two meta-analyses (Schwartz and Reis, 2000; Wong and Raabe, 2000) were not included. The meta-analysis of Wong and Raabe (2000) was an update of their earlier paper Wong and Raabe (1989). Forty-seven studies had cancer as endpoint. A literature search from October 2001 to December 2005 identified 24 meta-analysis of occupational cancer epidemiology (Sonoda et al., 2001; Wong, 2001; Boffetta, 2002; Gaertner and Thériault, 2002; Levy et al., 2002; Mastrangelo et al., 2002; Boffetta et al., 2003; Crump et al., 2003; Lubin, 2003; Van Maele-Fabry and Willems, 2003; Armstrong et al., 2004; Collins and Lineker, 2004; Goodman et al., 2004; Kurihara and Wada, 2004; Li et al., 2004; Su et al., 2004; Van Maele-Fabry and Willems, 2004; Borak et al., 2005; Bosetti et al., 2005; Buja et al., 2005; Cole and Rodu, 2005; Megdal et al., 2005; Shah et al., 2005; Takkouche et al., 2005).

### 2.3.1 Characteristics of the meta-analyses

The annual number of meta-analyses of occupational cancer epidemiology has risen during 1981-2005 (Figure 1). Out of the 71 meta-analyses of occupational cancer, twenty applied fixed effects models only. The numbers and proportions of random effects analyses increased during 1981-2005.

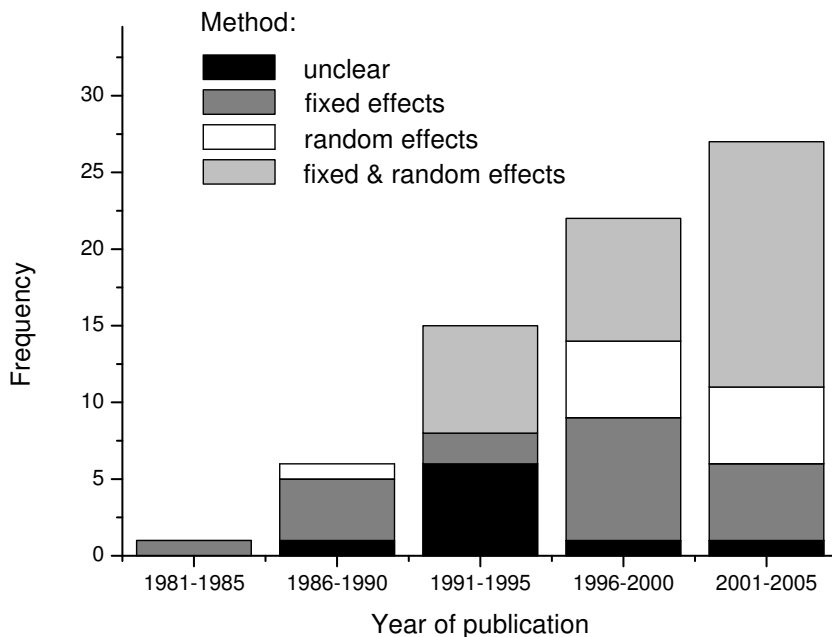


FIGURE 1. Frequency of meta-analyses in occupational cancer epidemiology by publication year and methods of meta-analyses.

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Out of 71 meta-analyses of occupational cancer, ten (five job title and five agent specific meta-analyses) reported results for pancreatic cancer (Table 3). One job title study on refinery workers (Wong and Raabe, 2000) is an update of a previous study (Wong and Raabe, 1989). All meta-analyses except one that included various study designs aggregated results of cohort studies. Two job-title specific meta-analyses addressed farmers, and four agent-specific meta-analyses dealt with organic solvents. The number of studies included in meta-analyses ranged from three to 82.

**TABLE 3.** Characteristics of meta-analyses in occupational pancreatic cancer epidemiology published up to December 2005.

Study	Job or Agent	No. of studies included	Type of studies included	Fixed/random effects	Meta parameter
<u>Job title studies:</u>					
Wong and Raabe (1989)	Refinery workers	11	Cohort	Fixed	Meta-SMR
Blair et al. (1992)	Farmers	20	Cohort	Fixed	Meta-SMR
Acquavella et al. (1998)	Farmers	27	Cohort, case-control,	Fixed/random	Meta-RR
Wong and Raabe (2000)	Refinery workers	25	Cohort	Fixed	Meta-SMR
Greenberg et al. (2001)	Chemical workers	82	Cohort	Fixed/random	Meta-SMR
<u>Agent studies:</u>					
Shore et al. (1993)	Ethylene oxide	11	Cohort	Fixed/random	Meta-SMR
Chen and Seaton (1996)	Organic solvents	29	Cohort	Fixed	Meta-SMR
Schwartz and Reis (2000)	Cadmium	3	Cohort	Fixed	Meta-SMR
Wartenberg et al. (2000)	Trichloroethylene	15	Cohort	Fixed	Meta-SMR/ Meta-SIR
Collins et al. (2001)	Formaldehyde	14	Cohort	Fixed/random	Meta-RR

The type of relative risk estimates was SMR or SIR in all job title specific meta-analyses and mixed (SMR/SIR/OR) in one meta-analysis (Table 4). Only one meta-analysis tested heterogeneity between aggregated studies. Strong associations with any job titles or agents did not be found in any meta-analyses, except for the Acquavella et al. (1998) study that reported a high nonpositive result for farmers.

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**TABLE 4.** The number and the type of the relative risk estimates and the results of the job title specific meta-analyses in occupational pancreatic cancer epidemiology published up to December 2005.

Study	No. of relative risk estimates	Type of relative risk estimates	Results of meta-analysis: MRR (95% CI)	p-value of heterogeneity
Wong et al. (1989) (refinery workers)	11	SMR	0.95 (0.85-1.05)	Not reported
Blair et al. (1992) (farmers)	20	SMR	0.98 (0.94-1.02)	Not reported
Acquavella et al. (1998) (farmers)				
All studies	28	SMR/PMR/OR	0.94 (0.86-1.02)	<0.00001
Follow-up studies	9	SMR	0.78 (0.74-0.82)	0.15
PMR-studies	11	PMR	1.05 (0.98-1.11)	0.04
Case-control studies	8	OR	1.01 (0.88-1.17)	0.92
Wong and Raabe (2000) (refinery workers)	25	SMR	0.88 (0.82-0.94)	Not reported
Greenberg et al. (2001) (chemical workers)				
All studies	82	SMR	1.00 (0.93-1.08)	Not reported
Male	76	SMR	1.01 (0.93-1.09)	Not reported
Female	14	SMR	0.93 (0.66-1.30)	Not reported
Latency > 10 Years	20	SMR	1.04 (0.85-1.26)	Not reported
Duration > 10 Years	11	SMR	1.13 (0.85-1.51)	Not reported
All studies	9	SIR	1.09 (0.78-1.54)	Not reported

The type of relative risk estimates was SMR or SIR in all agent-specific meta-analyses but one that consolidated mixed estimates (SMR/SIR/PMR/PIR/OR) in one (Table 5). Out of five agents specific meta-analyses four have tested heterogeneity between aggregated studies. Wartenberg et al. (2000) reported a high excess for trichloroethylene in SMR-studies on dry cleaners and laundry operators. Collins et al. (2001) reported a high excess risks for formaldehyde in different study types. For cadmium, Schwartz and Reis (2000) found an MRR 1.66 of a quit strong positive association for men, based on three SMR-studies.

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**TABLE 5.** The number and the type of the relative risk estimates and the results of the agent specific meta-analyses in occupational pancreatic cancer epidemiology published up to December 2005.

Study	No. of relative risk estimates	Type of relative risk estimates	Results of meta-analysis: MRR (95% CI)      p-value of heterogeneity	
Shore et al. (1993) (ethylene oxide)				
All studies	8	SMR	0.98 (0.69-1.36)	0.41
Latency (years)				
Brief	3	SMR	1.1 (0.4-2.3)	Not reported
Intermediate	4	SMR	0.8 (0.3-1.6)	Not reported
Long	4	SMR	1.1 (0.6-2.0)	Not reported
Intensity or frequency of exposure:				
Low	3	SMR	0.7 (0.1-2.1)	Not reported
Intermediate	4	SMR	1.0 (0.3-2.3)	Not reported
High	4	SMR	0.9 (0.5-1.5)	Not reported
Duration of exposure				
0-9 y	4	SMR	1.0 (0.5-1.6)	Not reported
> 10y	4	SMR	1.0 (0.5-1.5)	Not reported
Chen and Seaton (1996) (organic solvents)	29	SMR	0.91 (0.84-0.98)	> 0.1
Schwartz and Reis (2000)(cadmium)				
All studies	4	SMR	1.62 (0.94-2.79)	0.73
Male	3	SMR	1.66 (0.98-2.80)	0.89
Wartenberg et al. (2000) (trichloroethylene)				
Tier I (exposure best characterized)	3	SIR	1.2 (0.7-2.0)	Not reported
	4	SMR	0.9 (0.7-1.2)	Not reported
Tier II (exposure putative)	5	SMR	1.1 (0.9-1.3)	Not reported
Tier III (dry cleaner and laundry workers)	2	SIR	1.7 (1.2-2.6)	Not reported
	5	SMR	1.3 (1.0-1.7)	Not reported
Collins et al. (2001)(formaldehyde)				
All studies	14	SIR/SMR/ PMR/PIR/OR	1.1 (1.0-1.2)	0.12
Cohort studies	8	SIR/SMR	1.0 (0.8-1.2)	0.14
PMR/PIR-studies	4	PMR/PIR	1.2 (1.0-1.4)	0.61
Case-control studies	2	OR	1.0 (0.5-2.0)	0.03

### **2.3.2 Hierarchical Bayesian meta-analysis**

In the review of meta-analyses of occupational epidemiology (McElvenny et al., 2004) only one study used Bayesian methods (Biggerstaff et al., 1994). Our literature search from PubMed for period October 2001 to December 2005 did not identify any study of Bayesian meta-analysis of occupational epidemiology. Wraith and Mendersen (2006) recently published a hierarchical Bayesian meta-analysis of lung cancer and interaction with asbestos and smoking.

DuMouchel and Harris (1983) introduced hierarchical models for Bayesian meta-analysis. Recent advances in computational methods have made these methods available for combining the results of epidemiological studies. The fully Bayesian hierarchical model has been investigated extensively by DuMouchel (1990) and Abrams and Sanso (1998) using analytic approximations. Morris and Normand (1992) and Smith et al. (1995) applied sampling-based Markov chain Monte Carlo (MCMC) methods to random effects hierarchical Bayes models for meta-analysis. Carlin (1992) considered meta-analyses of both clinical trials and case-control studies from the Bayesian viewpoint. Biggerstaff et al. (1994) compared classical and Bayesian meta-analyses in studies of lung cancer and passive smoking in workplace. Tweedie et al. (1996) applied Bayesian models to meta-analysis of environmental tobacco smoking and lung cancer studies. DuMouchel (1995) investigated meta-analysis for dose-response models.

### **3. OBJECTIVES**

This study investigated the relationship between occupational determinants and pancreatic cancer.

The specific objectives were:

1. To identify and estimate associations between pancreatic cancer and occupational agents in a case-control study.
2. To extend and estimate the identification of associations between pancreatic cancer and occupational agents in a worldwide meta-analysis, using job title data, a job-exposure matrix, and different methods of meta-analysis.
3. To investigate the applicability of hierarchical Bayesian methods to the occupational meta-analysis data estimating associations between pancreatic cancer and occupational agents indirectly with FINJEM using job titles.

## 4. MATERIALS AND METHODS

### 4.1 Case-control study

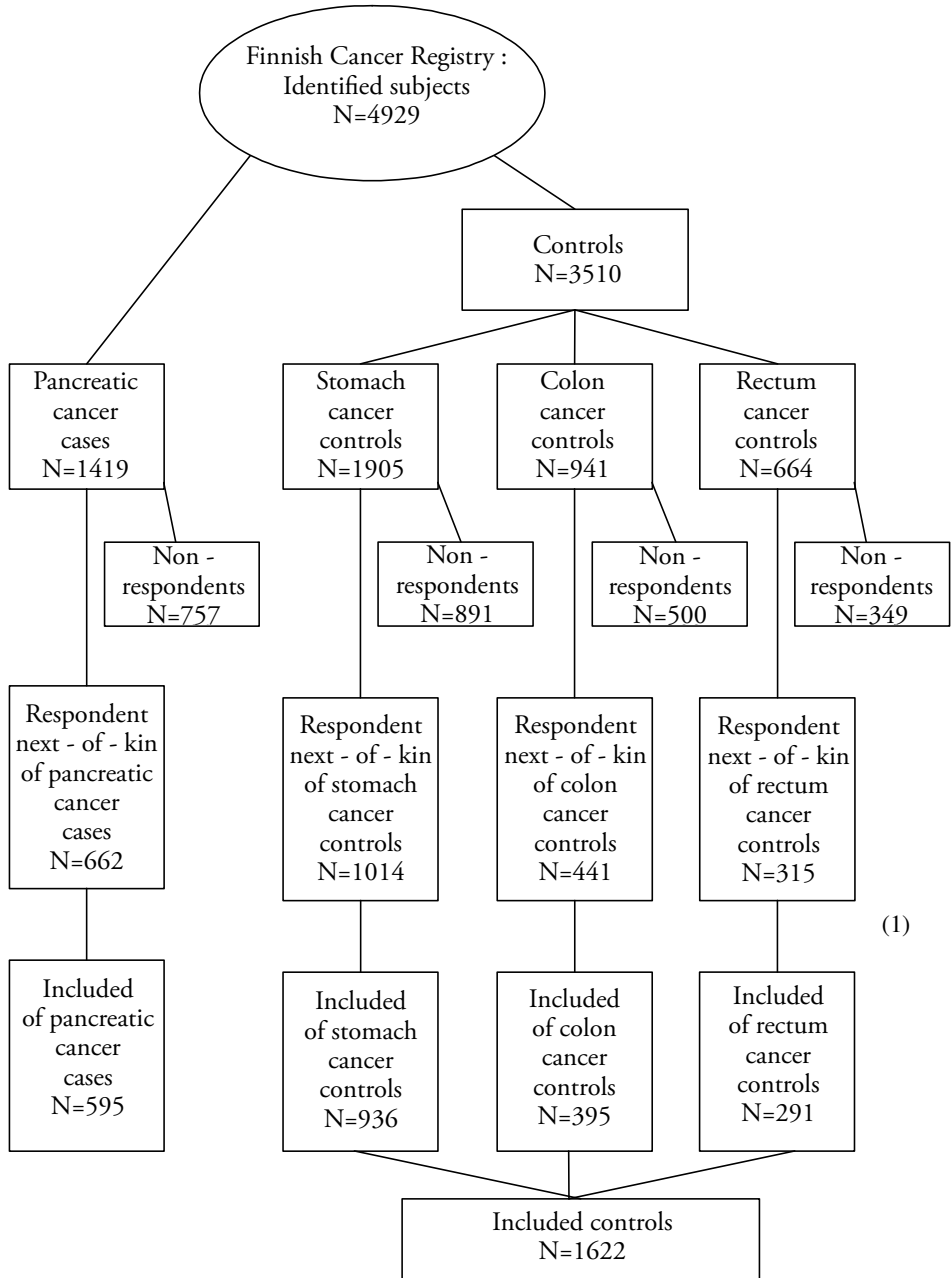
#### 4.1.1 Materials

In Study I the pancreatic cancer cases and stomach, colon and rectum cancer controls diagnosed in 1984-87 between the ages of 40 and 74 years in Finland and known to be dead by April 1, 1990 were identified at the Finnish Cancer Registry without matching. The study was restricted to the deceased because of the rapid fatality of pancreatic cancer and to reach a reasonable non-differential misclassification of determinant data (surrogate responders for both cases and controls).

A next-of-kin was identified for each case and control from the Finnish Population Registry, and a questionnaire was sent to each. Semi-structured questions requested information on lifetime occupational history of the deceased (branch, job task, employer, and duration of every period of employment); body built (thin/slim/normal/quite fat/fat/unknown); coffee consumption (not at all or irregularly/1-3/4-6/>6 cups per day/unknown); sugar consumption (none/little/moderate/much/unknown); consumption of distilled alcohol (none/moderate/much/unknown), wine, and beer (none/moderate/much/unknown); average daily number of cigarettes smoked (occasionally, little/1-9/10-20/>20 cigarettes per day/unknown) (all the preceding referring to the 1960s); onset of smoking (no/yes/unknown); age at giving up smoking; pancreatitis, diabetes, and biliary stones (no/yes/unknown); and years of diagnosis. Two reminders were mailed to those who did not respond to the initial questionnaire. The persons were encouraged to contact an interviewer by telephone if they felt it would be more convenient.

The response rate for cases was 47%, for stomach cancer controls 53%, for colon cancer controls 47%, and for rectum cancer controls 47%. The criteria for excluding subjects and the numbers of included subjects are in Figure 2. After the exclusions the final number of cases was 595 and that of controls 1,622 (936 stomach cancers, 395 colon cancers, and 291 cancers of the rectum).

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**FIGURE 2.** Subject ascertainment of the case-control study. Exclusions (1) endocrine pancreatic cancer cases, subjects with incomplete work histories, subjects with diagnostic pancreatitis before 1982, and administrators and managers.

## MATERIALS AND METHODS

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All reported jobs that lasted at least a year by the end of 1973 (to allow for a minimum lag period of 10 years between the last employment counted and diagnosis) were abstracted from questionnaires and coded by an experienced industrial hygienist according to the British Classification of Occupations of General Register Office (HMSO, 1966a) and the Standard Industrial Classification (HMSO, 1966b).

In the agent-specific study (I), the first exposure analysis (industrial hygiene, or “IH” survey) was based on a reconstruction of probable exposure to 17 selected agents: aromatic amines, asbestos, cadmium, chlorophenols, chromium (VI) compounds, engine exhaust, formaldehyde, gasoline, lead, mineral wool, polyaromatic hydrocarbons (PAHs), pesticides, silica, solvents, textile dust, welding, and wood dust. An experienced industrial hygienist determined the criteria for the exposure categories, reviewed the occupational histories, listed the probable agents of the individuals, and rated them by the level of exposure (none/low/high).

The second exposure analysis (“JEM analysis”) was a survey of potential agents by a job exposure matrix (JEM). The coded work histories were transformed into exposure indices of 50 chemical agents or other job characteristics with the help of the JEM constructed in Southampton, UK (Pannett et al., 1985). The JEM included for each agent two calendar periods (cutpoint 1950), the probability of exposure (0=none/1=low/2=high), and the level of exposure (0=none/1=low/2=high). Each case and control was assigned to exposure categories defined by the combination of the probability and level of exposure. For example, the assignment to category 2211 for some agent means that the worker is considered to have had a high probability and level of exposure before 1950 and a low probability and level after 1950. To condense the data for the analysis the category with zero probability and zero level before and after 1950 was labeled “no” exposure, high probability and high level before 1950 or/and after 1950 “substantial” exposure, and the remaining exposure categories “low”.

A third exposure analysis (“IH reanalysis”) was a dose-response analysis of the agents that were associated with excess risk of pancreatic cancer in previous analyses. Two industrial hygienists reclassified all subjects to exposure categories none/light/moderate/heavy. Assignment to heavy category required at least 10 years in high level of exposure, moderate less than 10 years in high level of exposure or at least 10 years in low level of exposure, and light less than 10 years in low level of exposure.

All coding of exposures of the industrial hygienists was done without knowing of the cancer site. Exposures were assessed up until end of 1974 to allow for an induction period of at least 10 years between exposure and end of follow-up (time of diagnosis for the cases).

### 4.1.2 Statistical methods

Unconditional logistic model was applied using the SAS program. All odds ratios (ORs) and 95% confidence intervals (CIs) for pancreatic cancer are adjusted for age (year), gender, smoking in the 1960s (no/yes), total alcohol consumption in the 1960s (five-category ordinal scale), and diabetes (no/yes); and all controls were pooled. Total alcohol consumption was coded as following: zero, if (spirits is none [wine/beer is none or moderate or much or unknown]) or (spirits is unknown and wine/beer is none); one if (spirits is moderate and wine/beer is none); two, if (spirits is moderate and [wine/beer is moderate or much or unknown]) or (spirits is unknown and [wine/beer is moderate or unknown]); three, if (spirits is much and [wine/beer is none or moderate or unknown]); four, if (spirits is much and wine/beer is much) or (spirits is unknown and wine/beer is much).

## 4.2 Meta-analysis

### 4.2.1 Materials

#### *Study identification and study selection*

A literature search of cohort, linkage, proportional, and case-control studies have performed in any language with data on occupations, occupational exposures, and pancreatic cancer in Medline, Toxline, and Cancerlit databases for the period 1969 to May 1998, with the following search conditions:

- (1) (occupational OR agriculture) AND neoplasms AND morbidity
- (2) (occupational OR agriculture) AND neoplasms AND mortality NOT morbidity
- (3) (occupational OR agriculture) AND neoplasms AND incidence NOT mortality NOT morbidity
- (4) (pancreatic OR digestive) AND occupational
- (5) (pancreatic OR digestive) AND case AND (control OR referent)

Studies from the reference lists of identified studies were also searched.

#### *Data extraction*

Appendix 1 shows the standardized data extraction form covering descriptors of the study, relative risk estimates, latency periods, and numbers of exposed cases. Five epidemiologists examined the reports and extracted the necessary data, using predefined rules and selecting the most unbiased estimates; choosing estimates adjusted for at least known risk factors for pancreatic cancer (age, gender, tobacco smoking), preferring social class adjusted relative risks over those unadjusted for social class and choosing relative risk estimates nearest to 20-y latency period. The extracted data were then centrally checked for consistency by two epidemiologists, and finally entered into a database and checked for correctness.

*Data analysis*

The studies were divided into (a) *agent-specific studies* with direct relative risk estimates for one or several of the 29 agents (Appendix 1), or for job titles with verified exposure(s) to the agent(s), and (b) *job-specific studies* without relative risk estimates for any of the selected agents but instead for one or more of the 150 job categories (Appendix 1), without verified exposure(s) to the agent(s). The agents were based on the Finnish job exposure matrix (FINJEM; Kauppinen et al., 1998). The list of job titles covered 150 entries in the Finnish social status classes 3, 4, and 5. Data for classes 1 and 2 represented the highest social classes and were excluded because the pertinent occupational chemical exposures were minimal or nonexistent. This exclusion may also have eliminated confounding from unknown determinants that may have been prevalent in high social classes.

Missing 95% CIs were recovered with Byar's approximation (Breslow and Day, 1997) in cohort studies, and using approximated estimates of variance of log odds ratio in case-control studies. The data was organized and analyzed by relative risk estimates rather than studies, since there were studies that considered more than one relative risk estimate separately (eg, genders, exposure or job title categories).

From the identified 1,903 studies, a total of 373 studies (112 agent studies and 261 job title studies) remained after the exclusions (Figure 3).

In the meta-analysis of occupational agents (Study II) 162 pancreatic cancer relative risk estimates were reported in 93 agent-specific studies, which represent 23 agents and over 2,836 pancreatic cancer cases. The 23 agents are shown in Table 6. One originally missing relative risk estimate for nickel (Shannon et al., 1991) has been added; see discussion of Seilkop (2001) and Ojajarvi and Partanen (2001).

The meta-analysis for chlorinated hydrocarbon solvents and related compounds (Study III) based on both the agent studies directly addressing exposure to one or several chlorinated hydrocarbon solvents and related compounds and the job title studies addressing to metal plating or dry cleaning, which represent the industries with the highest proportion of workers exposed to chlorinated hydrocarbons and related compounds. Data for chlorinated hydrocarbon solvents included 19 studies, 24 relative risk estimates and over 133 pancreatic cancer cases, and data for the two job titles in 22 studies, 35 relative risk estimates and over 519 pancreatic cancer cases.

The hierarchical Bayesian meta-analysis for job titles and agents (Study IV) was based on the data of 77 job title studies which represent 27 job titles, 151 relative risk estimates and over 3799 pancreatic cancer cases. At an agent data level, FINJEM (Kauppinen et al., 1998) provided proportions of exposed workers for the selected nine occupational agents in 27 job titles (Table 6). For the relative risk estimates of the individual studies, the results were coded into these job categories. The nine were selected because their meta-relative risks in Study II exceeded 1.1.

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**TABLE 6.** Agents included in the meta-analysis of occupational agents (Study III), and of job titles and agents in the hierarchical Bayesian meta-analysis (Study IV).

---

### *Agents, Study III:*

- |   |  |
|---|--|
| 1. Aliphatic and alicyclic hydrocarbon solvents                 | 12. Fungicides                               |
| 2. Aromatic hydrocarbon solvents (excluding aromatic amines)    | 13. Gasoline                                 |
| 3. Arsenic  | 14. Herbicides                               |
| 4. Asbestos   | 15. Insecticides                             |
| 5. Cadmium and cadmium compounds                                | 16. Iron and iron compounds                  |
| 6. Chlorinated hydrocarbon (CHC) solvents and related compounds | 17. Lead and lead compounds                  |
| 7. Chromium and chromium compounds                              | 18. Man-made vitreous fibers                 |
| 8. Diesel engine exhaust  | 19. Nickel and nickel compounds              |
| 9. Electromagnetic fields                                       | 20. Oil (including fluid, and cutting fluid) |
| 10. Flour dust  | 21. Polycyclic aromatic hydrocarbons (PAH)   |
| 11. Formaldehyde  | 22. Silica dust                              |
|   | 23. Wood dust                                |
- 

### *Job titles, Study IV:*

- |   |   |
|---|---|
| 1. Asphalt/highway workers                                  | 14. Machine / engine mechanics              |
| 2. Bench carpenters   | 15. Metal plating workers                   |
| 3. Bricklayers/plasterers/tile setters                      | 16. Metal smelting furnacemen               |
| 4. Cabinetmakers/joiners                                    | 17. Miners/shotfirers/quarry workers        |
| 5. Concrete mixer operators/ product workers/cement workers | 18. Painters/lacquered/floor layers         |
| 6. Concrete shutterers/finishers                            | 19. Plywood/fiberboard workers              |
| 7. Construction carpenters                                  | 20. Printers/pressmen/newspaper workers     |
| 8. Construction workers unspecified                         | 21. Sawyers                                 |
| 9. Electric machine operators                               | 22. Sheet metal workers                     |
| 10. Farmers   | 23. Smiths                                  |
| 11. Fitters/ assemblers                                     | 24. Stone cutters                           |
| 12. Foundry workers   | 25. Timbermen/lumbermen                     |
| 13. Laundry and dry cleaning workers                        | 26. Turners/toolmakers/machine-tool setters |
|   | 27. Wood working machine operators.         |
- 

### *Agents, Study IV:*

- |  |   |
|--|---|
| 1. Aliphatic and alicyclic hydrocarbon solvents (ALHC) | 5. Insecticides (INSC)                    |
| 2. Chlorinated hydrocarbon compounds (CHC)             | 6. Nickel and nickel compounds (NI)       |
| 3. Chromium and chromium compounds (CR)                | 7. Polycyclic aromatic hydrocarbons (PAH) |
| 4. Fungicides (FUNG)                                   | 8. Silica dust (SIL)                      |
|  | 9. Wood dust (WOOD).                      |
-

## MATERIALS AND METHODS

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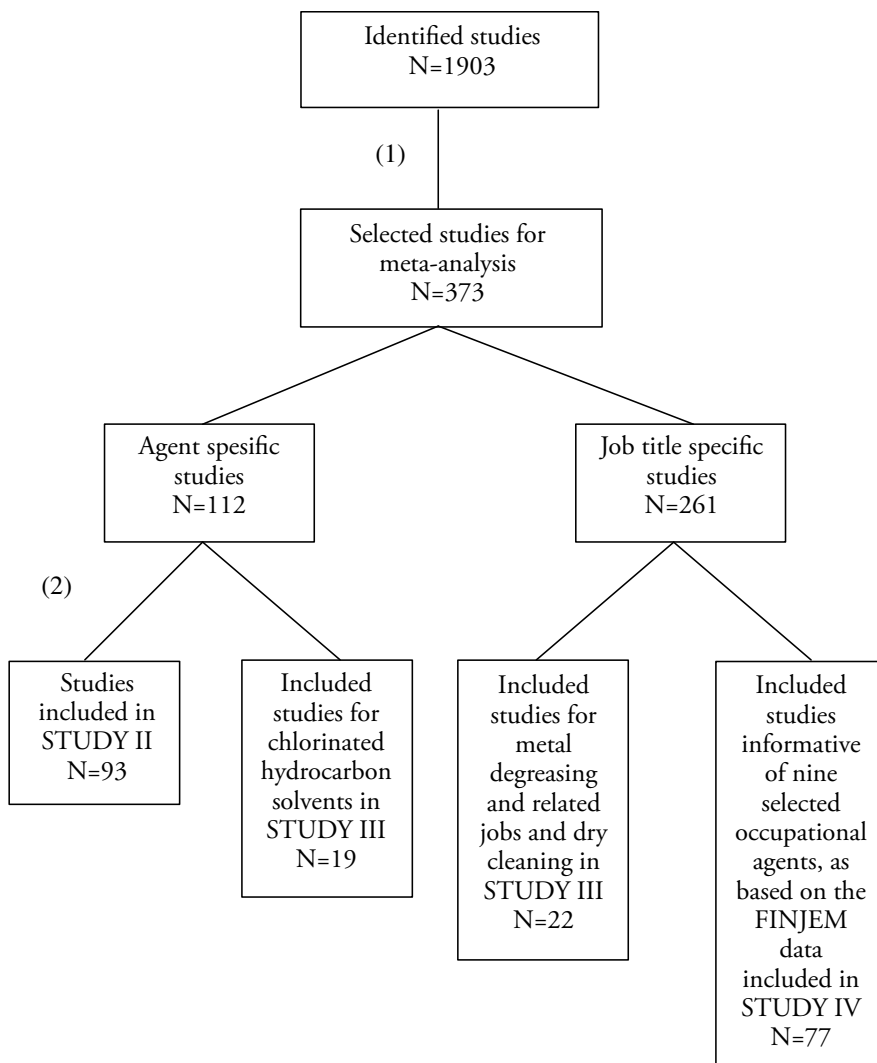


FIGURE 3. Flow diagram of the meta study

- (1) Excluded: studies that did not report on pancreatic cancer; did not represent the most recent update; reported insufficient data for the meta-analysis; did not report data for any job or occupational agent; did not report original results (reviews); reported on part of a larger population reported elsewhere; or reported on job categories or agent categories too broad or outside our list of job titles and agents.
- (2) Excluded all (10) ionizing radiation, radon and nine insecticide studies.

### 4.2.2 Statistical methods

#### *Meta-analysis of non-experimental data*

Meta-analysis is a statistical analysis which combines the results of several independent studies. This is a meta-analysis of non-experimental studies.

TABLE 7. The notation used in the meta-analytic models

$i$	index of relative risk estimates
$j$	index of parameters
$M$	number of relative risk estimates
$N$	number of parameters
$RR_i$	observed estimate of relative risk for relative risk estimate $i$
$RR_{Li}$	95% lower confidence limit of $RR_i$
$RR_{Ui}$	95% upper confidence limit of $RR_i$
$y_i$	observed $\ln(RR_i)$ of relative risk estimate $i$
$\theta_i$	true $\ln(RR_i)$ of relative risk estimate $i$
$s_i^2$	variance of $\ln(RR_i)$ for relative risk estimates $i$
$\sigma_\theta^2$	between-risk-estimates variance
$x_{ij}$	element of $M \times N$ relative risk estimate parameter matrix
$\beta_j$	mean of $\ln(RR_i)$ for parameter $j$

The formula of meta-analysis model is

$$(1) \quad \begin{aligned} y_i &= \theta_i + e_i \\ \theta_i &= \sum_j x_{ij} \beta_j + \varepsilon_i \\ e_i &\sim \text{Normal}(0, s_i^2) \\ \varepsilon_i &\sim \text{Normal}(0, \sigma_\theta^2), \end{aligned}$$

where  $s_i^2 = \ln(RR_{Li} / RR_{Ui}) / 3.92$ . If number of parameters  $N$  and  $x_{ij}$  are 1's and  $\sigma_\theta^2 = 0$  in the formula (1) indicating homogeneity between observed risk estimators, then the meta-analysis model is a *simple fixed effects model*, and if  $\sigma_\theta^2 > 0$  then the model is a *simple random effects model*. If  $N > 0$  and  $\sigma_\theta^2 = 0$ , the model is a *fixed effects meta-regression model*, and if  $N > 0$  and  $\sigma_\theta^2 > 0$ , the model is a *random effects meta-regression model*. Random effects models for meta-analysis are 2-level hierarchical models.

Making distributional assumptions for  $\beta_j$  and  $\sigma_\theta^2$

$$(2) \quad \begin{aligned} \beta_j &\sim p(\beta_j) \\ \sigma_\theta^2 &\sim p(\sigma_\theta^2), \end{aligned}$$

the model is a hierarchical Bayesian (HB) model for meta-analysis.

*Bayesian theory and Markov chain Monte Carlo technique*

Let  $\mathbf{Y}$  denote the observed data and  $\boldsymbol{\psi}$  unknown parameters. Bayes's theorem is

$$p(\boldsymbol{\psi}|\mathbf{Y}) = \frac{p(\mathbf{Y}|\boldsymbol{\psi}) p(\boldsymbol{\psi})}{p(\mathbf{Y})}$$

where the conditional probability distribution of  $\boldsymbol{\psi}$  given  $\mathbf{Y}$ ,  $p(\boldsymbol{\psi}|\mathbf{Y})$ , is called the posterior probability distribution,  $p(\mathbf{Y}|\boldsymbol{\psi})$  is the likelihood,  $p(\boldsymbol{\psi})$  is the prior probability distribution, and the denominator is a normalizing constant (Gelman et al., 2003).

In Bayesian inference, there are possible point estimators for  $\boldsymbol{\psi}$ , namely, a posterior mean, a posterior median and a posterior mode. In Bayesian statistics, a posterior probability interval is called a credible interval (CrI) which is Bayesian analogue of a frequentist confidence interval (CI).

A Markov chain Monte Carlo (MCMC) algorithm is known as Gibbs sampling. MCMC methods are numerically approximated by constructing chains by starting different initial values by Gibbs sampling (Gilks et al., 1996) and simulating the chains. The convergences of the chains can be assessed by examining Monte-Carlo errors and Gelman-Rubin statistics (Brooks and Gelman, 1998).

Let  $R$  denote the number of draws  $\boldsymbol{\psi}^{(1)}, \boldsymbol{\psi}^{(2)}, \dots, \boldsymbol{\psi}^{(R)}$ . Let the parameter be  $\boldsymbol{\psi} = (\psi_1, \psi_2, \dots, \psi_s)$ . Initializing the MCMC method, the parameter  $\boldsymbol{\psi}$  gets any convenient starting value  $\boldsymbol{\psi}^{(0)}$ . After performing so called burn-in of  $T$  iterations, the parameter  $\boldsymbol{\psi}^{(t)}$  has approximately the chain's limiting distribution, where  $t = T+1, T+2, \dots, T+M$ . The length of the burn in  $T$  depends on the starting value  $\boldsymbol{\psi}^{(0)}$  and the convergence of the parameter  $\boldsymbol{\psi}$ . The convergence of the parameter  $\boldsymbol{\psi}$  can be checked graphically in single-chain methods, and statistically in multi-chain methods such as a Monte Carlo error and Gelman-Rubin statistics (Brooks and Gelman, 1998). The Gibbs sampler starts with an initial value, and the convergence of the parameter  $\boldsymbol{\psi}^{(0)}$  has the following iterative procedure:

Draw  $\psi_1^{(1)}$  from  $p(\psi_1 | \psi_2^{(0)}, \psi_3^{(0)}, \dots, \psi_s^{(0)}, \mathbf{Y})$   
 Draw  $\psi_2^{(1)}$  from  $p(\psi_2 | \psi_1^{(1)}, \psi_3^{(0)}, \dots, \psi_s^{(0)}, \mathbf{Y})$   
 .  
 .  
 Draw  $\psi_s^{(1)}$  from  $p(\psi_s | \psi_1^{(1)}, \psi_2^{(1)}, \dots, \psi_{s-1}^{(1)}, \mathbf{Y})$   
 Draw  $\psi_1^{(2)}$  from  $p(\psi_1 | \psi_2^{(1)}, \psi_3^{(1)}, \dots, \psi_s^{(1)}, \mathbf{Y})$   
 .  
 .  
 and so on.

After each iteration there are new values for all elements of  $\boldsymbol{\psi}$ . One iteration consists of  $s$  draws from one-dimensional full conditional distribution. A unique limiting distribution for the Gibbs sampler is a full joint posterior distribution  $p(\boldsymbol{\psi} | \mathbf{Y})$ .

*Applications of meta-analysis for occupational data*

In the agent specific meta-analysis (Study II) and in the meta-analysis for chlorinated hydrocarbon solvents and related compounds (Study III), simple random effects (RE) models were applied for estimating the meta relative risks (MRRs), implying that  $\sigma_\theta^2$  is greater than zero in formula (1), and the weight of population  $i$  is  $1/(s_i^2 + \sigma_\theta^2)$ . The between-risk-estimate variance  $\sigma_\theta^2$  was estimated using the method proposed by DerSimonian and Laird (1986). In Study III for trichloroethylene and methylene chloride data, random effects linear meta-regression models were applied for log relative risk, implying that  $x_{ij}$  is a dose in formula (1).

Study IV is a first application of hierarchical Bayesian methods of meta-analysis on published epidemiological studies that associated the risk of pancreatic cancer with occupations, using higher-level data for occupational agents. Two different hierarchical Bayesian models for job titles (lower-level) and occupational agents (higher-level) were used. Non-Bayesian simple random effects models for job titles were also applied to check consistency with Bayesian results. A Finnish job-exposure matrix (FINJEM) provided the higher-level data (Kauppinen et al., 1998). This is a hierarchical Bayesian meta-analysis of occupations and pancreatic cancer based on studies that addressed to job title studies.

In the HB models let  $i = 1, \dots, M$  denotes the index of relative risk estimates from studies. Let  $j = 1, \dots, N$ ,  $k = 1, \dots, O$ , and  $l = 1, \dots, P$  denote the index of job titles, covariates, and agents, respectively. The number of relative risk estimates ( $M$ ) was 151, the number of job titles ( $N$ ) 27, the number of covariates ( $O$ ) five, and the number of occupational agents ( $P$ ) eight.

In the HB models  $x_{ij}$  is the element of relative risk estimates-job  $M \times N$ -matrix with the value of unity when relative risk estimates ( $RR_i$  and  $s_i$ ) were available for job  $j$  and zero

otherwise;  $w_{ik}$  is the element of relative risk estimates-covariate  $M \times O$ -matrix of 1:s and 0:s; and  $z_{jl}$  is s element of the job-exposure  $N \times P$ -matrix which comes from FINJEM. The relative risk estimate-covariate matrix included five dichotomized covariates: study type (case-control vs. cohort), publication year (cutpoint 1990), diagnosis of pancreatic cancer (histological vs. other), country (Denmark, Finland, Norway and Sweden vs. others) and time reference for job title (longitudinal vs. other). Appendix 2 shows job-exposure matrix used in the hierarchical Bayesian models where  $z_{jl}$  is the element of job-exposure  $N \times P$ -matrix, i.e., the proportion of exposed, as provided by FINJEM if over 20% of the workers in job category  $j$  were exposed to agent  $l$  on the period 1960-85 and zero otherwise.

Let  $\beta_j$  denote the parameter of job  $j$  representing the mean log of relative risks for job  $j$  for all studies combined and  $\sigma_\beta^2$  the variance of parameter  $\beta_j$ . Let  $\gamma_k$  denote the mean log of relative risks for covariate  $k$  for all studies combined, and  $\mu_\gamma$  and  $\sigma_\gamma^2$  its mean and variance, respectively. Let  $\pi_l$  denote the mean log of relative risks for agent  $l$  for all studies combined and  $\mu_\pi$  and  $\sigma_\pi^2$  its mean and variance, respectively. Let  $\text{Normal}(\mu, \sigma^2)$  denote the normal distribution with mean  $\mu$  and variance  $\sigma^2$ . Let  $\text{Gamma}(a, b)$  denote the gamma distribution with mean  $ab$  and variance  $ab^2$ .

The hierarchical Bayesian method of meta-analysis for job titles and occupational agents there were following distributional assumptions:

$$(3) \quad \begin{aligned} y_i &\sim \text{Normal}(\theta_i, s_i^2), & i=1, \dots, M \\ \theta_j &\sim \text{Normal}(\sum_j x_{ij} \beta_j + \sum_k w_{ik} \gamma_k, \sigma_\theta^2), & i=1, \dots, M; j=1, \dots, N; k=1, \dots, O \\ \beta_j &\sim \text{Normal}(\sum_l z_{jl} \pi_l, \sigma_\beta^2), & j=1, \dots, N; l=1, \dots, P \end{aligned}$$

and prior normal distributions for  $\gamma_k$  and  $\pi_l$

$$(4) \quad \begin{aligned} \gamma_k &\sim \text{Normal}(\mu_\gamma, \sigma_\gamma^2) & k=1, \dots, O \\ \pi_l &\sim \text{Normal}(\mu_\pi, \sigma_\pi^2), & l=1, \dots, P \end{aligned}$$

and prior gamma distributions to the precisions  $1/\sigma_\theta^2$  and  $1/\sigma_{\beta_j}^2$

$$(5) \quad \begin{aligned} 1/\sigma_\theta^2 &\sim \text{Gamma}(a, b) \\ 1/\sigma_{\beta_j}^2 &\sim \text{Gamma}(c, d) & j=1, \dots, N \end{aligned}$$

Figure 4 shows the directed acyclic graph (DAG), which represents equations (3)-(5). In the DAG single boundary squares contain observed data (relative risk estimates, job titles, and covariates from observed data and agents from FINJEM data). The circles represent unknown and must be estimated. The double squares are fixed parameters of prior distributions. The full arrows represent stochastic relationships and the dashed arrows functional relationships. The shaded nodes are normally distributed and these distributions are represented in the equations (3) and (4) and the non shaded circle nodes are gamma distributed with fixed parameters in the equation (5).

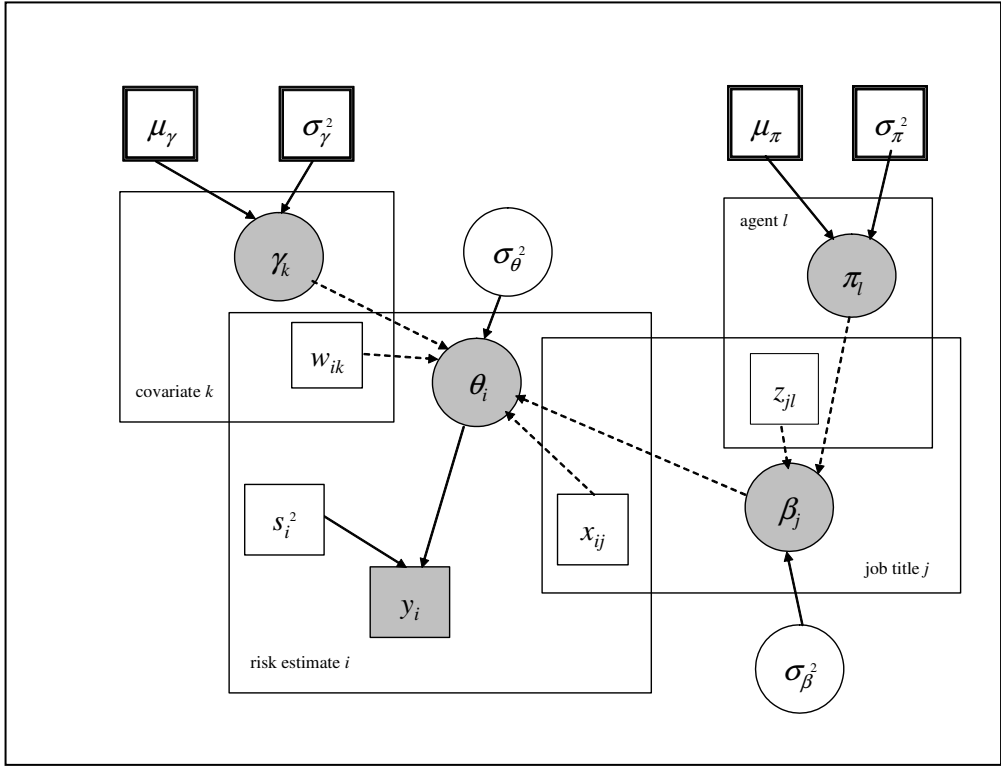


FIGURE 4. A directed acyclic graph for applying hierarchical Bayesian meta-analysis with data from FINJEM.

In both HB models the fixed parameters of prior distributions assumed to be followings:  $\mu_\gamma = \mu_\pi = 0$  and  $\sigma_\gamma^2 = \sigma_\pi^2 = 1$ . The following assumptions were made for gamma distributions in equation (5):

- HB model 1:  $a = b = c = d = 0.1$  meaning that the priors for the precisions are diffuse (Congdon, 2003)
- HB model 2:  $a = c = 0.001$  and  $b = d = 1$  meaning that the priors for precisions are quite diffuse or reasonable (Congdon, 2003; Wakefield, 2004).

A test of heterogeneity between studies was performed as a  $\chi^2$ -test with degrees of freedom less than the number of observed relative risk estimates for each agents in Study II and III, and for each job titles in Studies III and IV. Both the Egger's regression asymmetry test (Egger et al., 1997) and the Begg's adjusted rank correlation test (Begg and Mazumdar, 1994) were used to formally test publication bias in all meta-analyses. The statistical software package Stata 8 for Windows was used (Sharp and Stern 1997) in all simple

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random effects models for meta-analysis and random effects meta-regression models. In Study IV the MCMC methods constructing two chains starting different initial values by Gibbs sampling (Gilks et al., 1996). Chains were simulated by using the WinBUGS software (Spiegelhalter et al., 1999). The convergences of the chains were assessed by examining Monte-Carlo errors and Gelman-Rubin statistics (Brooks and Gelman, 1998). The WinBUGS program version 1.3 being freely available from <http://www.mrc-bsu.cam.ac.uk/bugs> was used in the hierarchical Bayesian models.

In the meta-analysis, the random-effects meta-estimates for job titles (Studies III and IV) and agents (Studies II and III) are calculated without covariates. In Study IV, the hierarchical Bayesian models for meta-analysis included five covariates (study type, publication year, diagnosis of pancreatic cancer, country, and time reference for job title). Antilogs of posterior medians were calculated as MRRs in Study IV, since the posterior median is preferable over posterior mean in preserving the antilog transformation.

## 5. RESULTS

### 5.1 Background data

#### 5.1.1 Case-control study

Table 8 describes the distribution of a number of background factors and potential confounders. The distributions of gender, age, obesity, and sugar consumption were very similar between the cases and the controls. The main differences were found in the higher proportion of cases consuming substantial alcohol, smoking over 20 cigarettes/day, and having history of biliary stones, diabetes, and pancreatitis.

TABLE 8. Distribution of some background factors between cases and controls in Study I.

Factor	Cases	Controls
Gender (men) %	61	62
Birth year: Mean (SD)	1922 (8)	1921 (8)
Obesity in 1960s (rather fat or fat) %	23	22
Coffee consumption in 1960s (over 6 cups/day) %	18	20
Sugar consumption (much in 1960s) %	13	13
Spirits (much in 1960s) %	8	6
Wine/beer (much in 1960s) %	8	4
Smoking (yes in 1960s) %	57	44
Smoking (over 20 cigarettes/d in 1960s) %	13	9
Biliary stones (ever) %	18	14
Diabetes (ever) %	13	10
Pancreatitis (diagnosed after 1982, ever) %	2	1

#### 5.1.2 Meta-analyses

In the meta-analyses, most observed relative risk estimates (in total 164 in Studies II and IV) were from Europe, closely followed by North America (135 relative risk estimates; Table 9). There were few studies from Central and Eastern Europe, Oceania and Asia, and none from Middle and South America or Africa. The annual number of studies was rising considerably during 1969-1998 (nine relative risk estimates during 1969-79 in Studies II and III; 98 relative risk estimates during 1980-89, and 206 relative risk estimates during 1990-98)

The agent specific meta-analyses (Study II) included predominantly industrial cohort studies (89 observed relative risk estimates), while the bulk of job title studies in Study VI were record linkage studies entirely based on linkage of extraneous databases on job

## RESULTS

titles (eg, census) and on outcomes (eg, death records; Table 10). Most studies addressed men; only 7% of observed relative risk estimates were for women. The cases represented all pancreatic cancers, irrespective of type. As most studies considered mortality, the diagnosis was in most observed relative risk estimates obtained from the death record. Exposure assessment was longitudinal for 128 relative risk estimates in Study II; job assessment was longitudinal for 107 relative risk estimates in Study IV.

**TABLE 9.** Distribution of observed relative risk estimates studied in Studies II-IV by location and publication year. Numbers are observed relative risk estimates.

	Study II	Study III		Study IV
		Agent	Job title	
<b>LOCATION</b>				
Denmark	2	-	5	10
Finland	17	1	2	23
Iceland	-	-	-	1
Norway	3	-	-	4
Sweden	7	1	1	18
Nordic	3	1	-	-
France	1	-	-	6
The Netherlands	2	-	-	2
U.K.	18	3	2	10
Czech Republic	-	-	-	1
Germany	3	-	-	2
Switzerland	-	-	-	4
Italy	10	-	-	14
Poland	1	-	-	-
USSR/Russia	1	1	-	-
Canada	23	3	2	3
U.S.A.	63	13	20	44
Canada and U.S.A.	-	-	-	1
Japan	3	1	3	3
Australia	1	-	-	1
New Zealand	-	-	-	2
U.K. and U.S.A.	-	-	-	2
Multiple countries	3	-	-	-
<hr style="border-top: 1px dashed black;"/>				
<b>PUBLICATION YEAR</b>				
1969-1979	2	-	-	7
1980-1989	58	8	19	40
1990-1998	102	16	16	104
<b>TOTAL</b>	<b>162*</b>	<b>24</b>	<b>35</b>	<b>151</b>

\* One study added (Shannon et al. 1991)

## RESULTS

**TABLE 10.** Characterization of the meta-analysis studies (Studies II-IV). Numbers are observed relative risk estimates, OR=odds ratio, SIR=standardized incidence ratio, SMR=standardized mortality ratio, HR=hazard ratio, RR=risk ratio, MOR=mortality odds ratio, PMR=proportional mortality ratio, and PCMR= proportional cancer mortality ratio.

	Study II	Study III		Study IV
		Agent	Job title	
<u>Study type</u>				
Record linkage	23	4	23	69
Industry cohort	89	16	8	67
Industry based (nested) case-control	7	1	-	-
Population or hospital based case-control	43	3	4	15
<u>Gender</u>				
Men	113	17	22	116
Women	8	4	9	13
Both gender or unspecified	41	3	4	22
<u>Cases</u>				
Exocrine pancreatic cancer only	32	4	-	5
All pancreatic cancers	128	19	32	135
Unspecified	2	1	3	11
<u>Diagnosis of cases</u>				
Histological	47	4	5	27
Other (clinical: radiology, necropsy, etc)	2	1	-	1
Mortality files	97	18	26	79
Mixed	9	-	-	21
Unknown	7	1	4	23
<u>Ascertainment of case</u>				
Mortality files	99	19	27	77
Cancer registry files	40	3	7	57
Hospital regards	21	2	-	7
Mixed	1	-	1	9
Unknown	1	-	-	1
<u>Risk measure</u>				
OR	50	3	1	15
SIR	17	3	4	54
SMR	70	13	6	69
HR	3	-	-	-
RR	4	1	3	23
MOR	-	-	3	-
PMR	18	4	14	-
PCMR	-	-	4	-
<u>Time reference for exposure/job title</u>				
Last or around diagnosis	17	2	3	8
Earlier cross-section	9	-	6	28
Lifetime longitudinal	47	2	-	4
Less than lifetime longitudinal	81	16	22	103
Other	1	1	-	-
Unknown	7	3	6	8
TOTAL	162*	24	35	151

\* One study added (Shannon et al. 1991)

## 5.2 Results of occupational determinants

### 5.2.1 Occupations

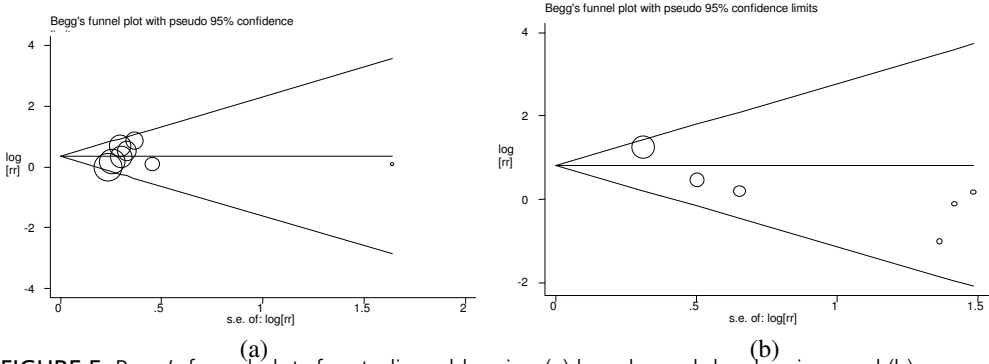
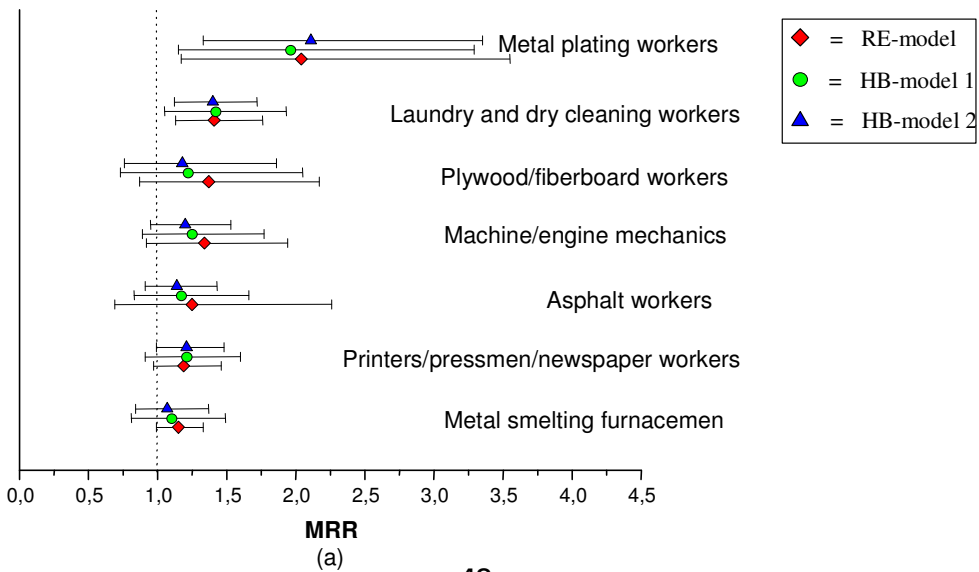
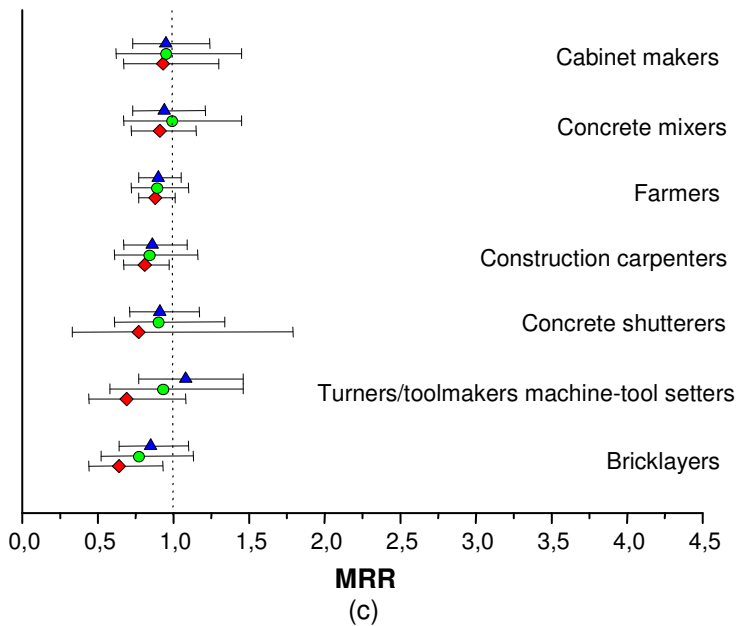
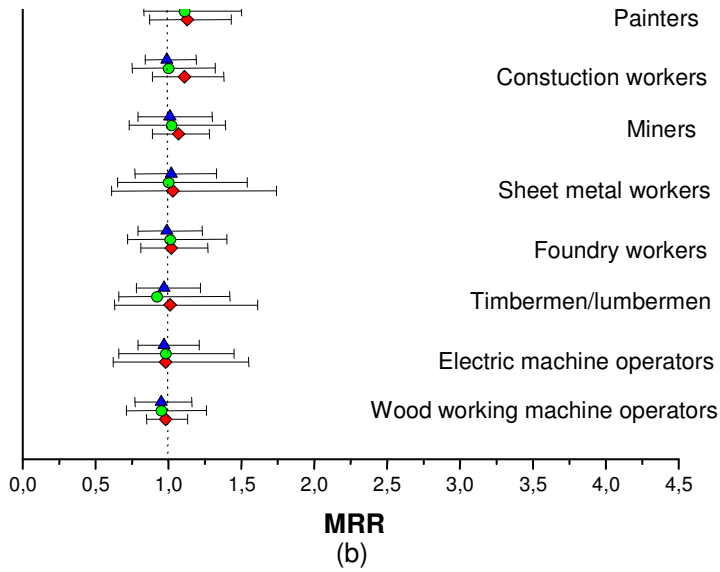


FIGURE 5. Begg's funnel plots for studies addressing (a) laundry and dry cleaning, and (b) metal plating workers: The sizes of graphic symbols representing the data are proportional to the inverse variance.  $\log[rr]$  is natural logarithm of relative risk and s.e. of  $\log[rr]$  standard error of natural logarithm of relative risk.

In Study IV, an evidence of heterogeneity in the relative risk estimates was found for studies addressing to asphalt workers, farmers, painters, and sawyers. Between-study heterogeneity was addressed by using random effects model. Testing publication bias with Begg's and Egger's test it was suspected only for studies addressing metal plating workers. Figure 5 shows Begg's funnel plot studies addressing (a) laundry and dry cleaning, and (b) metal plating workers. In the Figure 5 (b), there is an evidence of publication bias, while the other (a) appears unbiased.



## RESULTS



**FIGURE 6.** Results of 22 job titles from random effects (RE) and hierarchical Bayesian (HB) models for meta-analysis (MRR, meta relative risk, antilog of median).

## RESULTS

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In Study IV, the MRRs exceeded unity for 12 out of the total of 27 job titles in all meta-analyses, including the non-Bayesian and Bayesian models. In the RE models, MRRs exceeded unity in 16 job titles. For three job titles (metal plating workers, laundry and dry cleaning operators, and printers/pressmen/newspaper workers), MRRs were higher in one or the other of the two HB models. The remaining 11 job titles had MRRs <1 in the RE models. The MRRs were smaller in the HB models than in the RE model for wood working machine operators only.

The results of 22 job titles including more than one observed relative risk estimate are shown in Figure 6 where job titles with highest MRRs are in section (a) and lowest in section (b). The highest MRRs were found for studies addressing metal plating workers in HB model 2 (MRR 2.1, 95% CrI 1.3-3.4), in HB model 1 (MRR 2.0, 95% CrI 1.2-3.2), and in RE model (MRR 2.0, 95% CI 1.2-3.6), based on one OR, three SIR/SMR, and one RR estimates. The second highest excesses were found for studies on laundry and dry cleaning workers in HB model 1 (MRR 1.4, CrI 1.1-1.9), in HB model 2 (MRR 1.4, 95% CrI 1.1-1.8), and in RE model (MRR 1.4, 95% CI 1.1-1.8); seven SIR/SMR relative risk estimates. A decreased risk was found for bricklayers in RE model (MRR 0.6, 95% CI 0.4-0.9), in HB model 1 (MRR 0.8, 95% CrI 0.5-1.1), and in HB model 2 (MRR 0.9, 95% CrI 0.6-1.1).

### 5.2.2 Occupational agents

Table 11 presents selected results of occupational agents of the case-control study (Study I) and the meta-analysis (Studies II-IV). No strong associations with results for particular agents were shared by the case-control study and in the meta-analysis.

#### *Case-control study*

The highest excess risks for pancreatic cancer were found for exposure to aliphatic and alicyclic hydrocarbons (OR 1.6, 95% CI 1.0-2.6) and aromatic hydrocarbons (1.8, 1.1-2.8) in the IH reanalysis; ionizing radiation (4.3, 1.6-11) in the JEM analysis; and inorganic mineral dust in both the IH survey (2.0, 1.2-3.5) and in the JEM analyses (2.6, 1.5-4.8). In the IH survey an excess risk was found for high exposure to organic solvents (2.0, 1.0-4.1) and to pesticides (1.6, 0.8-3.4). Using colon cancer controls in the IH survey an excess risk for exposure to pesticides was higher (4.8, 1.1-22). Excesses over OR>1.3 and lower 95% CI>0.9 were found for acrylonitrile, chromium and high temperature on the JEM analysis. A strong negative association between pancreatic cancer and exposure to asbestos was found in the IH-survey analysis.

The corrected results for all solvents in IH survey analysis (Table 2 in Study I) are OR 1.38, 95% CI 0.89-2.13, with number of exposed cases 34.

## RESULTS

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### *Meta-analysis*

In Study II an evidence of heterogeneity in the estimates of relative risks across studies was found for studies addressing asbestos, electromagnetic fields, chlorinated hydrocarbon compounds, and man-made vitreous fibers. Between-study heterogeneity was addressed by using random effects model. Testing publication bias with Begg's and Egger's tests studies did not suggest publication bias for any agent.

Observed relative risk estimates and results by occupational agents and study types from Study II are shown in Appendix 3. In Study II, the highest excesses were found for chlorinated hydrocarbon compounds in the RE model (MRR 1.4, 95% CI 1.0-1.8; 20 relative risk estimates) and for nickel and nickel compounds (MRR 1.7; 95% CI 1.1- 2.5; five relative risk estimates; re-estimated including results of Shannon et al., 1991). For nickel the MRR was highest for case-control studies (MRR 2.0, 95% CI 1.2-3.2; two relative risk estimates: Appendix 3). In Study IV, excesses were found for chlorinated hydrocarbon compounds in HB model 1 (MRR 2.0, 95% CrI 1.0-4.1) and in HB model 2 (MRR 2.2, CrI 1.3-3.7), but the MRRs for nickel were only 1.0 and 1.2 in HB models 1 and 2, respectively. The MRRs and 95% CrIs for insecticides were in HB models 1 and 2 (MRR 1.5; 95% CrI 0.3-7.1) and (MRR 2.0, 95% CrI 0.5-7.4), respectively, and the result of the RE model was (MRR 1.5; 95% CI 0.6-3.7; three relative risk estimates).

In Study II, a high excess risk was found for SIR/SMR studies on asbestos (MRR 1.2, 95%CI 1.0-1.5; 20 relative risk estimates), whereas the case-control studies resulted in an MRR of 0.7 (95% CI 0.5-1.0; four relative risk estimates). An excess was found also for SIR/SMR studies for chromium and chromium compounds (MRR 2.3, 95% CI 0.9-5.8; six relative risk estimates) and for OR studies the MRR was 1.0 and 95% CI 0.7-2.0 based on three relative risk estimates. In the Study IV, the MRRs for chromium were 1.0 and 1.1 in the HB model 1 and 2, respectively.

RESULTS

TABLE 11. Results of occupational agents for the case-control study and the meta-analysis study.

AGENT	Case-control study:		Meta-analysis study:			
	Study I MRR* (95% CI)		Random effects models: Study II MRR (95% CI)	Study III MRR (95% CrI*)	Hierarchical Bayesian models: Model I MRR (95% CrI)	Study IV Model
Organic solvents	JEM* 1.3 (0.9-2.0)		-	-	-	-
Acrylonitrile	JEM: 2.1 (0.9-4.7)		-	-	-	-
Aliphatic alicyclic hydrocarbons	IH*: 1.6 (1.0-2.6)		1.3 (0.8-2.0)	-	1.1 (0.7-1.9)	1.1 (0.8-1.5)
Aromatic hydrocarbons	IH: 1.8 (1.1-2.8)		1.3 (0.9-1.7)†	-	-	-
Chlorinated hydrocarbons	IH: 1.1 (0.5-2.6)		1.4 (1.0-1.8)	-	2.0 (1.0-4.1)	2.2 (1.3-3.7)
Trichloroethylene	-		-	1.2 (0.8-2.0)	-	-
Methylene chloride	-		-	1.4 (0.8-2.5)	-	-
Vinyl chloride	-		-	1.2 (0.7-1.9)	-	-
Polychlorinated biphenyls	-		-	1.4 (0.6-3.3)	-	-
Other organic solvents	IH: 1.6 (0.9-6.0)		-	-	-	-
Organic dust	JEM: 1.0 (0.8-1.3)		-	-	-	-
Wood dust	IH: 1.3 (0.8-2.1)		1.2 (0.9-1.6)	-	1.0 (0.7-1.3)	1.0 (0.8-1.2)
Inorganic mineral dust	IH: 2.0 (1.2-3.5)		-	-	-	-
Asbestos	IH: 0.6 (0.4-0.9)		1.2 (1.0-1.5)§	-	-	-
Silica dust	-		1.4 (0.9-2.0)	-	0.9 (0.7-1.2)	0.9 (0.7-1.1)
Metals						
Chromium	IH: 0.9 (0.4-2.0)		2.3 (0.9-5.8)§	-	1.0 (0.5-2.3)††	1.1 (0.6-1.8)††
Lead	JEM: 1.4 (0.9-2.1)		1.1 (0.8-1.5)	-	-	-
Nickel	-		1.7 (1.1-2.5)#	-	1.0 (0.5-2.3)††	1.1 (0.6-1.8)††
Arsenic	JEM: 1.2 (0.9-1.8)		1.2 (0.5-2.6)**	-	-	-
Engine exhaust						
Polycyclic aromatic hydrocarbons	IH: 1.3 (0.7-2.6)		1.5 (0.9-2.4)	-	1.1 (0.8-1.6)	1.1 (0.9-1.5)
Pesticides	IH: 1.7 (0.8-3.4)		-	-	-	-
Fungicides	IH 1.4 (0.7-7.2)		1.3 (0.4-3.8)	-	1.1 (0.4-3.2)	0.9 (0.5-1.9)
Insecticides	-		1.5 (0.6-3.7)	-	1.5 (0.3-7.1)	2.0 (0.5-7.4)
Herbicides	JEM: 1.0 (0.8-1.2)		1.1 (0.8-1.5)§	-	-	-
Physical agents						
Ionizing radiation	JEM: 4.3 (1.6-11)		-	-	-	-
Ultraviolet light	JEM: 1.2 (0.8-1.9)		-	-	-	-

- Not estimated. \* OR, odds ratio; CI, confidence interval; MRR, meta relative risk; CrI, credible interval; JEM, job exposure matrix; IH, industrial hygiene expert assessment of exposures. † Estimate for both genders. § For cohort studies. # Re-estimated including results of Shannon et al. (1991). \*\*† For case-control studies. †† Nickel and chromium

## 6. DISCUSSION

In this study, excess risk of pancreatic cancer was confined to a small number of job titles, including metal plating workers, laundry and dry cleaning, plywood/fiberboard workers, machine/engine mechanics, asphalt workers printers/pressmen/newspaper workers, metal smelting furnacemen, and painters. These excesses were seen in all non-Bayesian and Bayesian meta-analyses. Heavy exposure to organic solvents and pesticides were consistently associated with pancreatic cancer. In addition, the non-Bayesian meta-analysis showed evidences of excess risks for occupational exposure to chlorinated hydrocarbon solvents and related compounds, and nickel and nickel compounds. The Bayesian meta-analysis for occupational exposure showed high excess risks to chlorinated hydrocarbon solvents and insecticides, but not for nickel. In Study II, there were only five studies addressing to nickel and all found an excess risk for pancreatic cancer. Workers exposing to nickel are exposed often also to other occupational agents such as chromium and chlorinated hydrocarbon solvents.

It appears that either environmental factors play a small etiologic role in the development of pancreatic cancer, or the involvement of yet unknown factors is high, or both. In addition, interactions between environmental and endogenous factors may be important in the etiology of pancreatic cancer.

### 6.1 Material and methods

The histological diagnosis of pancreatic cancer improves specificity and sensitivity (Engel et al. 1980; Mack, 1982). In addition to refinement of exposure assessment, endpoint delineation requires serious attention in pancreatic cancer epidemiology. Variations in diagnostic practices may obscure interpretations of differences in pancreatic cancer risk between populations and time periods. Of the histologically confirmed pancreatic cancer cases, 29 % may in fact not have originated in the pancreas (Lyon et al., 1989). Such misclassification rates induce biases in risk estimates for etiologic factors (Porta et al., 1994). For example, Garabrandt et al. (1993) compared, in a case-control study of pancreatic cancer, ORs for DDT family between cases representing death certificates and cases representing cytohistological verification. For death certificate cases the ORs ranged from 0.8 to 2.6 and for cytohistologically verified cases, from 15.4 to infinity. Similarly, in a study addressing the risk of pancreatic cancer associated with cigarette smoking, a substantial modification of risk by diagnostic certainty was observed (Silverman et al., 1996). Improved general diagnostic accuracy and homogeneous histologic and molecular-level subgroups of pancreatic cancer are expected to allow for an improvement in the assessment of etiologic factors (Jones et al., 1991).

### 6.1.1 Case-control study

The cases were all deceased, implying a high rate of autopsy and histological verification, thereby an enhancing diagnostic quality over preoperative diagnosis only. All endocrine pancreatic cancers were excluded (N=8).

Using cancer controls was based on the requirement of non-differential misclassification of determinant information. The control sites were selected to represent cancers with minimal occupational etiology. The selection was considered to increase the validity of the control entity, namely, representativeness of the controls in the industrial and occupational distributions of the source population, that is, occupationally active population. Use of cancer controls may result in effect masking if the control cancer shares an etiologic agent with the type of cancer under study. The likelihood of at least some exposures falling into this category cannot thus be ruled out.

Homogeneity of exposures is a prerequisite for meaningful determinant categories but is subject to tradeoff with study size. It presumably varied between branch, job and agent entities. Detailed more homogeneous categories could not be used, as the numbers would have dwindled rapidly. Three levels (light/moderate/heavy) were therefore adopted. Number of exposed cases varied by agent.

Forcing a number of potential confounders into the models controlled confounding. The major known confounders present in these data are included in the models, with the exception of diet, which was considered too unreliable to be ascertained in retrospect from the next-of-kin in a mail questionnaire. The dichotomous (yes/no in the 1960s) smoking variable may have left some residual confounding from smoking in some of the comparisons. Overall, confounding and control of confounding in studies of pancreatic cancer may present uncertainties, since the causes of this cancer are to an overwhelming degree unknown.

Nonresponse would bias results if it associated with the determinants under study. Response rate presumably depends on age, gender, and relation to study subject of the responder. The distributions of the responders in their relation to the study subjects were very similar between the cases and controls. This fact, combined with highly comparable age and gender distributions between the cases and the controls, and with the restriction that both the cases and the controls were decedents and contemporaneously diagnosed for cancer, makes it unlikely that response induced any serious asymmetry in response; hence, the likelihood of a serious bias in the results is low, and the major effect of response is reduction of effective study size.

In case-control studies of pancreatic cancer, it is difficult to avoid the use of proxy responders (Gold et al., 1985; Mack et al., 1986; Farrow and Davis, 1990), except in hospital-based prospective case-control studies (Clavel et al., 1989). The information provided by the next-of-kin is deficient to an unknown degree. Precision and accuracy may vary by branch, job title, number of jobs held by the study subjects, and time elapsed from job

assignment to questionnaire administration and, in addition, by age, gender, and relation to the subject of the responder. It has been reported (Lerchen and Samet, 1986) that wives may not completely report lifetime occupational histories provided by their husbands, but agreement improved substantially for reporting of the longest job held, which, in essence, was the one of interest in the present study. As all subjects for the present study were deceased cancer cases, we believe that the error distribution in the proxy information on job histories and confounders are similar between the cases and the controls. In both responses it may have an effect on the results and this is the weakness of this study. The implication is that any imperfections arising from a surrogate source of information would seem to add to overall imprecision of the occupational data, and some high excess risks may have been missed because of nondifferential errors. This may be compounded by the fact that we used a mail questionnaire, not a personal interview.

### **6.1.2 Meta-analysis**

Meta-analysis of non-experimental studies is becoming as common as of clinical trials. Several articles have discussed problems in non-experimental data (Morris, 1994; Wong and Raabe, 1998; Egger et al., 1998; Myers and Thompson, 1998). Most of occupational meta-analyses are aggregated non-experimental studies, usually cohort and/or case-control studies (McElvenny et al., 2004). Aggregating non-experimental studies, the main problems are combinability and heterogeneity of studies, study selection bias, publication bias, ecological bias, and confounding. Some meta-analyses reported between-study heterogeneity and yet used fixed effects models only, instead of random effects models.

#### *Combinability and heterogeneity*

Epidemiologic meta-analyses have imperfect combinability of results associated with different study types, methods, populations, exposure parameters and circumstances, and diagnostic specificities. In the meta-analyses, MRRs were calculated excluding the poor quality studies which represented proportional studies in the study design. Separate MRRs for cohort studies using internal controls, case-control studies, and SMR/SIR studies were calculated. Differences in results from different study types were not consistent. We therefore combined all study types in the hierarchical Bayesian meta-analysis. In the hierarchical Bayesian models, one covariate was study type (case-control vs. cohort).

Several studies were poorly characterized. There were even studies that did not specify whether the cohort consisted of men, women, or both. In the agent specific meta-analysis, the data were analyzed for known male and female relative risk estimates separately. Women were associated with slightly higher MRRs than men for chlorinated hydrocarbon compounds. There were only few studies for women in the job specific meta-analysis.

## DISCUSSION

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There was in all likelihood substantial heterogeneity across observed relative risk estimates in the quality and intensity of exposure and job title categories, in the intake route (respiratory, dermal, digestive) of exposure, time aspects of exposure (period, latency, duration, and intensity), applied scales of exposure, as well as in the quality of histological diagnosis of pancreatic cancer. Qualitative and quantitative differences in exposures have already been exemplified in connection with chlorinated hydrocarbon compounds and insecticides. Random effects models were used avoiding between-study heterogeneity. Based on a rough statistical test, heterogeneity in the estimates of relative risks was found for studies addressing to asbestos, electromagnetic fields, chlorinated hydrocarbon compounds, and man-made vitreous fibers in the agent specific study, and asphalt workers, farmers, painters and sawyers in the job specific study. As exposure levels were unknown, the problem of combining for different exposure levels and time parameters of exposure remain. These may weaken the results.

Some studies did not document exposure aspects at all, and no study provided a comprehensive documentation. Expert assessment, which represents an acceptable method of exposure assessment, was used in 25 relative risk estimates. Industrial hygiene measurements that represent a certain degree of objectivity were used as the prime source of exposure data in only four relative risk estimates. Exposure assessment based on job titles (57 relative risk estimates) is of lower quality, unless exposures happen to be highly homogeneous within job titles. In fact, some of the relative risk estimates represented rather homogeneous single-title cohorts.

Job exposure matrices (JEM) assess exposures better if the matrix is specific for branch, job title and even for company and time period. JEMs of variable degree of specificity were applied in 15 observed relative risk estimates. Most were relatively unspecific and thereby induced exposure misclassification. Misclassification, however, was likely to be non-differential, resulting in a tendency toward underestimation of the excess MRRs. However, Björk and Strömberg (2002) have reported that misclassification bias can occur in either direction. Multiple sources of exposure data were applied in 37 relative risk estimates. Agent specific and job title specific data were longitudinal in 128 and 112 relative risk estimates and lifelong in 47 and 4 relative risk estimates, respectively. The longitudinality of agents and job titles was thus well covered.

Misclassification rates for pancreatic cancer are marked, as noted earlier. In the agent specific meta-analyses, MRRs were higher for nine but lower for 10 relative risk estimates in which histological verification was applied, compared with no histological verification. Few job title studies had histological verification. In the simple job title RE meta-analyses, job specific MRRs were higher in eight and lower in seven relative risk estimates in which histological was applied (unpublished results). The results of meta-analyses did not differ between histological and non-histological diagnoses of pancreatic cancer.

## DISCUSSION

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### *Publication bias*

Nonpositive occupational findings from small studies were not likely to remain unpublished. Publication bias is not likely in this study, as very few small studies expressly considered the occupational determinants of pancreatic cancer. Publication bias was suspected only for the job title studies addressing metal plating workers and so that small high risk studies were unpublished. The agent studies did not show publication bias for any agent.

A counterargument may however be raised about cohort studies with multiple end-points. Some of these studies deleted results based on small numbers, occasionally for pancreatic cancer. This omission may have minor influence on the results of meta-analyses. Some case-control studies may have omitted results for rare exposures, with similar minor effect on the results of meta-analyses.

### *Selection of studies*

Major databases and lists of references of the studies were used for identifying of studies in any language. Studies not found in major databases are probably of low quality. Unpublished studies were not attempted to identify. The selection of studies did not be comprehensive lacking unpublished studies but it was consistent.

### *Extraction*

Extractor bias was minimized by the formal extraction procedure between the group of extractors and the central checking of the extraction. The procedure was also intended to guarantee the extraction of the relevant relative risk estimates in studies that offered several alternative relative risk estimates.

### *Reference populations*

Not all observed relative risk estimates in the data were strictly independent because in some studies an internal unexposed industrial population was used as the common reference for more than one exposed population. This was rare, however, and we consider the ensuing bias in the precision of MRR minimal. Reference populations are a problem in proportional studies, where the population basis is unknown. For most analyses, we excluded proportional studies for this reason. Comparability of relative risk estimates may be a problem in SMR and SIR studies because of the healthy worker effect. It is unknown to what extent the healthy worker effect and its components might have biased the results of meta-analysis.

### *Confounding*

Control of confounding is a problem in studies of pancreatic cancer, as tobacco smoking and diabetes are the only known common causes of this malignancy. Even a rough

measurement of confounding bias is difficult. Case-control studies are in principle best equipped for adjustment for confounders. Several of these studies did adjust for various factors. In other study types, adjustment was rare. Attempts to aggregate results over studies that adjusted for smoking failed because of small number of such studies. The number of adjusted relative risk estimates ranged from zero to two across the occupational agents. In all hierarchical Bayesian models for meta-analysis, confounding was controlled by forcing five potential confounders into the models.

### *Ecological bias*

Ecological or aggregated bias may emerge when using group level data for inferences on the individual level. Because, for instance whole group of exposed workers exposures as same proportion to occupational agents according JEM, it does not take account of the individual deviations. Ecological bias in average weakens relative risks (Gilks and Richardson, 1992).

In Study IV, the hierarchical Bayesian models operated on three levels: observed relative risk estimates from studies, group of job titles, and agents of exposure. An ecological bias may appear when proportions of agents from FINJEM observed at the job title level are applied to the relative risk estimates level. Two-level hierarchical Bayesian meta-analysis has been applied for clinical trials, but applications on non-experimental data are rare. Hierarchical Bayesian methods in ecological studies, including the ecological bias, have been discussed (Morgenstern, 1998; Greenland, 2001; Richardson and Best, 2003; Wakefield, 2004; Jackson et al., 2006). Even a simple meta-analysis involves an ecological bias, as outcomes are not available on the individual level (Greenland, 1998). The hierarchical Bayesian meta-analysis (Study IV) involved studies of job titles with external agent data (FINJEM) with unknown extrapolability and unknown exposure levels, hence liable to exposure misclassification. Inclusion of country as a covariate in the hierarchical Bayesian models presumably reduced the misclassification bias.

## **6.2 Substance considerations of the results**

### **6.2.1 Chlorinated hydrocarbon solvents and related compounds**

In Study II, the excess risk found for chlorinated hydrocarbon compounds was based on 20 observed relative risk estimates. Heterogeneity of RRs bordered significance ( $p = 0.05$ ) and may be explained by differences in the chemical structure and exposure level of the agents. In the hierarchical Bayesian meta-analysis (Study IV), the excess risk for CHC was also found based on exposures of three job titles, laundry and dry cleaning workers, metal plating workers, and printers/pressmen/newspaper workers, using the FINJEM interface for exposures assessment.

## DISCUSSION

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Various compounds with variable carcinogenic potential were analyzed in the study reports as worker exposures: trichloroethylene, tetrachloroethylene, 1,1,1-trichloroethane, methylene chloride, vinyl chloride, ethylene chlorohydrine, ethylene dichloride, bis(chloromethyl)ether, and polychlorinated biphenyls. Intensities and long term doses were characterized in most of the studies either poorly or not at all. For individual chlorinated hydrocarbon solvents, indications for weak excesses were found for trichloroethylene, tetrachloroethylene, methylene chloride, vinyl chloride, polychlorinated biphenyls (PCBs), and chlorohydrin manufacture, but not for carbon tetrachloride. The highest excesses were found also for workers in two job title categories, which were exposed mostly to chlorinated hydrocarbon solvents: metal degreasing and related jobs, and dry cleaning. Excesses were high for printers/pressmen/newspaper workers in the non-Bayesian random effects meta-analyses.

Experimental cancer studies and epidemiological studies suggest that environmental PCB mixtures are likely to pose a risk of cancer to humans (IARC, 1987). A case-control study of pancreatic cancer (Hoppin et al., 2000) found an OR 4.2 (95% CI 1.9-9.4) for >360 vs. <185 ng/g PCB in blood lipid. ). After closing our meta-analysis, May 1998, Kernan et al. (1999) have found a high excess risk for white female workers exposed to methylene chloride in their case-control study (OR 1.3; 95% CI 1.1-1.6).

In the meta-analyses, exposure to chlorinated hydrocarbon solvents and related compounds increased the risk of pancreatic cancer.

### 6.2.2 Insecticides

In Study II, the aggregated MRR for insecticides was 1.5 (95% CI 0.6 -3.7); in case-control studies it was 3.7 (0.3 to 43), based on the random effects model. The highest RR was obtained for exposure to DDT family (DDT, ethylan, DDD; OR 21.0; 95% CI 2.6-966; five exposed cases) in a case-control study nested in a chemical manufacturing cohort (Garabrant et al., 1993). Potential confounders included nitrophenol derivatives, clays, *N,N*-Dimethylformamide, dispersing agents, octane, and carbon tetrachloride. The other case-control study (Fryzek et al., 1997) was population based (Michigan, US), with self-reported exposures. Based on 21 exposed cases, it yielded an OR 1.5 (0.8 to 2.9) for organochlorine insecticides. Assuming an effect, the difference between the two point estimates might be due to qualitative and quantitative differences in exposures between manufacturing and agricultural application.

In the Bayesian meta-analysis, an excess risk for insecticides was found based on exposure in plywood/fiberboard workers. An excess risk for plywood/fiberboard workers was also found in the RE meta-analysis and in the HB meta-analysis.

After closing our meta-analysis, Beard et al. (2003) reported a high excess risk (SMR 5.3, 95% CI 1.1-15.4) for outdoor workers exposed to DDT in their cohort study. In this study, exposure to insecticides may increase risk of pancreatic cancer.

### 6.2.3 Nickel and nickel compounds, and chromium and chromium compounds

In Study II, the risk for nickel and nickel compounds was most evident in population based case-control studies, including one high positive finding (OR 2.1; 95% CI 1.2-3.8) (Siemiatycki et al., 1991). In hierarchical Bayesian meta-analysis, the excess risk was not found (based on exposure of seven job titles; fitter/assemblers, foundry workers, machine/engine mechanics, metal plating, metal smelting furnacemen, sheet metal workers, and turners/toolmakers/machine tool setters, by the FINJEM data). In the non-Bayesian random effects meta-analysis, the MRRs for these job titles ranged from 0.7 to 2.04, the lowest MRRs were for job titles on which workers were only exposed to nickel. Workers on the other job titles were exposed also some other agent(s) than nickel.

Weiderpass et al. (2003) reported a strong positive association between pancreatic cancer and exposure to nickel and nickel compounds in their Finnish female cohort study (RR 1.7; 95% CI 1.2-2.4). This study was not included in meta-analyses.

In Study II, the MRR for chromium and chromium compounds (1.4) was increased in all studies, including one high positive SMR finding (Franchini et al., 1983), but was not in excess in population-based case-control studies. In HB meta-analysis, nickel and chromium were combined, because the proportions of exposed workers were almost equivalent and the results were the same for both metals. Subsequently, Weiderpass et al. (2003) found a high excess of pancreatic cancer for chromium (RR 1.8; 95% CI 1.0-3.1) in Finnish women workers.

In this study, the results for exposure to nickel and nickel compounds were inconsistent.

### 6.2.4 Other agents

In Study II a weak increase was present for PAHs in all studies, in population based case-control studies, and in the two SMR/SIR studies. In HB meta-analysis the MRR for PAHs was 1.1 and 95% CrI (0.9-1.5). High positive findings were found in three studies (Romundstad et al., 2000a; Romundstad et al., 2000b; Weiderpass et al., 2003) after closing our meta-analysis.

The excess of silica dust reached significance in one (Study II) of three studies. Study II found a high excess for aliphatic and alicyclic hydrocarbon solvents. This finding was aggregated with the finding of no excess for alikeness ( $C_5-C_{17}$ ) in another population based study from Montreal (Siemiatycki et al., 1991) the result being MRR 1.3 (95% CI; 0.8-2.0) and in the HB meta-analysis was 1.1.

### **7. CONCLUSIONS**

1. Results of the case-control study suggest that heavy occupational exposure to organic solvents, especially to aliphatic hydrocarbon solvents, aromatic hydrocarbon solvents, and other solvents, but not chlorinated hydrocarbon solvents, may increase the risk of pancreatic cancer. Additional excess was found for exposure to ionizing radiation.

2. Results of the non-Bayesian and the Bayesian meta-analyses suggest that occupational exposure to some chlorinated hydrocarbon solvents and related compounds may increase the risk of pancreatic cancer. The finding was supported by high excesses from studies addressing metal degreasing and related jobs and dry cleaning. Additionally consistent excess risk was found for insecticides. Excesses associated with occupational exposure to nickel and nickel compounds were suggested in the random effects meta-analyses but not in the hierarchical Bayesian meta-analysis.

3. Hierarchical models used in this study are applicable in meta-analyses when studies addressing the agent(s) under study are lacking or very few, but several studies address job titles with potential exposure to these agents, and when studies addressing workers exposed to several agents. A job-exposure matrix or a formal expert assessment system is necessary in these situations. Hierarchical models for meta-analysis involving durations and intensities of exposure to occupational agents from job-exposure matrix should be developed.

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**APPENDIX 1.**

Study ID: \_\_\_\_\_

Abstractor: \_\_\_\_\_

checked, date \_\_/\_\_/199\_\_

entered, date \_\_/\_\_/199\_\_

**Pancreas cancer meta study  
Extraction form**

N. Jourenkova, A. Ojajärvi, T. Partanen

Contents:

Form 1: Study characterization

Form 2: Estimate extraction

Exposure-specific data

Job title data

**Form 1**  
**STUDY CHARACTERIZATION**

Characterize studies sent to you. Answer questions by circling appropriate code numbers. If results are presented for more than one population (e.g., subgroups such as race), fill in one form for each population.1.

Name of first author  
\_\_\_\_\_

2. Year of publication 19 \_\_\_\_\_

3. Country/countries  
\_\_\_\_\_

4. Study type (circle)

- 1 Administrative (linkage of administrative records, or PMR/MOR study)
- 2 Industrial cohort
- 3 Industry based (nested) case-control
- 4 Population or hospital based case-control

5. Cases

- 1 Exocrine pancreas only
- 2 All pancreas cancers
- 3 Other, \_\_\_\_\_
- 4 Unspecified

6. Diagnosis of pancreas cancer cases

- 1 Histological
- 2 Other (clinical: radiology, autopsy, etc.)
- 3 Mortality files
- 4 Mixed
- 5 Unknown

7. Ascertainment of pancreas cancer cases

- 1 Mortality files
- 2 Cancer registry files
- 3 Hospital records
- 4 Other \_\_\_\_\_
- 5 Mixed
- 6 Unspecified

8. Reference ("unexposed") population in **administrative and industrial cohort studies**

- 1 Country/other large population
- 2 Local population
- 3 Internal
- 4 Several reference populations
- 5 Death/case distribution (PMR)
- 6 Other

9. Control selection in case-control studies

- 1 Population
- 2 Other cancers in population
- 3 Hospital controls
- 4 Other \_\_\_\_\_
- 5 Mixed or multiple control series

10. Follow-up period for case ascertainment from 19\_\_ to 19\_\_

11. Cohort and administrative studies:

- Lost to follow-up
- 1 \_\_\_\_\_ %
  - 2 unspecified

12. Case-control studies:

Response rate  
Cases \_\_\_\_\_ %  
Controls \_\_\_\_\_ %

13. Source of **exposure** data (if chemical/physical exposures have been specified)

	yes	no
Industrial exposure measurements	1	2
Job-exposure matrix	1	2
Expert assessment	1	2
Job titles	1	2
Colleagues	1	2
Next-of-kin	1	2
Other _____	1	2
Mixed	1	2
Unspecified	1	2

14. Time reference for **exposure**

- 1 Last or around diagnosis
- 2 Earlier cross-section
- 3 Lifetime longitudinal
- 4 Less than lifetime longitudinal
- 5 Other \_\_\_\_\_
- 6 Unclear



**Form 2**  
**Estimate extraction**

Extract relevant estimates of relative risk. There are two different sections for estimate extraction: one for selected **exposures** (in case risks have been estimated for exposures), and another for selected **job titles**.

Extract measures of relative risks associated with specific exposures or job titles. Extract **the most unbiased estimate** if there is a choice. After reading carefully the paper, fill the form. Choose estimates adjusted for at least known risk factors for PC (age, gender, tobacco smoking), if there is a choice. Prefer social class adjusted RRs over RRs unadjusted for social class. Choose risk estimate nearest to 20-y latency period, if there is a choice.

Note that there are synonyms and there are closely related job titles. The alphabetic list in **Annex 1** tells you where to find them in the Job Title Data Table.

**EXPOSURE-SPECIFIC DATA**

Risk estimates adjusted for \_\_\_\_\_ years

Latency period \_\_\_\_\_ years

**P-VALUE ONLY IF CI IS NOT AVAILABLE**

Exposure	MEN				WOMEN				MEN + WOMEN OR UNSPECIFIED			
	RR	% CI	p (tail)	N obs. cases	RR	% CI	p (tail)	N obs. cases	RR	% CI	p (tail)	N obs. cases
1. Aliphatic (hydrocarbon) solvents												
2. Animal dust												
3. Aromatic (hydrocarbon) solvents, benzene, styrene (exclude aromatic amines)												
4. Arsenic												
5. Asbestos, crocidolite												
6. Bitumen fumes, asphalt fumes												
7. Cadmium												
8. Chlorinated (hydrocarbon) solvents (eg. trichloroethylene, tetrachloroethylene = perchloroethylene), halogenated hydrocarbons, methylene chloride, vinyl chloride monomer												
9. Chromium, chromate pigments, ferrocobaltium												
10. Diesel engine exhaust or unspecified engine exhaust												
11. Env. tob. smoke at work												
12. Flour dust												
13. Formaldehyde												
14. Fungicides, fungus control agents, chlorophenols												
15. Gasoline (Am), petrol (Br)												
16. Gasoline engine exhaust												
17. Herbicides (chlorophenoxy, phenoxy), weed killers, defoliant												
18. Insecticides, insect control agents, or unspecified (organochlorine) pesticides, DBCP, DDT												



**JOB TITLE DATA**

Risk estimates adjusted for \_\_\_\_\_ years  
 Latency period \_\_\_\_\_ years  
 P-VALUE ONLY IF CI IS NOT AVAILABLE

Job title	MEN				WOMEN				MEN + WOMEN OR UNSPECIFIED			
	RR	% CI	p (tail)	N obs. cases	RR	% CI	p (tail)	N obs. cases	RR	% CI	p (tail)	N obs. cases
1. Airline captain/pilot												
2. Artist/display decorator/layout/designer												
3. Asphalt worker/highway worker												
4. Assembler (machine/metalware)/ aircraft manufacturing worker/ worker in automobile engine and part manufacturing complex/worker in construction equipment and diesel engine manufacturing plant/ aircraft factory/automobile industry/ automotive engine manufacturing plant/capactor manufacturing/ motor vehicle manufacturing/ worker employed in cable manufacture plant/worker in bearing manufacture plant												
5. Baker												
6. Basket/brush maker												
7. Bath attendant												
8. Beautician/cosmetologist												
9. Bench carpenter												
10. Bookbinder												
11. Brewer/brewerage maker/brewery worker												
12. Bricklayer/plasterer/tile setter												
13. Butcher/sausage maker/ slaughterer/meat worker/worker in meat department of supermarket												
14. Cabinetmaker/joiner												

Job title	MEN				WOMEN				MEN + WOMEN OR UNSPECIFIED			
	RR	% CI	p (tail)	N obs. cases	RR	% CI	p (tail)	N obs. cases	RR	% CI	p (tail)	N obs. cases
15. Cannery (tinney) worker												
16. Charworker/cleaner/sewage plant worker												
17. Chimney sweep												
18. Chocolate/confectionary manufacturer												
19. Cold and hot metal rolling worker												
20. Concrete mixer operator/concrete product worker/cement worker												
21. Concrete shutter/finisher												
22. Construction carpenter												
23. Construction machine operator/ heavy construction equipment operator												
24. Construction worker unspecified, construction laborer/worker												
25. Cook, chef												
26. Cooker/furnaceman (chemical processing)												
27. Crane operator												
28. Crusher/grinder/calender operator (chem. processing)												
29. Customs officer/border guard												
30. Dairy worker/dairy cattle worker												
31. Distiller												
32. Electric machine operators												
33. Electro/electronic equipment assembler/transformer-assembly/capacitor manufacturing worker/carbon electrode manufacturing worker/ worker employed at transformer manufacturing plant/battery manufacture/transformer manufacturing plant												
34. Electrician/electrical (utility) worker												

Job title	MEN				WOMEN				MEN + WOMEN OR UNSPECIFIED			
	RR	% CI	p (tail)	N obs. cases	RR	% CI	p (tail)	N obs. cases	RR	% CI	p (tail)	N obs. cases
35. Electronics/telecommunications workman/worker in telecommunication industry												
36. Farm/agricultural worker												
37. Farmer/dairy farmer/rice grower/ agriculture												
38. Fibre processor												
39. Fireman/fire fighter												
40. Fisher/fisherman												
41. Fitter/assembler												
42. Flight attendant/steward												
43. Forestry job												
44. Forklift operator												
45. Foundryman/primary aluminum foundry (worker)/ steel foundry worker												
46. Fur farmer												
47. Furrier/fur worker/fur industry job/gardener/orchard worker												
48. Gardener/park												
49. Gasoline (service) station attendant/petrol pump attendant/ filling station attendant/person employed in fuel distribution/ petroleum marketing and distribution worker												
50. Glass moulder												
51. Glass/ceramics decorator/ dipper												
52. Glass/ceramics kilnman												
53. Glass/clay maker												
54. Glazier												
55. Goldsmith/silversmith												
56. Grain miller/corn wet-milling worker/ flour mill worker/worker in grain industry/flour industry												
57. Graphic occupation												

Job title	MEN				WOMEN				MEN + WOMEN OR UNSPECIFIED			
	RR	% CI	p (tail)	N obs. cases	RR	% CI	p (tail)	N obs. cases	RR	% CI	p (tail)	N obs. cases
58. Hairdresser/barber												
59. Heat treater/hardener/temperer												
60. High voltage electric machine fitter												
61. Hotel/restaurant matron												
62. Housekeeper/home help/caretaker/janitor												
63. Industrial sewer												
64. Insulation worker/insulator												
65. Jewellery job/jewelry worker												
66. Kitchen assistant												
67. Knitting machine operator												
68. Laboratory/chemist												
69. Labourer												
70. Laundry/launderer/dry cleaning job												
71. Leather sewer												
72. Lithographer												
73. Livestock breeder												
74. Lumberjack/logger												
75. Machine setter/rigger (not in textile)												
76. Machine (automobile) /engine mechanic/bus garage worker/ worker at aircraft maintenance facility												
77. Mailman/newspaper delivery												
78. Mail/tele work, other or unspecified												
79. Maintenance personal												
80. Metal plating/coating, chromium plating worker/ metal components manufacturing worker/ nickel plater/ worker in die-casting and electroplating plant												

Job title	MEN					WOMEN					MEN + WOMEN OR UNSPECIFIED					
	RR	% CI	p (tail)	N obs. cases	from page	RR	% CI	p (tail)	N obs. cases	from page	RR	% CI	p (tail)	N obs. cases	from page	
81. Metal smelting furnaceman/ aluminum (reduction plant)/coke plant/coke oven worker/worker producing ferroalloys and stainless steel/coke oven plant of Carrara/ Copper smelter/ferroalloy industry																
82. Milliner/hatmaker																
83. Miner (coal/gold/uranium)/shot firer/ quarry/rock salt worker/rubber worker/worker mining and milling attapulgite clay																
84. Mineral processing																
85. Motor vehicle driver (taxi, truck, tractor, lorry, van, bus, coach)/ teamster/professional driver.																
86. Moulder																
87. Nurse/nursing assis/attendant																
88. Office receptionist/messenger																
89. Optician																
90. Packer/labeller																
91. Painter (art)																
92. Painter/lacquered/floor layer																
93. Paper product worker																
94. Paper/cardboard mill worker/ cellulose fiber production worker/ cellulose triacetate-fiber worker/ pulp and paper mill worker																
95. Pharmacy job/pharmaceutical worker/pharmacy technician/ pharmaceutical plant																
96. Photographer/cameraman																
97. Photographic laboratory assistant																
98. Physician/dentist																
99. Plastic product worker/plastic manufacturing industry																
100. Plumber/pipefitter																
101. Plywood/fibreboard worker																

Job title	MEN				WOMEN				MEN + WOMEN OR UNSPECIFIED			
	RR	% CI	p (tail)	N obs. cases	RR	% CI	p (tail)	N obs. cases	RR	% CI	p (tail)	N obs. cases
102. Policeman												
103. Potter												
104. Precision instrument maker												
105. Printer/pressman/newspaper worker/newspaper web pressman/printing industry												
106. Processed food maker												
107. Pulp mill worker												
108. Radio/TV transmitter												
109. Railway engine												
110. Railway personal, other, unspecified												
111. Refinery worker/oil (refinery) worker/petrochemical worker/petroleum refinery and chemical plant worker/producing and pipeline worker/worker from petroleum refineries/worker in petroleum manufacturing and distribution industry/Mobil Corporation/oil distribution centre (UK) oil industry/oil refinery/petroleum industry												
112. Reinforced concrete layer/stone-mason/construction ironworker												
113. Rod layer												
114. Rubber production worker/curing worker (rubber)/reclaim worker (rubber)/rubber (tyre) industry												
115. Salesman, sales worker, commercial traveler												
116. Sawyer												
117. Seatarer, sailor, seaman, deckhand												
118. Sheet metal worker												
119. Shoe sewer												
120. Shoemaker/worker/repairer												

Job title	MEN				WOMEN				MEN + WOMEN OR UNSPECIFIED			
	RR	% CI	p (tail)	N obs. cases	RR	% CI	p (tail)	N obs. cases	RR	% CI	p (tail)	N obs. cases
121. Shop job												
122. Smith												
123. Sole fitter												
124. Spinning operator												
125. Stationary engine/machinery operator												
126. Stevedore												
127. Stone/granite cutter												
128. Sugar processing worker												
129. Tanner/fellmonger/dresser/tannery worker/leather tanner/leather worker/ leather tanning industry/ tanning industry												
130. Taylor/seamstress/garment industry												
131. Telephone installer/lineman/cable joiner/repairman												
132. Textile finisher/dyer/dyestuffs worker												
133. Textile inspector												
134. Textile machine setter operator												
135. Textile/leather patternmaker/cutter												
136. Timberman/lumberman												
137. Tobacco industry worker												
138. Turner/toolmaker/machine tool setter												
139. Typist/data clerk/computing												
140. Typographer												
141. Upholster												
142. Waiter/waitress/bartender												
143. Warehouseman												
144. Watchmaker												
145. Weaving machine operator, carpet worker												
146. Welder (arc)/steel welder/flame cutter/												



APPENDIX 2.

Job title	Proportion exposed to chemical agent									
	ALHC	CHC	FUNG	INSC	NI/CR	PAH	SIL	WOOD		
Asphalt workers	-	-	-	-	-	0.72	-	-	-	-
Bench carpenters	-	-	-	-	-	-	-	-	-	1
Bricklayers	-	-	-	-	-	-	1	-	-	-
Cabinet makers	-	-	-	-	-	-	-	-	-	1
Cement workers	-	-	-	-	-	-	1	-	-	-
Concrete shutters	-	-	-	-	-	-	0.90	-	-	-
Construction carpenters	-	-	-	-	-	-	0.76	-	-	1
Construction workers	-	-	-	-	-	-	0.22	-	-	-
Electric machine operators	-	-	-	-	-	-	0.29	-	-	-
Farmers	-	-	0.25	-	-	-	-	-	-	-
Fitters/assemblers	-	-	-	-	0.42	-	-	-	-	-
Foundry workers	-	-	-	-	0.25	-	-	0.44	-	-
Laundry and dry cleaning workers	-	0.39	-	-	-	-	-	-	-	-
Machine/engine mechanics	-	-	-	-	0.33	1	-	-	-	-
Metal plating workers	-	0.92	-	-	0.46	-	-	-	-	-
Metal smelting furnacemen	-	-	-	-	0.41	1	1	-	-	-
Miners	-	-	-	-	-	1	1	-	-	-
Painters	0.98	-	-	-	-	-	-	-	-	-
Plywood/fiberboard workers	-	-	0.33	0.33	-	-	-	-	-	0.66
Printers/pressmen/newspaper workers	0.33	0.20	-	-	-	-	-	-	-	-
Sawyers	-	-	0.45	-	-	-	-	-	-	1
Sheet metal workers	-	-	-	-	0.38	-	-	-	-	-
Smiths	-	-	-	-	-	1	-	-	-	-
Stone cutters	-	-	-	-	-	-	0.87	-	-	-
Timbermen/lumbermen	-	-	-	-	-	-	-	-	-	0.56
Turners/toolmakers/ machine-tool setters	-	-	-	-	0.50	1	-	-	-	-
Wood working machine operators	-	-	-	-	-	-	-	-	-	1

ALHC = aliphatic and alicyclic hydrocarbon solvents, CHC = chlorinated hydrocarbon compounds, FUNG = fungicides, INSC = insecticides, NI/CR = nickel/chromium, PAH = polycyclic aromatic hydrocarbons, SIL = silica dust, WOOD = wood dust, - = proportion exposed is zero

### APPENDIX 3.

#### AGENT

##### STUDY TYPE

Study	RR	95 % CI	Weight
<b>Results of meta-analysis:</b>			
	<b>MRR</b>	<b>95% CI</b>	
<i>Heterogeneity</i>			

#### ALIPHATIC AND ALICYCLIC HYDROCARBON SOLVENTS:

##### OR:

Study I (1995)	1.6	1.0 - 2.6	19.1
Siemiatycki (1991)	1.0	0.7 - 1.4	32.0
<b>Aggregate (OR studies):</b>	<b>1.3</b>	<b>0.8 - 2.0</b>	
	$\chi_1^2 = 2.9$	$p = 0.09$	

#### ANIMAL DUST:

##### [PMR:

Magnani et al. (1987)	1.0	0.6 - 1.6	
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#### AROMATIC HYDROCARBON SOLVENTS:

##### OR:

Greenland et al. (1994)	0.6	0.2 - 1.9	2.7
Study I (1995)	1.8	1.1 - 2.8	18.1
Mack et al. (1985)	0.6	0.3 - 1.2	8.0
Siemiatycki (1991)	0.8	0.5 - 1.4	14.5
<b>Aggregate (OR studies):</b>	<b>0.9</b>	<b>0.5 - 1.6</b>	
	$\chi_3^2 = 9.7$	$p < 0.05$	

##### SIR / SMR:

Acquavella et al. (1993)	2.9	0.1 - 16	0.6
Anttila et al. (1998)	1.3	0.4 - 2.9	4.0
Bond et al (1992)	0.5	0.2 - 1.1	4.0
Decoufle et al. (1983)	1.6	0.0 - 5.6	0.6
Frentzel-Beyme (1978)	2.8	0.3 - 10.2	1.3
Kogevinas et al. (1994)	1.1	0.8 - 1.5	30.8
Sathiakumar et al (1998)	0.7	0.4 - 1.2	12.2
Wong (1987)	0.9	0.4 - 1.8	6.7
Wong et al. (1994)	1.3	0.5 - 2.5	6.7

**Aggregate (SIR / SMR studies):** **1.0** **0.8 - 1.3**  
 $\chi_8^2 = 6.6$   $p = 0.6$

**Aggregate (all studies):** **1.0** **0.8 - 1.3**  
 $\chi_{12}^2 = 16.6$   $p = 0.2$

##### [PMR:

Magnani et al. (1987)	1.2	0.9 - 1.7	
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#### ARSENIC:

##### HR:

Tollestrup et al. (1995)	1.4	0.2 - 11.6	0.9
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##### OR:

Mack et al. (1985)	1.0	0.3 - 5.5	3.6
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Siemiatycki (1991)	1.2	0.4 - 3.8	3.0
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**Aggregate (OR studies):** **1.1** **0.5-2.7**  
 $\chi_1^2 = 0.1$   $p = 0.8$

**Aggregate (OR and HR studies):** **1.2** **0.5 - 2.6**  
 $\chi_2^2 = 0.1$   $p = 0.96$

##### SMR:

Enterline (1995)	0.9	0.4 - 1.5	10.3
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**Aggregate (all studies):** **1.0** **0.6 - 1.6**  
 $\chi_3^2 = 0.4$   $p = 0.9$

#### ASBESTOS:

##### OR:

Greenland et al. (1994)	0.8	0.4 - 1.8	6.4
Study I (1995)	0.6	0.5 - 1.0	29.3
Mack et al. (1985)	0.5	0.2 - 1.2	4.8
Siemiatycki (1991)	1.3	0.6 - 2.7	6.8

**Aggregate (OR studies)** **0.7** **0.5 - 1.0**  
 $\chi_3^2 = 4.4$   $p = 0.2$

##### SIR / SMR:

Acheson et al. (1984)	1.0	0.8 - 1.2	115
Armstrong et al. (1979)	1.2	0.6 - 2.6	7.0
Brown et al. (1994)			
White: Men	1.5	0.6 - 3.0	5.8
Women	0.7	0.2 - 1.8	3.0
Black: Men	1.3	0.3 - 3.3	3.0
Cammarano et al. (1986)	3.6	0.1 - 19.9	0.4
Dement et al. (1994)			
Men	1.5	0.7 - 2.7	9.4
Women	1.0	0.3 - 2.5	3.0
Enterline et al. (1987)	1.1	0.5 - 2.1	6.5
Gustavsson and Reuterwall (1990)	0.6	0.1 - 2.1	1.2
Magnani et al. (1996)			
Men	1.1	0.5 - 2.1	7.5
Women	0.5	0.0 - 2.9	0.5
McDonald et al. (1993)	1.1	0.8 - 1.4	36.9
Ohlson et al. (1984)	1.1	0.6 - 1.9	11.3
Seidman et al. (1986)	2.3	1.1 - 4.5	7.3
Selikoff and Seidman (1981)	2.8	1.8 - 4.2	20.7
Sun et al. (1997)	1.4	0.6 - 2.9	5.7
Tsai et al. (1996)	0.7	0.3 - 1.4	6.6
Wilczynska et al. (1996)	1.1	0.4 - 2.3	4.9
Woitowitz et al. (1986)	1.6	0.4 - 4.1	3.0

**Aggregate (SIR / SMR studies):** **1.2** **1.0 - 1.5**  
 $\chi_{19}^2 = 28.9$   $p = 0.1$

**Aggregate (all studies):** **1.1** **0.9 - 1.4**  
 $\chi_{23}^2 = 44.8$   $p < 0.01$

##### [PMR:

Magnani et al. (1987)	0.9	0.7 - 1.2	
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## CADMIUM:

### **OR:**

Study I (1995) 0.8 0.2 - 2.9 2.2

### **SMR:**

Elinder et al. (1985) 0.7 0.3 - 1.4 5.8

**Aggregate (all studies):** 0.7 0.4 - 1.4  
 $\chi^2_1 = 0.03$   $p = 0.9$

### **[PMR:**

Magnani et al. (1987) 1.3 0.9 - 1.8 ]

## CHLORINATED HYDROCARBON SOLVENTS AND RELATED COMPOUNDS:

### **OR:**

Greenland et al. (1995) 1.6 0.8 - 3.3 8.0

Siemiartycki (1991)

Chlorinated alkanes 0.8 0.4 - 1.5 5.5

Chlorinated alkenes 0.9 0.3 - 2.6 2.3

**Aggregate (OR studies):** 1.2 0.7 - 1.9  
 $\chi^2_2 = 1.9$   $p = 0.4$

### **IRR:**

Hearne et al. (1990) 2.6 1.0 - 5.3 5.7

**Aggregate (OR and IRR studies):** 1.4 0.8 - 2.4  
 $\chi^2_3 = 4.4$   $p = 0.2$

### **SIR/ SMR:**

Anttila et al. (1995) 2.0 1.0 - 3.7 9.5

Axelsson et al. (1994) 0.3 0.0 - 1.4 0.6

Benson and Teta (1993) 4.9 1.6 - 11.4 3.9

Brown (1987)

Men 0.6 0.0 - 3.5 0.5

Women 0.5 0.0 - 2.7 0.5

Gibbs et al. (1996)

Men 0.6 0.1 - 1.7 2.2

Women 0.5 0.0 - 2.9 0.5

Lanes et al. (1993) 0.8 0.1 - 3.0 1.3

Nakamura (1983) 2.9 0.6 - 8.4 2.1

Sinks et al. (1992) 0.7 0.1 - 2.5 1.5

Simonato et al. (1991) 0.7 0.1 - 2.0 2.1

Smulevich et al. (1988) 1.7 0.4 - 5.0 2.2

Spirtas et al. (1991) 0.8 0.5 - 1.4 12.1

Tomenson et al. (1997) 1.0 0.2 - 2.1 2.2

Wong et al. (1991) 1.0 0.5 - 1.8 9.4

Yassi et al. (1994) 4.4 1.5 - 10.9 3.9

### **Aggregate**

**(SIR/SMR studies):** 1.3 0.9 - 2.0  
 $\chi^2_{15} = 25.3$   $p < 0.05$

**Aggregate (all studies):** 1.4 1.0 - 1.8  
 $\chi^2_{19} = 29.9$   $p = 0.05$

### **[PMR:**

Chiazzi and Ferenze (1981)

Men 1.1 0.8 - 1.6

Women 1.2 0.5 - 2.4

Magnani et al. (1987)

Carbon tetrachloride 1.1 0.8 - 1.5

Polychlorinated biphenyls 0.9 0.6 - 1.4 ]

## CHROMIUM AND CHROMIUM COMPOUNDS:

### **OR**

Study I (1995) 0.9 0.4 - 2.0 5.7

Mack et al. (1985) 1.1 0.4 - 3.5 3.3

Siemiartycki (1991) 1.1 0.6 - 2.0 10.6

**Aggregate (OR studies):** 1.0 0.7 - 1.6  
 $\chi^2_2 = 0.3$   $p = 0.9$

### **SIR / SMR:**

Axelsson et al. (1980) 0.6 0.0 - 3.5 0.5

Cammarano et al. (1986) 3.6 0.1 - 19.9 0.4

Franchini et al. (1983) 20.0 2.3 - 72.2 1.2

Kano et al. (1993) 1.0 0.0 - 5.6 0.6

Langård et al. (1990) 1.6 0.3 - 4.6 2.2

Sheffet et al. (1982) 1.5 0.6 - 3.1 5.8

**Aggregate (SIR / SMR studies):** 2.3 0.9 - 5.8  
 $\chi^2_5 = 8.4$   $p = 0.1$

**Aggregate (all studies):** 1.4 0.9 - 2.3  
 $\chi^2_8 = 11.8$   $p = 0.2$

### **[PMR:**

Magnani et al. (1987) 1.3 1.0 - 1.7 ]

## DIESEL ENGINE EXHAUST:

### **OR:**

Study I (1995) 0.9 0.5 - 1.5 12.7

Mack et al. (1985) 0.5 0.2 - 1.2 4.8

Siemiartycki (1991) 1.1 0.9 - 1.3 115

**Aggregate (OR studies):** 1.0 0.7 - 1.3  
 $\chi^2_2 = 3.2$   $p = 0.2$

### **RR:**

Boffetta et al. (1988) 1.4 0.9 - 2.0 24.5

### **HR:**

Van Den Eeden

and Friedman (1993) 1.4 0.9 - 2.3 15.3

**Aggregate (RR and HR studies):** 1.4 1.3 - 1.9  
 $\chi^2_1 = 0.0$   $p = 0.9$

### **Aggregate**

**(RR, HR and OR studies):** 1.1 0.9 - 1.4  
 $\chi^2_4 = 5.8$   $p = 0.2$

### **SIR / SMR:**

Gustavsson and

Reuterwall (1990) 0.6 0.1 - 2.1 1.2

Howe et al. (1983) 0.9 0.8 - 1.1 198

**Aggregate (SIR / SMR studies):** 0.9 0.8 - 1.1  
 $\chi^2_1 = 0.3$   $p = 0.6$

**Aggregate (all studies):** 1.0 0.9 - 1.2  
 $\chi^2_6 = 9.4$   $p = 0.2$

**ELECTROMAGNETIC FIELDS:*****SIR / SMR :***

Baris et al. (1996)	2.4	0.8 - 6.9	3.3
Milham (1988)	0.6	0.4 - 0.9	23.7
Milham (1985)	1.1	0.8 - 1.5	38.9
Tynes et al. (1992)	1.2	1.0 - 1.4	158
Tynes et al (1994)	1.2	0.7 - 1.8	16.0

***Aggregate (all studies):*** **1.1 0.8 - 1.4**  
 $\chi_4^2 = 9.8$   $p < 0.05$

***[PMR:***

Magnani et al. (1987)	1.0	0.6 - 1.5 ]
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**FLOUR DUST:*****OR:***

Siemiatycki /1991	1.1	0.3 - 3.2
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***[PMR:***

Magnani et al. (1987)	0.9	0.4 - 1.9 ]
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**FORMALDEHYDE:*****OR:***

Study I (1995)	0.6	0.3 - 1.4	6.0
Siemiatycki (1991)	0.5	0.3 - 1.0	10.6

***Aggregate (OR studies):*** **0.5 0.3 - 1.6**  
 $\chi_2^2 = 4.7$   $p = 0.1$

***SMR:***

Gardner et al. (1993)	1.0	0.7 - 1.4	32.0
Levine et al. (1984)	1.0	0.3 - 2.6	3.1
Stayner et al. (1988)	0.5	0.2 - 1.2	3.9

***Aggregate (SMR studies):*** **0.9 0.7 - 1.3**  
 $\chi_2^2 = 1.4$   $p = 0.5$

***Aggregate (all studies):*** **0.8 0.5 - 1.0**  
 $\chi_4^2 = 6.5$   $p = 0.3$

***[PMR:***

Hansen and Olsen (1996)	1.1	0.3 - 3.2
Magnani et al. (1987)	0.9	0.4 - 1.9 ]

**FUNGICIDES:*****OR:***

Study I (1995)	1.4	0.3 - 7.2	1.4
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***RR:***

Ramlow et al. (1996)	1.3	0.3 - 5.0	2.0
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***Aggregate (all studies):*** **1.3 0.4 - 3.8**  
 $\chi_1^2 = 0.0$   $p = 0.9$

**GASOLINE:*****OR:***

Study I (1995)	0.7	0.3 - 1.6	6.7
Siemiatycki (1991)	1.1	0.8 - 1.5	38.9

***Aggregate (OR studies):*** **1.0 0.8 - 1.4**  
 $\chi_1^2 = 1.0$   $p = 0.3$

***SMR:***

Lynge et al. (1997)			
Men	0.9	0.6 - 1.2	32.0
Women	0.2	0.0 - 1.3	1.6

***Aggregate (SMR studies):*** **0.9 0.6 - 1.3**  
 $\chi_1^2 = 0.9$   $p = 0.5$

***Aggregate (all studies):*** **1.0 0.8 - 1.2**  
 $\chi_3^2 = 2.4$   $p = 0.5$

**HERBICIDES:*****OR:***

Fryzek et al. (1997)	0.9	0.7 - 1.8	17.2
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***SIR / SMR:***

Asp et al. (1994)	1.1	0.3 - 2.8	3.1
Coggon et al. (1986)	0.7	0.3 - 1.4	7.6
Hooiveld et al. (1998)	2.5	0.7 - 6.3	3.2
Kogevinas et al. (1997)	0.9	0.7 - 1.3	43.5
Leet et al. (1996)	5.9	0.1 - 32.7	0.4
Lynge (1985)	0.6	0.1 - 1.7	2.2
Ott et al. (1987)	0.7	0.1 - 2.0	2.1
Sathiakumar et al. (1996)	1.8	0.4 - 5.3	2.1
Swaen et al (1992)	3.5	0.7 - 10.1	2.2

***Aggregate (SIR / SMR studies):*** **1.1 0.8 - 1.5**  
 $\chi_8^2 = 9.9$   $p = 0.3$

***Aggregate (all studies):*** **1.0 0.8 - 1.3**  
 $\chi_9^2 = 10.1$   $p = 0.3$

***[PMR:***

Magnani et al. (1987)	0.7	0.3 - 1.5 ]
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**INSECTICIDES:*****OR:***

Fryzek et al. (1997)	1.5	0.8 - 2.9	9.3
Garabrant et al. (1993)	21.0	2.6 - 966	0.4

***Aggregate (OR studies):*** **3.7 0.3 - 43.3**  
 $\chi_1^2 = 2.9$   $p = 0.1$

***SIR / SMR :***

Brown (1992)	0.8	0.3 - 1.7	5.8
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***Aggregate (all studies):*** **1.5 0.6 - 3.7**  
 $\chi_2^2 = 4.3$   $p = 0.1$

***[PMR:***

Cocco et al. (1997a)	0.6	0.1 - 1.6 ]
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**IRON AND IRON COMPOUNDS:*****OR:***

Siemiatycki (1991)	1.3	0.7 - 2.5
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**LEAD AND LEAD COMPOUNDS:*****HR:***

Tollestrup et al. (1995)	1.4	0.1 - 11.6	0.9
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***OR:***

Study I (1995)	1.2	0.7 - 1.9	17.3
Siemiatycki (1991)	1.1	0.7 - 1.7	19.5

**Aggregate (OR studies):** 1.1 0.8 - 1.6  
 $\chi_1^2 = 0.1$   $p = 0.80$

**Aggregate (HR and OR studies):** 1.1 0.8 - 1.6  
 $\chi_2^2 = 0.1$   $p = 1.0$

**SMR:**  
 Cocco et al. (1997b) 1.0 0.4 - 2.1 5.8

**Aggregate (all studies):** 1.1 0.8 - 1.5  
 $\chi_3^2 = 0.2$   $p = 1.0$

[PMR:  
 Magnani et al. (1987) 1.7 1.0 - 2.9 ]

**MAN-MADE VITREOUS FIBERS:**

**OR:**  
 Study I (1995) 0.8 0.5 - 1.3 16.8  
 Mack et al. (1985) 0.3 0.1 - 0.8 3.55  
 Siemiatycki (1991) 1.4 0.6 - 3.1 5.70

**Aggregate (OR studies):** 0.8 0.4 - 1.5  
 $\chi_2^2 = 5.2$   $p = 0.1$

**RR:**  
 Claude and Frenzel-  
 Beyme (1986) 6.8 1.0 - 45.2 1.1

**Aggregate (OR and RR studies):** 0.9 0.4 - 2.2  
 $\chi_3^2 = 9.9$   $p < 0.05$

**SMR:**  
 Boffetta et al. (1997) 1.1 0.8 - 1.5 37.5

**Aggregate (all studies):** 1.0 0.6 - 1.6  
 $\chi_4^2 = 10.7$   $p < 0.05$

**NICKEL:**

**OR:**  
 Mack et al. (1985) 1.5 0.4 - 5.7 2.2  
 Siemiatycki (1991) 2.1 1.2 - 3.8 11.6

**Aggregate (OR studies):** 2.0 1.2 - 3.2  
 $\chi_1^2 = 0.2$   $p = 0.6$

**SMR:**  
 Andersson et al. (1985) 1.2 0.01 - 6.2 0.4  
 Cammarano et al. (1986) 3.6 0.1 - 19.9 0.4  
 Shannon et al. (1991) 1.3 0.7 - 2.3 10.5

**Aggregate (SMR studies):** 1.3 0.8 - 2.4  
 $\chi_2 = 0.4$   $p = 0.8$

**Aggregate (all studies):** 1.7 1.1 - 2.5  
 $\chi_4^2 = 1.6$   $p = 0.8$

**OIL MIST:**

**OR:**  
 Bardin et al. (1997) 1.0 0.8 - 1.3 61.3  
 Greenland et al. (1994) 0.8 0.4 - 1.5 7.9  
 Mack et al. (1985) 0.5 0.2 - 1.0 5.9

**Aggregate (OR studies):** 0.8 0.6 - 1.3  
 $\chi_2^2 = 3.3$   $p = 0.2$

**SMR:**  
 Acquavella et al. (1993) 0.7 0.1 - 2.6 1.5  
 Decoufle (1978) 0.3 0.0 - 1.5 0.4  
 Tolbert et al. (1992) 0.9 0.7 - 1.0 134

**Aggregate (SMR studies):** 0.9 0.7 - 1.0  
 $\chi_2^2 = 0.6$   $p = 0.8$

**Aggregate (all studies):** 0.9 0.8 - 1.0  
 $\chi_5^2 = 4.4$   $p = 0.5$

[PMR:  
 Park and Mirer (1996) 3.6 1.0 - 12.6 ]

**POLYAROMATIC HYDROCARBONS:**

**OR:**  
 Study I (1995) 1.3 0.7 - 2.6 8.9  
 Siemiatycki (1991) 1.4 0.6 - 3.1 5.7

**Aggregate (OR studies):** 1.4 0.8 - 2.3  
 $\chi_1^2 = 0.01$   $p = 0.9$

**SIR / SMR:**  
 Cammarano et al. (1986) 3.6 0.1 - 19.9 0.4  
 Moulin et al. (1989) 2.8 0.3 - 10.2 1.3

**Aggregate (SIR / SMR studies):** 3.0 0.7 - 13.2  
 $\chi_1^2 = 0.0$   $p = 0.9$

**Aggregate (all studies):** 1.5 0.9 - 2.4  
 $\chi_3^2 = 1.0$   $p = 0.8$

**SILICA DUST:**

**OR:**  
 Study I (1995) 2.0 1.2 - 3.5 12.9  
 Siemiatycki (1991) 1.1 0.7 - 1.8 17.2

**Aggregate (OR studies):** 1.5 0.8 - 2.7  
 $\chi_1^2 = 2.7$   $p = 0.1$

**SMR:**  
 Checkoway et al. (1997) 1.2 0.6 - 2.1 8.4

**Aggregate (all studies):** 1.4 0.9 - 2.0  
 $\chi_2^2 = 3.0$   $p = 0.2$

[PMR:  
 Magnani et al. (1987) 1.0 0.7 - 1.4 ]

**WOOD DUST:**

**OR:**  
 Study I (1995) 1.3 0.8 - 2.1 15.5  
 Mack et al. (1985) 0.7 0.3 - 1.6 5.5  
 Mikoczy et al. (1996) 1.73 0.1 - 30.8 0.5  
 Siemiatycki (1991) 1.2 0.8 - 1.8 23.4

**Aggregate (all studies):** 1.2 0.9 - 1.6  
 $\chi_3^2 = 1.7$   $p = 0.6$

[PMR:  
 Magnani et al. (1987) 1.4 0.7 - 2.7 ]

#### APPENDIX 4.

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## **ORIGINAL PUBLICATIONS**



# Pancreatic Cancer and Occupational Exposures

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We conducted a nationwide case-control study in Finland to identify occupational risk factors for pancreatic cancer. We constructed the occupational exposure histories for 595 incident cases of primary exocrine cancer of the pancreas and of 1,622 cancer controls, using three different methods. We found elevated odds ratios (OR) for ionizing radiation [OR = 4.3; 95% confidence interval (CI) = 1.6–11.4], nonchlorinated solvents (OR = 1.6–1.8), and pesticides (OR = 1.7; 95% CI = 0.8–3.4). Asbestos, chromates, cleaning agents, waxes,

polishes, and most other exposures were not meaningfully associated with pancreatic cancer. Inorganic dust containing crystalline silica (OR = 2.0; 95% CI = 1.2–3.5), heat stress (OR = 2.2; 95% CI = 0.8–6.6), and rubber chemicals including acrylonitrile (OR = 2.1; 95% CI = 0.9–4.7) emerged as previously unsuspected risk factors. Occupational exposure probably has a small role in the etiology of pancreatic cancer in the present-day industrialized or postindustrial work environment. (*Epidemiology* 1995;6:498–502)

**Keywords:** pancreatic cancer, chemical agents, solvents, pesticides, silica, heat, acrylonitrile, ionizing radiation, case-control study, job-exposure matrix.

Pancreatic cancer is a highly fatal malignancy with a largely unknown etiology. The only extrinsic factor that has consistently been associated with pancreatic cancer is tobacco smoking.<sup>1</sup> The possible contribution of alcoholic beverages and coffee drinking has been widely studied and discussed, but the evidence for causal associations is not convincing.

Studies on occupational cancer have indicated an excess of pancreatic cancer among workers in a number of industries<sup>2</sup> such as the chemical industry, metallurgy, and aluminum production, but the findings are unspecific and inconsistent. Table 1 lists occupational chemical and other agents that have been associated with an excess risk in epidemiologic studies. Most of the associations emerged in one study only, and many of them may be chance findings. Polycyclic aromatic hydrocarbons, nitrogen oxides, aromatic amines, aluminum, lead, radioactive elements, and pesticides have also been identified in tobacco smoke,<sup>1</sup> but there is no solid evidence that these, or any other individual chemical agents, cause pancreatic cancer.

The purpose of the present study was to identify occupational risk factors for pancreatic cancer by applying several approaches in the assessment of previously suggested and other occupational exposures. This paper

deals with chemical and physical agents. The risks associated with occupational titles and industries have been reported in another paper.<sup>13</sup>

## Subjects and Methods

In this community-based case-control study, all cases deceased by April 1, 1990, who had contracted primary exocrine pancreatic cancer [*International Classification of Diseases*, 9th revision (ICD-9), 157, N = 1419] in Finland in 1984–1987 at the age of 40–74 years were identified from the files of the Finnish Cancer Register. The control series comprised 3510 deceased subjects who had contracted stomach cancer (ICD-9 151; N = 1950), colon cancer (ICD-9 153; N = 941), or rectal cancer (ICD-9 154; N = 664), chosen by using similar age and period criteria as for the case series. The control sites were selected as representing cancers that are not known to have substantial occupational etiologies.

Lifelong work histories were collected by a postal questionnaire sent to the next-of-kin traced through the Population Registry of Finland. The relatives were requested to list the employers, facilities, occupations, and calendar years of work of the subjects under study. Information on the somatic type of the subject, consumption of coffee, alcohol, tobacco, and sugar in the 1960s, and diagnosed pancreatitis, diabetes mellitus, and gallstones was also obtained. The response rate after two reminders was 47% for the cases and 50% for the controls. The responder was a spouse for 67% of the cases and 70% of the controls, offspring for 29% vs 27%, respectively, or another relative for 4% vs 2%, respectively. The responders for cases recalled 2.16 jobs per case, and those for controls recalled 2.13 jobs per control on average.

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**TABLE 1. Previous Studies on Occupational Exposures Reporting an Increased Risk of Pancreatic Cancer**

Agent	Country	References
Aluminum	France, USA	3, 4
Aromatic amines	England	5
Asbestos	USA, Poland	6, 7
Ashes and soot	Canada	8
Brass dust	Canada	8
Chromates	England	5
Combustion products of coal, natural gas, and wood	Canada	8
Copper fumes	Canada	8
Cotton dust	USA	6
Cleaning agents	Canada	8
Grain dust	Canada	8
Hydrogen fluoride	Canada	8
Inorganic insulation dust	Canada	8
Ionizing radiation	England	5
Lead fumes	Canada	8
Nickel compounds	Canada	8
Nitrogen oxides	Canada	8
Paint thinners	Sweden	9
Paints	England	5
Pesticides	USA	10, 11, 12
Phenol-formaldehyde	Canada	8
Plastic dust	Canada	8
Polycyclic aromatic hydrocarbons from coal and wood	Canada	8
Rayon fibers	Canada	8
Stainless steel dust	Canada	8
Sulfuric acid	Canada	8
Synthetic adhesives	Canada	8
Tin compounds and fumes	Canada	8
Waxes and polishes	Canada	8
Zinc fumes	Canada	8

We excluded histologically confirmed cases of endocrine pancreatic cancer (N = 8), nonrespondents (N = 2497), subjects with very incomplete work histories (N = 77), subjects with diagnosed pancreatitis (N = 22), and administrators and managers (N = 71). After exclusions, 595 cases and 1622 controls (936 stomach cancers, 395 colon cancers, 291 rectal cancers) remained. The percentage of men was 61% among cases and 62% among controls. The mean year of birth was 1922 among cases and 1921 among controls.

Because there was no strong *a priori* hypothesis on occupational causes of pancreatic cancer, we adopted an exposure assessment strategy that first aims at screening a large amount of chemical and physical agents (the industrial hygiene survey and job-exposure matrix analysis) and then inspects the findings more closely in terms of cumulative exposure (industrial hygiene reassessment).

The first exposure analysis ("IH survey") was based on a reconstruction of probable exposure to 17 selected agents. An experienced industrial hygienist (RD) fixed criteria for the exposure classes, reviewed the occupational histories, listed the probable exposures of the subjects, and rated them by the level of exposure (none/low/high).

The second exposure analysis ("JEM analysis") was a survey of potential exposures by a job-exposure matrix (JEM). The coded work histories were transformed into exposure indices of 50 agents with the help of the JEM constructed in Southampton, UK.<sup>14</sup> The JEM assigned

each case and control into exposure categories defined by the combination of the probability (none/low/high) and level (none/low/high) of exposure. To condense the data for further analysis, the category with both high probability and high level of exposure was labeled "substantial" exposure and analyzed separately from the joint category of all other grades of exposure, the latter being subsumed under "light" exposure.

The third exposure analysis ("IH reanalysis") was a detailed reanalysis of the agents that were associated with an elevated odds ratio (OR) in previous analyses. We applied the following criteria in the selection of agents for further analysis: OR of at least 1.5 at the lower or higher category of exposure; number of exposed cases at least five per exposure category; and exposure-response trend increasing or flat. Two industrial hygienists (TK, RD) reclassified all subjects according to the estimated cumulative exposure. The classes used were "none," "light," "moderate," and "heavy." Assignment to the class "heavy" required at least 10 years of work in conditions where the level of exposure was "high." "Moderate" referred to less than 10 years' employment in "high" exposure or at least 10 years' employment in "low" exposure. "Light" referred to less than 10 years' employment in "low" exposure. We considered the level "high" if it was likely to have exceeded 50% either of the threshold limit value (TLV) or of the biological exposure index (BEI) adopted by the American Conference of Governmental Industrial Hygienists (ACGIH).<sup>15</sup> We took frequent dermal contact with an agent able to penetrate the skin to imply "high" exposure. The assessment of dermal exposure was based on toxicologic information (chemical agent able to be absorbed through the skin) and the experience of the industrial hygienists (that spills to the skin occur in the occupation considered). The hygienists also specified further such chemically heterogeneous exposures as solvents and pesticides. We excluded all subjects whose exposure status was indeterminate from the analyses.

We carried out all exposure assessments without knowledge of the case/control status of the subjects. We assessed exposures through 1974 to allow for an induction period of at least 10 years between the onset of exposure and the end of the follow-up.

We calculated odds ratios and 95% confidence intervals (CI) by using the unconditional logistic regression model (PROGRAM PACKAGE PC-SAS R.6.04). The following potential confounders were included in the model: age (years), gender, smoking in the 1960s (no/yes), history of diabetes mellitus (no/yes), and alcohol consumption in the 1960s (four-category ordinal scale). We pooled all controls in the analyses. We analyzed separately subjects who had contracted cancer before age 56 years in IH reassessment, on the premise that effects of exposure might be more readily detectable among relatively young people.

## Results

Table 2 presents the results based on the IH survey. Some agents previously reported to be associated with

TABLE 2. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Pancreatic Cancer and Occupational Exposures on the Basis of Industrial Hygienic Survey of Work Histories; ORs (Probable Exposure vs No Exposure) Are Adjusted for Age, Gender, Tobacco Smoking, Diabetes Mellitus, and Alcohol Consumption; All Controls Pooled; NEC = Number of Exposed Cases

Exposure	NEC	OR	95% CI
Aromatic amines	3	1.87	0.41-8.48
Asbestos	20	0.58	0.35-0.97
Cadmium	3	0.77	0.20-2.88
Chlorophenols	2	1.35	0.25-7.22
Chromium (VI) compounds	8	0.86	0.38-1.96
Engine exhaust	19	0.89	0.51-1.53
Formaldehyde	8	0.63	0.28-1.38
Gasoline	9	0.72	0.34-1.55
Lead	26	1.10	0.68-1.78
Mineral wool	25	0.81	0.50-1.30
Polycyclic aromatic hydrocarbons	14	1.33	0.69-2.57
Pesticides	13	1.60	0.80-3.19
Silica	45	0.89	0.62-1.28
Solvents (all levels)	20	1.22	0.73-2.07
Solvents (high level)	14	2.01	0.98-4.10
Textile dust	12	0.95	0.48-1.88
Welding	30	0.81	0.53-1.27
Wood dust	25	1.30	0.79-2.14

pancreatic cancer showed indications of an elevated risk here as well. The OR for aromatic amines was 1.9 in the IH survey and 1.7 in the JEM analysis (0.9 for substantial exposure, two exposed cases). We examined ionizing radiation only by JEM (OR = 4.3; 95% CI = 1.6-11). Lead and its compounds had an OR of 1.1 in the IH survey, and 1.4 in the JEM analysis.

We observed some effects for agents not previously reported to be associated with pancreatic cancer. These included acrylonitrile (OR = 2.1; 95% CI = 0.9-4.7; JEM), beryllium (OR = 1.8; 95% CI = 0.7-4.5; JEM), heat (OR = 2.2; 95% CI = 0.8-6.6; JEM), inorganic dusts (OR = 2.6; 95% CI = 1.5-4.8; JEM), pesticides (OR = 1.6; 95% CI = 0.8-3.2; IH survey), and organic solvents (OR = 2.0; 95% CI = 1.0-4.1; high level in the IH survey, OR = 1.3; 95% CI = 0.9-2.0; light exposure in JEM). In addition, we found an OR of 1.8 (95% CI = 1.2-2.7) for light exposure to cold, but only 1.0 (95% CI = 0.8-1.2) for substantial exposure in the JEM analysis.

Except for cold, which showed a decreasing exposure-response relation, we conducted an IH reassessment that took into consideration not only the probability and level of exposure, but also the duration of exposure for all of the above exposures. Statistical analysis could be carried out for inorganic dust, lead and its compounds, pesticides, and organic solvents (Table 3). The small number of exposed cases did not allow a formal statistical analysis for other agents. The results of the IH reassessment are summarized as follows:

Acrylonitrile exposure could not be regarded as probable for any subject. Six cases (1.0%) and five controls (0.3%) had been potentially exposed to acrylonitrile while working in the rubber industry.

Aromatic amines have been used, for example, as rubber chemicals and in the dyeing of textiles, fur, and

TABLE 3. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Pancreatic Cancer and Occupational Exposures on the Basis of Detailed Reassessment of Exposures by Industrial Hygienists; ORs (Exposure vs No Exposure) Are Adjusted for Age, Gender, Tobacco Smoking, Diabetes Mellitus, and Alcohol Consumption; All Controls Pooled; NEC = Number of Exposed Cases

Agent	Cumulative Exposure*	NEC	OR	95% CI
Inorganic dust containing crystalline silica	Heavy	2	—†	
	Moderate	13	2.56	1.20-5.47
	Light	8	2.00	0.81-4.92
	All	23	2.02	1.17-3.49
Lead and lead compounds	Heavy	2	—†	
	Moderate	16	1.12	0.61-2.05
	Light	10	1.21	0.56-2.63
	All	28	1.19	0.74-1.90
Pesticides	Heavy	11	1.97	0.81-4.79
	Moderate	8	2.00	0.80-5.01
	Light	5	1.33	0.45-3.90
	All	13	1.68	0.83-3.37
Solvents	Heavy	3	1.02	0.24-4.43
	Moderate	16	1.12	0.61-2.05
	Light	10	1.21	0.56-2.63
	All	28	1.19	0.74-1.90
Aliphatic hydrocarbon solvents	Heavy	8	2.24	0.84-5.98
	Moderate	14	1.52	0.78-2.98
	Light	12	1.50	0.73-3.09
	All	34	1.63	1.04-2.55
Aromatic hydrocarbon solvents	Heavy	7	1.32	0.48-3.66
	Moderate	14	1.62	0.82-3.20
	Light	12	1.93	0.90-4.14
	All	34	1.79	1.13-2.84
Chlorinated hydrocarbon solvents	Heavy	9	1.77	0.67-4.68
	Moderate	8	1.11	0.47-2.58
	Light	2	—†	
	All	10	0.97	0.46-2.04
Other organic solvents	Heavy	3	—†	
	Moderate	8	2.22	0.83-5.94
	Light	10	1.46	0.67-3.19
	All	5	1.22	0.41-3.64
All (<56 years)	All	23	1.57	0.92-2.70
	All (<56 years)	7	1.98	0.65-6.03

\* Heavy: duration at least 10 years and high level; moderate: at least 10 years low level or under 10 years high level; light: under 10 years low level; for definitions of low and high levels, see Subjects and Methods.

† Few data (number of exposed cases less than 5).

leather. Four cases (0.6%) and nine controls (0.5%) had worked in jobs where exposure to aromatic amines was possible. Specific chemicals or actual exposures, however, could not be verified from work places.

Beryllium and its compounds have not been widely used in Finland. Less than 100 workers are currently exposed.<sup>16</sup> Most of the subjects assigned as potentially exposed to beryllium by the JEM were probably nonexposed.

Heat exposure was substantial for six cases (1.0%) and eight controls (0.5%). Typical jobs carried out in hot environments were smelting, casting, and furnace control in steel mills or foundries.

Inorganic dust containing silica was associated with pancreatic cancer in IH reanalysis (Table 3). The high-

est ORs were found in the category of moderate exposure (OR = 2.6; 95% CI = 1.2–5.5) and in the young age stratum (<56 years) (OR = 6.4; 95% CI = 1.2–35). The category of heavy exposure, which included two cases and seven controls, was too small for formal analysis. Exposure originated typically from dusty jobs in stone quarries, mines, foundries, or construction sites.

Ionizing radiation may occur, for example, in underground mining (radon) or in health services while using x-ray equipment or radioisotopes. After the exclusion of veterinarians, dentists, and physicians, who are usually only occasionally exposed, three cases (0.5%) and four controls (0.2%) with a potential for higher exposure remained. The exposed cases had been employed as x-ray assistant, radiologist, and underground miner. The occupations of the exposed controls were x-ray technician, x-ray assistant, nurse involved in x-raying, and tester/operator of x-ray equipment.

We found slight excess risk for lead and lead compounds (Table 3). We saw no obvious exposure-response relation. The category of heavy exposure comprised two cases and two controls. Typical jobs entailing exposure to lead were typesetting in printing shops, metal-plate works in garages, plumbing, lead battery making, and welding or painting in shipyards.

Pesticides are applied in forestry work, horticulture, agriculture, and wood preservation. The IH reanalysis provided results similar to those from the cruder IH survey but revealed a slightly increasing exposure-response relation. No case or control was heavily exposed to pesticides. Seven cases were exposed to insecticides in greenhouses or strawberry fields, five to phenoxy herbicides in forestry or maintenance of roadsides, and one to seed disinfectants in grain milling.

We evaluated organic solvents in four mutually exclusive subcategories (Table 3). The ORs for aliphatic hydrocarbons, aromatic hydrocarbons, and other solvents (for example, alcohols, esters, ketones) were all between 1.2 and 2.2, and the highest ORs were in the category of heavy exposure. With all exposed categories combined, the OR for aliphatic hydrocarbon solvents was 1.6 (95% CI = 1.0–2.6) and for aromatic hydrocarbon solvents, 1.8 (95% CI = 1.1–2.8). Chlorinated hydrocarbon solvents differed from other solvents, showing no elevated ORs. Typical jobs with exposure were painting, car repair (exposure to gasoline), paint manufacturing, varnishing of furniture, cleaning of rollers in printing shops, lamination of polyester products, and gluing of footwear.

## Discussion

Our results provide some support for hypotheses generated in previous studies (Table 1). Exposure to ionizing radiation showed an elevated OR of 4.3 in the crude JEM analysis and of about 2.5 when the analysis was restricted to occupations regularly involving x-ray apparatus or radioisotopes.

Heavy exposure to organic solvents was consistently associated with pancreatic cancer. We separated differ-

ent types of solvents in the detailed analysis, in which we found an excess risk from exposure to aliphatic hydrocarbons, aromatic hydrocarbons, and other solvents, but not to chlorinated hydrocarbons. Many of the workers were classified as having been exposed to more than one subtype of solvents. The excess in one category is therefore reflected in other categories. A Swedish case-control study reported an excess of pancreatic cancer among subjects exposed to paint thinners (relative risk of 2.5 using population controls, and 1.4 using hospital controls).<sup>9</sup> Findings possibly due to exposure to solvents have been reported among dry-cleaning workers (mainly exposed to chlorinated hydrocarbons),<sup>17</sup> jewelry workers (exposed to chlorinated hydrocarbons during metal cleaning),<sup>18</sup> and printing workers (exposed to hydrocarbon solvents during cleaning of rolls).<sup>19</sup> On the other hand, in many studies of painters, who generally have been heavily exposed to mixed solvents, pancreatic cancer was not in excess.<sup>20</sup>

An excess of pancreatic cancer in workers exposed to pesticides was found in three previous studies.<sup>10–12</sup> One specifically studied dichlorodiphenyltrichloroethane (DDT).<sup>12</sup> Some pesticides, such as nicotine, lindane, zineb, and benomyl, were occasionally mentioned in questionnaires obtained from the next-of-kin of cases. Phenoxy herbicides (2,4-dichlorophenoxy)acetic acid (2,4-D) and (2,4,5-trichlorophenoxy)acetic acid (2,4,5-T) were frequently used in forestry in the 1950s and 1960s in Finland. Nevertheless, mortality and morbidity due to pancreatic cancer were close to expected in a recent cohort study among Finnish herbicide sprayers.<sup>21</sup>

Weak indications of an excess were found for aromatic amines (actual exposure uncertain) and polycyclic aromatic hydrocarbons (only in the IH survey).

We found inorganic dust containing crystalline silica to be associated with pancreatic cancer in the IH reassessment of the exposures. This association, however, has not been observed in large studies among heavily exposed workers and silicotic patients.<sup>22</sup>

Work in a hot environment and the related hyperthermia have not been previously related to pancreatic cancer, to our knowledge. Some typical work places with heat exposure, for example, steel mills and foundries, involve possibly confounding exposures such as polycyclic aromatic hydrocarbons, metal fumes, and carbon monoxide. Worldwide incidence and mortality figures indicate that pancreatic cancer is probably more common in temperate than in tropical climates, which argues against the connection between heat stress and pancreatic cancer.<sup>23</sup>

Acrylonitrile was associated with an elevated OR in the JEM analysis, but most of the subjects were probably exposed to various rubber chemicals that might be carcinogenic.

The validity of the study, including the reliability of diagnostic classification, appropriateness of the controls, confounding, precision, and lack of potential bias of the questionnaire data, surrogate source of information, and nonresponse, have been discussed in our previous pa-

per.<sup>13</sup> Here, the most important validity aspects relate to the quality of occupational histories and of exposure assessment.

Poor comparability between occupational histories of cases and controls may result in differential misclassification bias. The low response rate typical of this kind of study does not bias results unless response information is related to both exposure and disease status. We tried to limit this problem by excluding all living cases and controls and by using similar data collection and coding procedures. Occupational histories obtained from the next-of-kin are likely to be incomplete, but the main (long-term) jobs are usually well recalled. Missing short-term jobs may decrease sensitivity of exposure assessment, but they do not affect specificity, which is likely to be high if only very probable exposures are accepted. Occupational exposures are relatively rare (prevalence often 0–5%) in community-based studies, and therefore the misclassification bias is low when specificity of exposure assessment is high. We therefore think that the low response rate and the use of the next-of-kin as the source of information are not serious flaws in the present study.

The JEM technique was tested separately by using the material from the Finnish study on liver cancer, which resembled the present study in its design.<sup>24</sup> The misclassification bias of the British JEM was high when light and substantial exposure categories were collapsed, but weak for the category of substantial exposure. Our rationale for using a JEM in this study was to screen rapidly for the effects of 50 agents. We then reassessed all elevated ORs against the original occupational histories to exclude false-positive exposures in the IH reassessment.

Although the IH reassessment was the best feasible method in this study, information on the occupational history from the next-of-kin was often inaccurate and did not allow quantitative calculation of cumulative exposure. Furthermore, this procedure may not account for differences in exposure for workers having the same occupation. Misclassification is likely, especially between ordinal exposure classes (light/moderate/heavy). The exposure-response relation tends to level off because the OR for the highest class becomes attenuated and that of the lowest class tends to rise artificially.

To improve the comparability of exposure information between the cases and controls, we restricted our study to deceased subjects. This restriction may introduce bias if the exposures under study are associated with survival. We did not have any data to examine whether the lower survival among pancreatic cancer cases compared with controls biased our results.

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# Occupational exposures and pancreatic cancer: a meta-analysis

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## Abstract

**Objectives**—Consolidation of epidemiological data on pancreatic cancer and worksite exposures.

**Methods**—Publications during 1969–98 were surveyed. Studies without verified exposures were excluded. Meta-analyses were conducted on data from 92 studies covering 161 populations, with results for 23 agents or groups of agents. With a standard format, five epidemiologists extracted risk estimates and variables of the structure and quality of each study. The extracted data were centrally checked. Random meta-models were applied.

**Results**—Based on 20 populations, exposure to chlorinated hydrocarbon (CHC) solvents and related compounds was associated with a meta-risk ratio (MRR) of 1.4 (95% confidence interval (95% CI) 1.0 to 1.8). Nickel and nickel compounds were considered in four populations (1.9; 1.2 to 3.2). Excesses were found also for chromium and chromium compounds (1.4; 0.9 to 2.3), polycyclic aromatic hydrocarbons (PAHs) (1.5; 0.9 to 2.5), organochlorine insecticides (1.5; 0.6 to 3.7), silica dust (1.4; 0.9 to 2.0), and aliphatic and alicyclic hydrocarbon solvents (1.3; 0.8 to 2.8). Evidence on pancreatic carcinogenicity was weak or non-positive for the following agents: acrylonitrile (1.1; 0.0 to 6.2); arsenic (1.0; 0.6 to 1.5); asbestos (1.1; 0.9 to 1.5); diesel engine exhaust (1.0; 0.9 to 1.3); electromagnetic fields (1.1; 0.8 to 1.4); formaldehyde (0.8; 0.5 to 1.0); flour dust (1.1; 0.3 to 3.2); cadmium and cadmium compounds (0.7; 0.4 to 1.4); gasoline (1.0; 0.8 to 1.2); herbicides (1.0; 0.8 to 1.3); iron and iron compounds (1.3; 0.7 to 2.5); lead and lead compounds (1.1; 0.8 to 1.5); man-made vitreous fibres (1.0; 0.6 to 1.6); oil mist (0.9; 0.8 to 1.0); and wood dust (1.1; 0.9 to 2.5). The occupational aetiological fraction of pancreatic cancer was estimated at 12%. In a sub-population exposed to CHC solvents and related compounds, it was 29%; to chromium and chromium compounds, 23%; to nickel and nickel compounds, 47%; to insecticides, 33%; and to PAHs, 33%.

**Conclusion**—Occupational exposures may increase risk of pancreatic cancer. High quality studies are called for on interactions between occupational, environmental, and lifestyle factors as well as

## interactions between genes and the environment.

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**Keywords:** pancreatic cancer; occupational exposure; meta-analysis

Some 180 000 pancreatic cancers are registered annually in the world. It is highly and rapidly fatal and represents the fifth leading cause of deaths from cancer in industrialised countries and is 50%–100% more common in men than in women. It is not consistently associated with socioeconomic status within national populations, although there is a tendency toward higher age adjusted risk in richer than poorer countries.<sup>1–3</sup> Incidence has risen in industrialised countries since the 1960s and subsequently levelled off in several populations.<sup>4</sup>

The causes of pancreatic cancer are mostly unknown. Tobacco smoking is the single established common cause. The proportion of cases attributable to smoking has been estimated at 5%–50%, depending on the population.<sup>3</sup> Epidemiology of pancreatic cancer has suffered from bias due to high misclassification rate, notably prominent when case definition has been based only on death certificates. This has resulted in inconsistencies in the results on the aetiological role of environmental and occupational determinants of pancreatic cancer.<sup>3–6</sup>

We identified published epidemiological studies about pancreatic cancer and job titles, industrial branches, and occupational exposures, and conducted a meta-analysis of the role of 23 chemical or physical agents present in the working environment that affect the aetiology of pancreatic cancer.

## Materials and methods

The literature search covered the Medline, Toxline, and Cancerlit databases for the period 1969 to May 1998, with the following search conditions:

- (1) (occupational OR agriculture) AND neoplasms AND morbidity
- (2) (occupational OR agriculture) AND neoplasms AND mortality NOT morbidity
- (3) (occupational OR agriculture) AND neoplasms AND incidence NOT mortality NOT morbidity
- (4) (pancreatic OR digestive) AND occupational
- (5) (pancreatic OR digestive) AND case AND (control OR referent)

The search was accompanied by a scan of the lists of reference of the identified studies. In all, 1902 studies were identified. A total of 365 studies remained after exclusion of studies that did not report on pancreatic cancer; that did not represent the most recent update; that reported insufficient data for the meta-analysis; that did not report data for any job or occupational agent; that did not report original results (reviews); that reported on part of a larger population reported elsewhere; and that reported on job categories or agent categories too broad or outside our list of job titles and agents. The agents were based on the FINJEM job exposure matrix.<sup>7</sup> The list of job titles covered 150 entries in the Finnish social status categories 3, 4, and 5. Data for categories 1 and 2 represented the highest social categories and were excluded because the relevant occupational chemical and physical exposures were minimal or non-existent. The chemical and physical agents considered were the following 23 agents or groups of agents: aliphatic and alicyclic hydrocarbon solvents; aromatic hydrocarbon solvents (excluding aromatic amines); arsenic; asbestos; cadmium and cadmium compounds; chlorinated hydrocarbon (CHC) solvents and related compounds (excluding organochlorine insecticides); chromium and chromium compounds; diesel engine exhaust; electromagnetic fields, flour dust, formaldehyde, fungicides, gasoline, herbicides, insecticides, iron and iron compounds; lead and lead compounds; man made vitreous fibres; nickel and nickel compounds; oil mist (including machining fluid and cutting fluid); polycyclic aromatic hydrocarbons (PAH); silica dust; and wood dust.

The studies were divided into (a) agent specific studies with direct risk estimates for one or several of the 23 agents, or for job titles with verified exposure(s) to the agent(s), and (b) job specific studies without risk estimates for any of the selected agents but instead for one or more of the 150 job categories without verified exposure(s) to the agent(s). This report is based on the data set from agent specific studies only (92 studies presenting data for 161 different exposed populations).<sup>8-99</sup>

Standardised data extraction forms (available from the corresponding author) covered characteristics of the study (publication year, country, study type, case definition, source of cases, reference population, selection of control subjects, follow up period, loss to follow up, response rates, sources of exposure or job data, time reference for exposure or job; risk measure, cohort admission, lag periods, exposure-response, job title coding applied), risk estimates, latency periods, and numbers of exposed cases.

Five epidemiologists (AO, TP, NJ, EW, CW) read the reports and extracted the necessary data, using predefined rules. The main principles of extraction were to extract:

- Relevant, unbiased estimates of relative risk
- Measures of relative risks associated with specific exposures and job titles

- The most unbiased estimate if there is a choice and choose:
- Estimates adjusted for at least known risk factors for pancreatic cancer (age, sex, tobacco smoking), if there was a choice
- Social class adjusted risk ratios over those unadjusted for social class
- Risk estimate nearest to 20 y latency period, if there is a choice.

The extracted data were then centrally checked for consistency (AO, TP) and finally entered into a database and checked for correctness.

We recovered missing 95% CIs with Byar's approximation<sup>100</sup> in cohort studies, and with variance of log odds ratio in case-control studies.

Simple random effects models<sup>101</sup> were applied in estimating the meta-risk ratios (MRR). Fixed effects models were used only on occasion for comparison with results from random effects models. Standard errors of log of

Table 1 Characterisation of the 92 agent specific studies

	Populations (n)
Study type:	
Administrative (linkage of administrative records or PMR/PCMR/MOR studies)	23
Industrial cohort	88
Industry based (nested) case-control study	7
Population or hospital based case-control study	43
Cases:	
Exocrine pancreatic cancers only	32
All pancreatic cancers	127
Unspecified	2
Diagnosis of cases:	
Histological	47
Other (clinical: radiology, necropsy, etc)	2
Mortality files	96
Mixed	9
Unknown	7
Ascertainment of cases:	
Mortality files	98
Cancer registry files	40
Hospital records	21
Mixed	1
Unspecified	1
Sex:	
Men	112
Women	8
Both men and women or unspecified	41
Risk measure:	
SMR (standardised mortality ratio)	68
SIR (standardised incidence ratio)	17
PMR (proportional mortality ratio)	18
MOR (mortality odds ratio)	1
HR (hazard ratio)	3
OR (odds ratio)	50
RR (risk ratio)*	4
Source of exposure data:	
Industrial hygiene measurements	4
Job exposure matrix	15
Expert assessment	25
Job titles†	57
Other‡	19
Mixed	37
Unknown	4
Time reference of exposure:	
Last or around diagnosis	17
Earlier cross section	9
Lifetime longitudinal	47
Less than lifetime longitudinal	80
Other	1
Unknown	7
Total	161

\*Ratio of risks or cumulative incidences in exposed and unexposed cohorts.

†Job titles with specifically verified exposure(s) to the relevant agent(s).

‡Employment duration, biological monitoring, employer record, registry of chemicals, self reporting.

risk ratios (RRs), when not given, were recovered as the log of the ratio of upper and lower 95% CIs divided by 3.92. A test of the heterogeneity was performed as a  $\chi^2$  test with degrees of freedom equal to one less than the number of populations. The public domain software package *computer programs for epidemiologic analysis* (PEPI; <http://www.usd-inc.com/pepi.html>), version 3.0, and the statistical software package *Stata* release 5 were used.<sup>102</sup>

Population aetiological fractions were estimated as  $PEF=p-p/MRR$ , and aetiological fractions among the exposed groups as  $EEF=1-1/MRR$  for each agent where excesses were observed. The proportion of pancreatic cancer cases who were exposed (p), was calculated as  $\Sigma$ exposed cases/ $\Sigma$ all cases, summing over studies that provided the necessary numbers. The PEFs were based on MRRs from population based and hospital based case-control studies only, whereas the EEFs were based on MRRs from all except proportional studies. Aetiological fractions were not calculated for agents with no indication of increased risk.

The data were organised and analysed by populations rather than studies. This was because most studies considered more than one subpopulation defined by exposure. A total of 161 populations were covered in agent specific studies (table 1). Most (85) populations were from North America, closely followed by Western Europe (63). There were few populations from Central and Eastern Europe, Oceania, and none from Middle and South America, Asia, or Africa. The annual number of studies has been rising considerably during 1969–8 (two studies during 1969–79; 58 studies during 1980–9, and 101 studies during 1990–8).

Industrial cohort (88 populations) and case-control (50 populations) studies were the most common agent specific studies (table 1). The cases represented predominantly all pancreatic

cancers, irrespective of type. As most studies considered mortality, the diagnosis was in most populations obtained from the death record. Less than 5% of the populations were women. Exposures were assessed in 57 populations through job titles; in 25 through expert assessments; in 15 through job exposure matrices (JEMs); and in 60 through other, mixed, or unexplained methods. Industrial hygiene measurements were explicitly applied in four populations only. Exposure assessment was longitudinal for 127 populations.

Reference populations in cohort studies represented predominantly national or other large populations (57 studies). Fewer studies (23) used local populations as the reference; even fewer (seven) used an internal reference. Follow up for case ascertainment began usually during 1940–79 (99 studies) and spanned in most studies a period of  $\geq 10$  years (98 studies). Losses to follow up in agent specific cohort studies were minor or moderate (<5% in 44 studies but unknown in 51 studies) but were more marked in job branch cohort studies. Agent specific cohorts were rather evenly distributed between entry cohorts, cross sectional cohorts, and mixed cohorts.

Case-control studies used variable periods of case ascertainment. Most agent specific case-control studies (44) used cancer or population controls. Response rates were  $\leq 80\%$  for the cases, and  $\leq 90\%$  in the controls. Sixteen studies did not report response rates.

## Results

The aggregated results for the occupational agents are shown in table 2. Random effects models without covariates were used. Proportional studies (four) representing 18 populations, were excluded from most analyses because of poor quality. The study by Magnani *et al.*<sup>62</sup> although reported as a case-control study, used job and branch data as well as diagnoses of pancreatic cancer from death certificates only. We therefore treated it as a proportional mortality rate (PMR) study.

Significant excesses were found for nickel and nickel compounds (MRR 1.9; 1.2 to 3.2; four populations) and CHC solvents and related compounds (1.4; 95% CI 1.0 to 1.8; 20 populations). Non-significant excesses over  $MRR > 1.3$  were found for PAHs; organochlorine insecticides; silica dust; and chromium and chromium compounds.

Table 3 shows the MRRs after stratification by sex and diagnostic quality. Only seven studies presented results for women. For CHC solvents and related compounds, the MRR for women (1.8; 95% CI 0.7 to 5.8; three populations) was higher than for men (1.3; 0.9 to 1.9; 14 populations). The MRR remained essentially unchanged irrespective of whether histological verification of diagnoses of pancreatic cancer was done or not. For chromium and chromium compounds and for PAHs, the excess risks disappeared in studies that had histological diagnoses, whereas for nickel and nickel compounds, the MRR was increased in populations with and without histological verification of the cases.

Table 2 Populations (n), metarisk estimates (MRRs) (95% CIs), ranges of point estimates and p values for heterogeneity by occupational agents (proportional studies excluded: simple random effects models with no covariates)

Agent	n	MRR	95% CI	Range of point estimate	p Value
Aliphatic and alicyclic hydrocarbon solvents	2	1.3	0.8 to 2.0	1.0–1.6	0.09
Aromatic hydrocarbon solvents	13	1.0	0.8 to 1.3	0.5–2.9	0.2
Arsenic	4	1.0	0.6 to 1.6	0.9–1.4	0.9
Asbestos	24	1.1	0.9 to 1.4	0.5–3.6	0.004
Cadmium and cadmium compounds	2	0.7	0.4 to 1.4	0.7–0.8	0.9
Chlorinated hydrocarbon solvents and related compounds	20	1.4	1.0 to 1.8	0.3–4.9	0.05
Chromium and chromium compounds	9	1.4	0.9 to 2.3	0.6–20	0.2
Diesel engine exhaust	7	1.0	0.9 to 1.2	0.5–1.4	0.2
Electromagnetic fields	5	1.1	0.8 to 1.4	0.6–2.4	0.04
Flour dust	1	1.1	0.3 to 3.2		
Formaldehyde	5	0.8	0.5 to 1.0	0.5–1.0	0.3
Fungicides	2	1.3	0.4 to 3.8	1.3–1.4	0.9
Gasoline	4	1.0	0.8 to 1.2	0.2–1.1	0.5
Herbicides	10	1.0	0.8 to 1.3	0.6–5.9	0.3
Insecticides	3	1.5	0.6 to 3.7	0.8–21.0	0.1
Iron and iron compounds	1	1.3	0.7 to 2.5		
Lead and lead compounds	4	1.1	0.8 to 1.5	1.0–1.4	1.0
Man made vitreous fibres	5	1.0	0.6 to 1.6	0.3–6.8	0.03
Nickel and nickel compounds	4	1.9	1.2 to 3.2	1.2–3.6	0.9
Oil mist	6	0.9	0.8 to 1.0	0.3–1.0	0.5
Polycyclic aromatic hydrocarbons (PAHs)	4	1.5	0.9 to 2.5	1.3–3.6	0.8
Silica dust	3	1.4	0.9 to 2.0	1.1–2.0	0.2
Wood dust	4	1.1	0.8 to 1.5	0.7–1.7	0.3

Table 3 Populations (n), metarisk estimates (MRRs) (95% CIs) by occupational agents, sex, and quality of diagnosis: (proportional studies are excluded: simple random effects models with covariates)

Agent	Sex						Histological diagnosis								
	Men			Women			Unspecified or both			Yes			No		
	n	MRR	95% CI	n	MRR	95% CI	n	MRR	95% CI	n	MRR	95% CI	n	MRR	95% CI
Aliphatic and alicyclic hydrocarbon solvents										2	1.3	0.8 to 2.0			
Aromatic hydrocarbon solvents	6	0.7	0.6 to 1.0				7	1.3	0.9 to 1.7	4	1.0	0.6 to 1.8	9	1.0	0.7 to 1.2
Arsenic	3	0.9	0.6 to 1.6							2	1.1	0.5 to 2.7	2	0.9	0.5 to 1.6
Asbestos	18	1.3	1.0 to 1.5	3	0.8	0.4 to 1.7	3	0.6	0.4 to 0.8	3	0.7	0.4 to 1.2	21	1.2	1.0 to 1.5
Chlorinated hydrocarbon solvents and related compounds	14	1.3	0.9 to 1.9	3	1.8	0.7 to 4.6	3	1.6	0.8 to 2.9	4	1.2	0.7 to 2.1	16	1.4	1.0 to 2.1
Chromium and chromium compounds	7	1.8	0.9 to 3.6				2	0.9	0.5 to 1.8	3	1.0	0.7 to 1.6	6	2.3	0.9 to 5.8
Diesel engine exhaust	5	1.1	0.9 to 1.3				2	0.9	0.6 to 0.9	3	1.1	0.9 to 1.2	4	1.0	0.9 to 1.1
Electromagnetic fields	6	1.1	0.9 to 1.3							6	1.1	0.9 to 1.3	6	1.1	0.9 to 1.3
Formaldehyde	3	0.8	0.5 to 1.3				2	0.6	0.3 to 1.1	2	0.5	0.3 to 0.9	3	0.9	0.7 to 1.3
Gasoline	2	1.0	0.8 to 1.3							2	1.0	0.8 to 1.4	2	0.9	0.6 to 1.3
Herbicides	8	1.2	0.8 to 2.0				2	0.9	0.7 to 1.2				9	1.1	0.8 to 1.5
Insecticides	2	0.7	0.4 to 1.5				2	3.7	0.3 to 43.3				3	1.2	0.3 to 4.3
Lead and lead compounds	3	1.1	0.8 to 1.6							2	1.1	0.8 to 1.6	2	1.0	0.5 to 2.2
Man made vitreous fibres	2	1.8	0.8 to 3.8				3	0.9	0.7 to 1.2	3	0.8	0.5 to 1.2	2	1.2	0.8 to 1.6
Nickel and nickel compounds	3	2.0	1.2 to 3.5							2	2.0	1.2 to 3.2	2	1.6	0.4 to 6.9
Oil mist	4	0.9	0.8 to 1.0				2	0.5	0.3 to 1.1				6	0.9	0.7 to 1.2
Polycyclic aromatic hydrocarbons (PAHs)	3	1.8	0.8 to 3.4							2	1.4	0.8 to 2.3	2	3.0	0.7 to 13.2
Silica dust	2	1.1	0.8 to 1.5							2	1.5	0.8 to 2.6			
Wood dust							3	1.1	0.7 to 1.7	3	1.2	0.9 to 1.6			

Table 4 presents results by study type. For CHC solvents and related compounds, cohort studies with internal reference and case-control studies yielded an MRR of 1.4 (95% CI 0.8 to 2.4; four populations). In studies that used general populations as the reference (SMR/SIR studies), MRR was 1.3 (0.9 to 2.0; 16 populations). For the lower quality proportional studies, it was 1.1 (0.9 to 1.3; four populations).

For nickel and nickel compounds the MRR was highest for case-control studies (2.0; 95% CI 1.2 to 3.2; two populations). For chromium and chromium compounds it was highest in SMR/SIR studies (2.3; 0.9 to 5.8; six populations), as for PAHs it was (3.0; 0.7 to 13.2; two populations).

For asbestos, the 20 SMR/SIR populations yielded a significant MRR of 1.2 (95% CI 1.0 to 1.5), whereas the four case-control populations resulted in an MRR of 0.7 (0.5 to 1.0).

Two cohort studies with an internal reference yielded a significant MRR of 1.4 (95% CI 1.3 to 1.9) for diesel engine exhaust, which was, however, not confirmed in case-control and SMR/SIR studies, the overall MRR remaining at 1.0 (95% CI 0.9 to 1.2).

For insecticides, the overall MRR was 1.5 (95% CI 0.6 to 3.7). For the two case-control studies, both based on cytological diagnoses, it was 3.7 (95% CI 0.3 to 43.3), which was not confirmed in the one occupational cohort mortality study. All insecticide results

Table 4 Populations (n), metarisk ratios (MRRs) (95% CIs), by study type (proportional studies excluded: simple random effects models with no covariates)

Agent	Case-control studies and cohort studies with internal reference			SMR/SIR studies		
	n	MRR	95% CI	n	MRR	95% CI
Aliphatic and alicyclic hydrocarbon solvents	2	1.3	0.8 to 2.0			
Aromatic hydrocarbon solvents	4	0.9	0.5 to 1.6	9	1.0	0.8 to 1.3
Arsenic	3	1.2	0.5 to 2.6	1	0.9	0.4 to 1.5
Asbestos	4	0.7	0.5 to 1.0	20	1.2	1.0 to 1.5
Cadmium and cadmium compounds	1	0.8	0.2 to 2.9	1	0.7	0.3 to 1.4
Chlorinated hydrocarbon solvents and related compounds	4	1.4	0.8 to 2.4	16	1.3	0.9 to 2.0
Chromium and chromium compounds	3	1.0	0.7 to 1.6	6	2.3	0.9 to 5.8
Diesel engine exhaust	5	1.1	0.9 to 1.4	2	0.9	0.8 to 1.1
Electromagnetic fields				5	1.1	0.8 to 1.4
Flour dust	1	1.1	0.3 to 3.2			
Formaldehyde	2	0.5	0.3 to 1.6	3	0.9	0.7 to 1.3
Fungicides	2	1.3	0.3 to 3.8			
Gasoline	2	1.0	0.8 to 1.4	2	0.9	0.6 to 1.3
Herbicides	1	0.9	0.7 to 1.8	9	1.0	0.8 to 1.3
Insecticides	2	3.7	0.3 to 43.3	1	0.8	0.3 to 1.7
Iron and iron compounds	1	1.3	0.7 to 2.5			
Lead and lead compounds	3	1.1	0.8 to 1.6	1	1.0	0.4 to 2.1
Man made vitreous fibres	4	0.9	0.4 to 2.2	1	1.1	0.8 to 1.5
Nickel and nickel compounds	2	2.0	1.2 to 3.2	2	1.6	0.4 to 6.9
Oil mist	3	0.8	0.6 to 1.3	3	0.9	0.7 to 1.0
Polycyclic aromatic hydrocarbons (PAHs)	2	1.4	0.8 to 2.3	2	3.0	0.7 to 13.2
Silica dust	2	1.5	0.8 to 2.7	1	1.2	0.6 to 2.1
Wood dust	4	1.2	0.9 to 1.6			

Table 5 Populations (n), population aetiological fractions (PEFs), aetiological fractions among exposed (EEFs), (95% CIs)

Agent	Population aetiological fraction (PEF)					Aetiological fraction among exposed (EEF)					
	n	Proportion exposed	MRR	95% CI	PEF	95% CI	n	MRR	95% CI	EEF	95% CI
Aliphatic and alicyclic hydrocarbon solvents	2	0.094	1.3	0.8 to 2.0	0.022	0.00 to 0.047	2	1.3	0.8 to 2.0	0.23	0.00 to 0.50
Chlorinated hydrocarbon solvents and related compounds	3	0.061	1.2	0.7 to 1.9	0.010	0.00 to 0.029	20	1.4	1.0 to 1.8	0.29	0.00 to 0.44
Chromium and chromium compounds	3	0.034	1.1	0.7 to 1.6	0.003	0.00 to 0.013	9	1.4	0.9 to 2.3	0.29	0.00 to 0.57
Fungicides	1	0.0034	1.4	0.3 to 7.2	0.001	0.00 to 0.0029	2	1.3	0.4 to 3.8	0.23	0.00 to 0.74
Insecticides	1	0.067	1.3	0.7 to 2.5	0.016	0.00 to 0.040	3	1.5	0.6 to 3.7	0.33	0.00 to 0.73
Iron and iron compounds	2	0.11	1.1	0.8 to 1.6	0.010	0.00 to 0.041	1	1.3	0.7 to 2.5	0.23	0.00 to 0.60
Lead and lead compounds	2	0.063	2.0	1.2 to 3.2	0.032	0.011 to 0.043	4	1.9	1.2 to 3.2	0.47	0.17 to 0.69
Nickel and nickel compounds	2	0.029	1.4	0.8 to 2.3	0.008	0.00 to 0.016	4	1.5	0.9 to 2.4	0.33	0.00 to 0.58
Polycyclic aromatic hydrocarbons (PAHs)	2	0.063	1.5	0.8 to 2.7	0.021	0.00 to 0.040	3	1.4	0.9 to 2.0	0.29	0.00 to 0.50
Silica dust	4	0.062	1.2	0.9 to 1.6	0.01	0.00 to 0.023	5	1.2	0.9 to 1.6	0.17	0.00 to 0.38
Wood dust	4	0.062	1.2	0.9 to 1.6	0.01	0.00 to 0.023	5	1.2	0.9 to 1.6	0.17	0.00 to 0.38

Only agents with both MRRs >1.0 considered. Negative lower confidence bounds of PEFs and EEFs forced to zero. MRR=meta risk ratio, as estimated from population based and hospital based case-control studies for PFF, and all but proportional studies for EEF.

concerned organochlorine compounds. There were 12 further studies that considered unspecified pesticides. This group of agents was considered to be too heterogeneous in exposures and was dropped from the analysis.

Given the low proportions of the populations that were exposed, the PEFs remained low, from 0.1%–3% (table 5). Assuming independence between exposures, summing up of the PEFs resulted in an overall aetiological fraction of 12% for workplace exposures. The agent specific EEFs ranged from 9% to 47%, with wide 95% CIs. In a subpopulation exposed to nickel and nickel compounds, the EEF was 47% (95% CI 17 to 69%); to PAHs, 33% (0 to 58%); to insecticides, 33% (0 to 73%); to CHC solvents and related compounds, 29% (0 to 44%); to chromium and chromium compounds, 29% (0 to 57%); and to aliphatic and alicyclic solvents, 23% (0 to 50%).

## Discussion

### EVIDENCE

The excess risk found for CHC solvents and related compounds was based on 20 populations. Heterogeneity of RRs was nearly significant and may be explained by differences in the quality and exposure level of the agents. Various compounds with variable carcinogenic potential were mentioned as worker exposures: trichloroethylene, tetrachloroethylene, 1,1,1-trichloroethane, methylene chloride, vinyl chloride, ethylene chlorohydrine, ethylene dichloride, bis(chloromethyl)ether, and polychlorinated biphenyls. Intensities and long term doses were characterised in most of the studies either poorly or not at all.

The risk for nickel and nickel compounds was most evident in population based case-control studies. For chromium and chromium compounds, the MRR was non-significantly increased in all studies, but was not in excess in population based case-control studies. For PAHs, a non-significant increase was present in all studies, in population-based case-control studies, and in the two SMR/SIR studies. These findings could have occurred by chance.

The excess of silica dust reached significance in one<sup>52</sup> of three studies. This same Finnish population-based case-control study found a significant excess for aliphatic and alicyclic hydrocarbon solvents. This finding was aggre-

gated with the finding of no excess for alkanes (C<sub>5</sub>-C<sub>17</sub>) in another population based study from Montreal,<sup>79</sup> the result being an MRR of 1.3 (95% CI 0.8 to 2.0).

Two case-control studies,<sup>41 42</sup> both based on cytological diagnoses, one SMR study,<sup>24</sup> and one PMR study<sup>31</sup> considered exposure to organochlorine insecticides. The insecticidal agents listed as exposures were 1,1-bis(4-chlorophenyl)-2,2,2-trichloroethane (DDT), chlordane, heptachlor, endrin, aldrin, dieldrin, bulan, chlorfenethol, chloropropylate, dicofol, ethylan, methoxychlor, and tetrachlorodiphenylethane (TDE). Excluding the PMR study, the aggregated MRR was 1.5 (95% CI 0.6 to 3.7). In case-control studies it was 3.7 (0.3 to 43) based on the random effects model, and 1.7 (0.9 to 3.2) based on the fixed effects model (heterogeneity p=0.09). The highest RR was obtained for exposure to the DDT family (DDT, ethylan, DDD; OR 21.0; 95% CI 2.6 to 966; five exposed cases) in a case-control study nested in a chemical manufacturing cohort.<sup>42</sup> Potential confounders included nitrophenol derivatives, clays, N,N-dimethylformamide, dispersing agents, octane, and carbon tetrachloride. The other case-control study<sup>41</sup> was population based (Michigan, US), with self reported exposures. Based on 21 exposed cases, it yielded an OR of 1.5 (95% CI 0.8 to 2.9) for organochlorine insecticides. Assuming an effect, the difference between the two point estimates might be due to qualitative and quantitative differences in exposures between manufacturing and agricultural application.

There is a possibility of effect modification of environmental or occupational determinants by lifestyles (tobacco, alcohol, coffee) or dietary factors. These interactions were not considered in the studies. Also, genetic factors may interact with environmental or occupational exposures.

### COMBINABILITY AND HETEROGENEITY

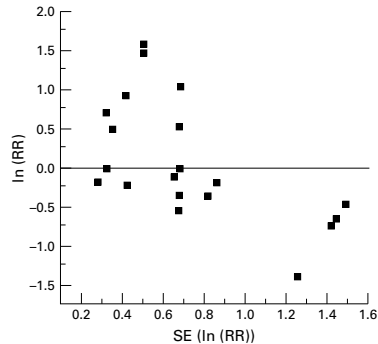
Epidemiological meta-analyses have imperfect combinability of results associated with different study types, methods, populations, exposure circumstances, and diagnostic specificities. We calculated MRRs including and excluding the poorest quality studies (proportional studies). We also calculated separate MRRs for cohort studies with internal controls,

case-control studies, SMR/SIR studies, and the few proportional studies. Differences in results from different study types were not consistent.

Several populations were poorly characterized. There were even studies that did not specify whether the cohort consisted of men, women, or both. We analysed the data for known male and female populations separately, and found data for women to be associated with a slightly higher MRR than data for men for CHC solvents and related compounds.

There was in all likelihood substantial heterogeneity across populations in the quality and intensity of exposure categories, in the intake route (respiratory, dermal, or other) of exposure, time aspects of exposure (period, latency, duration, quality, and intensity), and applied scales of exposure, as well as in the quality of diagnosis of pancreatic cancer. Qualitative and quantitative differences in exposures have already been exemplified in connection with CHC solvents and related compounds and organochlorine insecticides. Based on a rough statistical test, significant heterogeneity of risk was found for asbestos, electromagnetic fields, CHC solvents and related compounds, and man made vitreous fibres. Some studies did not document the exposure aspects at all, and no study provided a full documentation. Expert assessments, which represent an imperfect yet acceptable method of exposure assessment, were used in 25 populations. Industrial hygiene measurements that represent a certain degree of objectivity were used as the prime source of exposure data in only four populations. Exposure assessment based on job titles (57 populations) are of lower quality, unless the exposures are highly homogeneous within job titles. However, some of the populations represented rather homogeneous single title cohorts. Job exposure matrices assess exposures better if the matrix is specific for branch and job title, even for company and period. The JEMs of variable degree of specificity were applied in 15 populations. Most were relatively unspecific and thereby induced exposure misclassification. Misclassification, however, was likely to be non-differential, resulting in underestimation of the MRR. Multiple sources of exposure data were applied in 37 populations. Exposure data were longitudinal in 127 populations and lifelong in 47 populations. The longitudinality of exposures was thus well covered.

Misclassification rates for pancreatic cancer are marked, particularly when the diagnosis is based on death certificate only. This adds to the bias in the meta estimates towards the null value. Garabrandt *et al*<sup>12</sup> showed what the magnitude of the impact may be in a single study. They compared, in a case-control study of pancreatic cancer, ORs for the DDT family between cases representing death certificates and cases representing cytological verification. For death certificate cases the ORs ranged from 0.8 to 2.6; for cytologically verified cases, from 15.4 to infinity. In our meta-analysis, agent specific MRRs were higher for nine agents but lower for 10 agents in populations in



Funnel plot for chlorinated hydrocarbon solvents. Natural log of risk ratio ( $\ln(RR)$ ) plotted against imprecision ( $SE$  of  $\ln(RR)$ ). The unit of the plot is study population.

which histological verification was applied, compared with no histological verification. For CHC solvents and related compounds, the two MRRs were practically identical. For PAHs and chromium, the MRRs were higher in populations with histological diagnoses.

#### PUBLICATION BIAS

Publication bias is not likely in this study, as very few small studies expressly considered the occupational determinants of pancreatic cancer. Non-positive occupational findings from small studies therefore were not likely to remain unpublished. Also, a funnel plot for CHC solvents and related compounds, for which an excess risk was found (figure), did not identify a concentration of small studies (high  $SE$  of  $\ln(RR)$ ) at high RRs. Publication bias therefore may be claimed to be minimal or non-existent. Negative results based on reasonably large numbers are unlikely to remain unpublished.

A counterargument may be raised about cohort studies with multiple end points. Some of these studies deleted results based on small numbers, occasionally for pancreatic cancer. This omission may have minor influence on the metaresults. Some case-control studies may have omitted results for rare exposures, with similar minor effect on the metaresults.

#### SELECTION OF STUDIES

We used major databases and lists of references of the studies for the identification of studies. Studies not found in major databases are probably of lower quality. For the same reason and because of the cost we did not try to identify unpublished studies.

#### EXTRACTION

Extractor bias was minimised by the formal extraction procedure between the extractors, and the central checking of the extraction. The procedure was also intended to guarantee the extraction of the relevant risk estimates in studies that offered several alternative risk estimates.

#### REFERENCE POPULATIONS

Not all populations in the data were strictly independent because in some studies an internal unexposed industrial population was used as the common reference for more than one exposed population. This was rare, however, and we consider the ensuing bias in the precision of MRR to be minimal. Reference populations are a problem in proportional studies, where the population basis is unknown. For most analyses, we excluded proportional studies for this reason. Comparability of populations may be a problem in SMR and SIR studies because of the healthy worker effect. It is unknown to what extent the healthy worker effect and its components might have biased our metaresults.

#### CONFOUNDING

Control of confounding is a problem in studies of pancreatic cancer, as tobacco smoking and diabetes are the only known common causes of this malignancy. Even a rough measurement of confounding bias is difficult. Case-control studies are in principle best equipped for adjustment for confounders. Several of them did adjust for various factors. In other study types, adjustment was rare. Attempts to aggregate results over studies that adjusted for smoking failed because of small numbers of such studies. The number of available populations for which adjustment was done ranged from zero to two across the occupational agents.

#### AETIOLOGICAL FRACTIONS

Aetiological fractions were unstable both statistically and substantially. The PEFs were highly dependent of the variable occupational exposure patterns across populations and periods. The variability concerns the proportions of exposed subjects, and intensities and time patterns of exposures. Also, the technical definitions of exposed varied between studies. The same holds for EEFs, with the exception that the proportion of exposed subjects is not a concern.

#### Conclusions

The aetiological fraction of pancreatic cancer due to occupational exposures within a population was estimated at 12%. This may be an underestimate because of misclassification of exposures and end points in the studies. The aetiological fractions among exposed subjects was highest at 47% in people occupationally exposed to nickel and nickel compounds. The implication is that if smoking explains 20%–25% of pancreatic cancers and occupational and general environmental factors 15%–20% at maximum in a typical “western” adult population, the bulk of the risk remains unexplained. Further risk factors are likely to be found in inherited susceptibility, dietary habits, interactions between lifestyles, environmental, occupational, and genetic factors, or other yet unrecognised factors.

Results of this metaanalysis suggest that occupational exposure to some CHC solvents and related compounds may increase the risk

of pancreatic cancer. The excess may be pronounced in women. Excesses associated with occupational exposure to chromium and chromium compounds and nickel and nickel compounds were suggested. More limited evidence was found for organochlorine insecticides, silica dust, and aliphatic and alicyclic hydrocarbon solvents.

Future research into the aetiology of pancreatic cancer should concentrate on more refined assessment of exposure and end points, assessment of interactions between occupational and environmental factors, lifestyle (tobacco, alcohol, coffee, diet), and interactions between genes and the environment. Future research therefore calls for large studies, complex measures, and refined statistical methods.

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## Risk of Pancreatic Cancer in Workers Exposed to Chlorinated Hydrocarbon Solvents and Related Compounds: A Meta-Analysis

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This is a meta-analysis of occupational exposures to chlorinated hydrocarbon (CHC) solvents and pancreatic cancer, based primarily on studies that addressed exposure directly (agent studies) and secondarily on studies that reported data without verification of individual CHC exposures (job title studies), all of which were listed in databases for the period January 1969 to May 1998. Standardized extraction of data and double-checking of consistency of data extraction by five extractors were done. Simple random models estimated meta-relative risks. Suggestive weak excesses were found for trichloroethylene (meta-relative risk (MRR) = 1.24, 95% confidence interval (CI): 0.79, 1.97), polychlorinated biphenyls (MRR = 1.37, 95% CI: 0.56, 3.31), methylene chloride (MRR = 1.42, 95% CI: 0.80, 2.53), and vinyl chloride (MRR = 1.17, 95% CI: 0.71, 1.91) but not for carbon tetrachloride. One study addressed tetrachloroethylene (MRR = 3.08, 95% CI: 0.63, 8.99); another investigated chlorohydrin production (MRR = 4.92, 95% CI: 1.58, 11.4). Exposure-response meta-analyses for trichloroethylene and methylene chloride failed to reveal trends. Job title studies on metal degreasing and dry cleaning revealed significant MRRs (2.0 and 1.4, respectively). Publication bias was unlikely. Confounding may have remained insufficiently controlled. Unless the results are seriously biased by exposure or endpoint misclassification or by confounding, strong causal associations between CHC compounds and pancreatic cancer can be judged unlikely. Interactions between environmental and occupational agents, lifestyle factors, and genetic susceptibility remain a possibility, but the data for this meta-analysis did not address interactions. *Am J Epidemiol* 2001;153:841–50.

hydrocarbons, chlorinated; meta-analysis; occupational exposure; pancreatic neoplasms; solvents

Chlorinated hydrocarbon (CHC) solvents and related compounds cover a variety of chemicals with industrial and research applications. Occupational exposures may occur in rubber and plastics production, chemical manufacturing, the

pharmaceutical industry, the metal industry, dry cleaning, paint removal, and laboratories. Trichloromethane (chloroform) and tetrachloromethane (carbon tetrachloride) are applied mainly as laboratory solvents. Trichloroethylene, tetrachloroethylene (perchloroethylene), and 1,1,1-trichloroethane have been used mainly in dry cleaning and metal degreasing. Dichloromethane (methylene chloride) is applied in metal degreasing and paint removal. Chloroethylene, better known as vinyl chloride, is a vinyl monomer used in the manufacture of plastics. Polychlorinated biphenyls (PCBs) have been used in the manufacturing of electric capacitors and transformers. Vinyl chloride is a group 1 carcinogen (carcinogenic to humans) in the classification of the International Agency for Research on Cancer (IARC). Trichloroethylene, tetrachloroethylene, and PCBs are group 2A carcinogens (probably carcinogenic to humans). Dichloromethane, carbon tetrachloride, and chloroform are group 2B carcinogens (possibly carcinogenic to humans). A number of other CHC solvents and related compounds have been and are being used and produced. (For IARC evaluations, see the IARC website (1)).

We have reported results of an epidemiologic meta-analysis of pancreatic cancer and 25 chemicals or groups of chemicals encountered in occupational environments (2). An excess was found for CHC solvents and related compounds. This report is an in-depth analysis of this excess.

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Abbreviations: CHC, chlorinated hydrocarbon; CI, confidence interval; IARC, International Agency for Research on Cancer; MRR, meta-relative risk; PCBs, polychlorinated biphenyls; SMR, standardized mortality ratio.

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## MATERIALS AND METHODS

We conducted a literature search of cohort, linkage, proportional, and case-control studies with data on occupations, occupational exposures, and pancreatic cancer in the MEDLINE, TOXLINE, and CANCERLIT databases for the period January 1969 to May 1998. Lists of reference were scrutinized for further data. Details of identification of studies and extraction of data have been reported (2). In short, a standardized form was designed and applied in data extraction. The form covered 1) designators of the study (publication year, country, study type, case definition, source of cases, reference population, selection of control subjects, follow-up period, loss to follow-up, response rates, sources of exposure/job data, and time reference for exposure/job); 2) type of risk measure(s) used; 3) cohort admission (cross-sectional/longitudinal/period); 4) availability of lagged data; 5) availability of exposure-response data; 6) coding system of job titles (e.g., international, national, industry specific, or plant specific); 7) risk estimates for predefined sets of agents and job titles, expressed as point estimates of relative risk and their confidence intervals; 8) length of lag periods, if applied; and 9) numbers of exposed cases. Items 7–9 were extracted separately for each agent, exposure category, job title, and gender, if genders were analyzed separately. Using the standard form, five epidemiologists (A. O., T. P., N. J., E. W., and C. W.) extracted relevant estimates of relative risk and items 1–9 above. The most unbiased and agent-specific relative risk estimates were sought. Estimates adjusted for social class were preferred over those not adjusted for social class. Estimates adjusted for known risk factors for pancreatic cancer (age, gender, diabetes mellitus, and tobacco smoking) and those closest to the 20-year latency period were

**TABLE 1. Distribution of populations in agent (chlorinated hydrocarbon solvents and related compounds) and job title (metal degreasing and related jobs, dry cleaning) studies, by country and publication year**

	Agent studies	Job title studies
<b>Country</b>		
Canada	3*	2
Denmark		5
Finland	1	2
Japan	1	3
Sweden	1	1
United Kingdom	3	2
United States	13	20
USSR/Russia	1	
Multiple countries	1	
<b>Publication year</b>		
1969–1979		
1980–1989	8	19
1990–1998	16	16
<b>Total</b>	<b>24</b>	<b>35</b>

\* Number of populations.

chosen, if available. When confidence intervals were not provided, they were recovered by using Byar's approximation (3) for cohort data and using variance of the log of the odds ratio for case-control data. Two authors (A. O., T. P.) double-checked all filled-in extraction forms and corrected for any inconsistencies.

**TABLE 2. Characterization of agent (chlorinated hydrocarbon solvents and related compounds) and job title (metal degreasing and related jobs, dry cleaning) studies, 1969–1998**

	Agent studies	Job title studies
<b>Study type</b>		
Administrative (linkage of administrative records; PMR*/PCMR* studies)	4†	23
Industrial cohort	16	8
Industry-based (nested) case-control study	1	
Population- or hospital-based case-control study	3	4
<b>Cases</b>		
Exocentric pancreatic cancers only	4	
All pancreatic cancers	19	32
Unspecified	1	3
<b>Diagnosis of cases</b>		
Histologic	4	5
Other (clinical: radiology, autopsy, etc.)	1	26
Mortality files	18	3
Mixed		
Unknown	1	1
<b>Ascertainment of cases</b>		
Mortality files	19	27
Cancer registry files	3	7
Hospital records	2	
Unspecified		1
<b>Gender</b>		
Men	17	22
Women	4	9
Both men and women	3	4
<b>Risk measure</b>		
SMR*	13	6
SIR*	3	4
PMR	4	14
PCMR		4
MOR*		3
OR*	3	1
RR*	1	3
<b>Total</b>	<b>24</b>	<b>35</b>

\* PMR, proportional mortality ratio; PCMR, proportional cancer mortality ratio; SMR, standardized mortality ratio; SIR, standardized incidence ratio; MOR, mortality odds ratio; OR, odds ratio; RR, risk ratio: ratio of risks or cumulative incidences in exposed and unexposed cohorts.

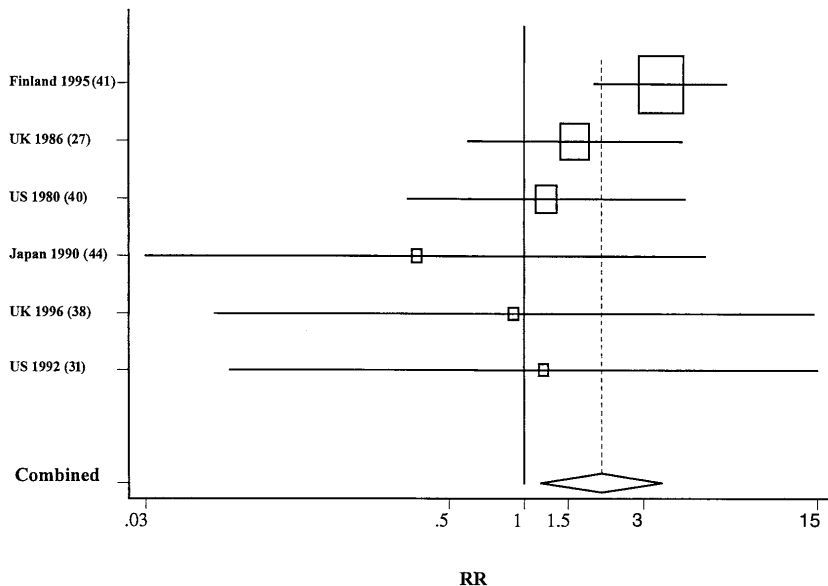
† Number of populations.

The studies were divided into two categories: 1) agent studies: those that provided risk estimates directly for one or several of 25 chemical or physical workplace agents, and 2) job title studies: those that did not provide risk estimates for any of the selected agents but did so for one or more of 150 job categories. This report is primarily based on results of agent studies directly addressing exposure to one or several CHC solvents or related compounds. Chloroform was excluded, with most of the studies relating to exposure to chlorinated drinking water rather than to occupational exposure (for evaluation, see reference 4). We identified 19 occupational agent studies (5–23) for CHC solvents and related exposures. Supporting secondary evidence was sought from job title studies, that is, studies that reported data for job titles or industries involving CHC exposures without verification of individual exposures. Metal degreasing and related jobs and dry cleaning represented the industries with the highest proportion of workers exposed to CHC solvents. We identified 22 job title studies (24–45) with risk estimates for workers in these industries.

We ran random meta-regression models for single and multiple predictors, but the data suggested application of simpler models. Simple random effects models (46) without covariates were therefore applied in estimating the meta-relative risks. Results from fixed-effects models were comparable and are not presented. A test of heterogeneity was performed as a chi-square test with degrees of freedom equal to one less than the number of populations. For

trichloroethylene and methylene chloride, data were available for rough exposure-response analysis. Two studies (5, 20) presented exposure-response data for trichloroethylene: one (20) using an artificial exposure index and the other (5) based on biomonitoring data on a metabolite, namely, trichloroacetic acid in urine ( $\mu\text{mol/liter}$ ). We dichotomized exposure data in both studies into “low” and “high” levels of exposure, as explained in Results, and coded them as 1 and 2, respectively. Results for men and women in the study by Spirtas et al. (20) were treated as separate data. Three studies (10, 12, 21) had exposure-response data for methylene chloride. Two of them (12, 21) supplied data as our preferred cumulative exposure dimensionality (ppm-years), one (10) just as ppm. We estimated midpoint ppm-years for Hearn et al. (12) and Tomenson et al. (21) and transformed ppm in the paper by Gibbs et al. (10) into ppm-years by a multiplier of 15 (average duration of exposure in years, as inferred from the report). The transformations are explained in Results. For trichloroethylene and methylene chloride data, random linear meta-regression models were applied for the log of relative risk. The software package STATA release 5 (47) was applied throughout.

We organized and analyzed the data by populations rather than by studies, since there were studies that considered more than one population separately (e.g., genders, exposure categories). Pancreatic cancer risks were reported for 24 nonoverlapping occupational populations in the agent



**FIGURE 1.** Relative risks (RR) and their 95 percent confidence intervals in job title studies, January 1969 to May 1998. Metal degreasing and related jobs. Proportional studies excluded. Areas of squares are proportional to precision on the inverted variance dimensionality; lines indicate 95 percent confidence intervals from the random effects model. The oblique parallelogram indicates the meta-relative risk and its 95 percent confidence interval. Test for heterogeneity:  $\chi^2$  (5 df) = 5.8;  $p$  = 0.328.

studies and for 35 populations in job title studies (13 populations in metal degreasing and related jobs and 22 dry cleaning populations). Numbers of populations by country and period of publication are shown in table 1.

Agent studies were predominantly industrial cohort studies, while the bulk of job title studies were based on linkage of administrative records or on proportional analyses. Most studies addressed mortality. Seventeen populations in agent studies were male, four were female, and three were mixed. Populations in job title studies followed a similar gender distribution (table 2). The study by Magnani et al. (14), though reported as a case-control study, was based on occupational and endpoint data from death certificates only, augmented by a job-exposure matrix for a number of agents. We treated this as a proportional study.

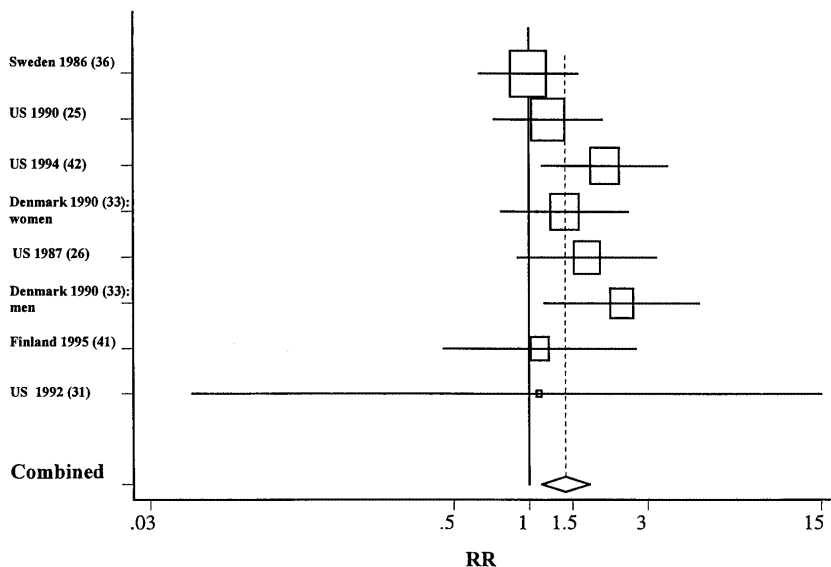
## RESULTS

Exposure to CHC solvents and related compounds was associated with an excess risk of pancreatic cancer (meta-relative risk (MRR) = 1.4, 95 percent confidence interval (CI): 1.0, 1.8; 20 populations, range of point estimates 0.3–4.9, heterogeneity  $p = 0.05$ ) in agent studies, exclusive of proportional studies that are of lower quality because of lack of population denominators for rate calculation. This result is not highly informative, since it refers to a number of CHC compounds different in chemical composition and

biologic activity. The details of the analysis are therefore not presented. A somewhat restricted set of CHCs (mostly trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane) was represented by job title studies on metal degreasing and related jobs and on dry cleaning. The studies on metal degreasing revealed an MRR of 2.0 (95 percent CI: 1.2, 3.6, six populations (figure 1)). Those for dry cleaning had an MRR of 1.4 (95 percent CI: 1.1, 2.4, eight populations (figure 2)). Exposures to nonchlorinated solvents have occurred in many of these populations, however.

Agent studies addressing trichloroethylene (5, 6, 11, 16, 20) showed weak indications of excess risk (MRR = 1.24, 95 percent CI: 0.79, 1.97) (table 3). Of the three largest studies, two (5, 11) reported an excess, while the third (20) did not. The study by Anttila et al. (5) verified exposures by biologic monitoring. No exposure-response gradient was seen in the exposure-response meta regression analysis (table 4).

The study by Anttila et al. (5) was the only one to address tetrachloroethylene directly. It found a nonsignificant excess standardized incidence ratio of 3.08 (95 percent CI: 0.63, 8.99) (table 5). The MRR for methylene chloride, based on four studies (10, 12, 13, 21), was 1.42 (95 percent CI: 0.80, 2.53) (table 6). The excess was driven entirely by the biggest study (12), which reported a more than twofold incidence rate ratio for subjects in photographic film manufacture in the United States, with more than 25 years of latency. No



**FIGURE 2.** Relative risks (RR) and their 95 percent confidence intervals in job title studies, January 1969 to May 1998. Dry cleaning. Proportional studies excluded. Areas of squares are proportional to precision on the inverted variance dimensionality; lines indicate 95 percent confidence intervals from the random effects model. The oblique parallelogram indicates the meta-relative risk and its 95 percent confidence interval. Test for heterogeneity:  $\chi^2 (7) = 6.8; p = 0.451$ .

**TABLE 3. Agent studies of trichloroethylene**

Study/ country	Study type	Gender	Histologic verification of diagnoses	Industry/exposure	Relative risk	95% CI*	No. of exposed cases	Concomitant exposures
Spirtas et al., 1991 (20), United States	SMR*	M*F*	No	Aircraft maintenance facility				Large no. of chemicals
				All men (cumulative exposure)†	0.83	[0.45, 0.39]‡	14	
				Low	0.90	[0.33, 1.95]	6	
				Medium	0.75	[0.15, 2.19]	3	
				High	0.81	[0.26, 1.88]	5	
				All women (cumulative exposure)†	0.81	[0.09, 2.89]	2	
			High	1.25	[0.14, 4.51]	2		
Siemiatycki, 1991 (16), Canada	OR*	M	Yes	Machinists; aircraft mechanics; industrial equipment mechanics†	0.9	0.1, 3.2]	2	Solvents; metallic dust; PAH*, alkanes
Greenland et al., 1994 (11), United States	OR	M	No	Transformer assembly facility†	1.64	0.82, 3.29	NG*	PCBs*, machining fluid; asbestos; solvents; synthetic resins
Axelson et al., 1994 (6), Sweden	SIR*	MF	Likely	Various industries† Exposures verified with biologic monitoring	0.25	0.01, 1.38	1	Epichlorohydrin; mineral oils
Anttila et al., 1995 (5), Finland	SIR	MF	Yes	Degreasing, rubber works, gluing, dry cleaning, etc.†	2.00	[0.96, 3.68]	10	Tetrachloroethylene; 1,1,1-trichloroethane
				Exposures verified with biologic monitoring ≥10 years from 1st measurement				
				U-TCA* < 100 µm/liter	1.61	0.59, 3.50	6	
				U-TCA ≥ 100 µm/liter	1.31	0.27, 3.50	3	
Aggregate of †-marked results					1.24	0.79, 1.97		

\* CI, confidence interval; SMR, standardized mortality ratio (industrial cohort mortality study with external reference); M, male; F, female; OR, odds ratio (case-control study); PAHs, polycyclic aromatic hydrocarbons; NG, not given; PCBs, polychlorinated biphenyls; SIR, standardized incidence ratio (industrial cohort incidence study with external reference); U-TCA, urinary concentration of trichloroacetic acid.

† Populations used in calculating meta-relative risks and 95 percent confidence intervals.

‡ Numbers in brackets recovered by authors of this study.

exposure-response gradient was seen in the exposure-response meta-regression analysis (table 7).

For vinyl chloride monomer and polyvinyl chloride, the MRR was 1.17 (95 percent CI: 0.71, 1.91) (table 8) in four agent studies (15, 17, 19, 22). These were incidence and mortality studies in cohorts of employees in vinyl chloride monomer and polyvinyl chloride production, with relative risks ranging from 0.7 to 2.86 in the individual studies.

**TABLE 4. Exposure-response meta-analysis for trichloroethylene: codings and results, 1969–1998\***

	X: our coding
Spirtas et al. (20) (cumulative exposure)	
Low index (<5)	1
Medium index (5–25)	1
High index (>25)	2
Anttila et al. (5) (mean U-TCA† level (µm/liter))	
<100	1
≥100	2

\* Results:  $\ln(\text{meta-relative risk}) = 0.184 - 0.0886X$ ; 95% confidence interval for slope: -1.000, 0.823.

† U-TCA, urine trichloroacetic acid.

The excess for PCBs (MRR = 1.37, 95 percent CI: 0.56, 3.31) (table 9) was heavily driven by a mortality cohort study of employees in a Canadian transformer manufacture facility (23). This study reported standardized mortality ratios (SMRs) ranging between 2.9 to 12.9, depending on the subgroup. Cohort enrollment in this study started in 1947. High risk concentrated on those who were first employed prior to 1960 (SMR = 6.8, 95 percent CI: 2.2, 15.8) and in departments with the greatest exposure to transformer fluid (SMR = 9.8, 95 percent CI: 2.6, 25.0). All but one of the 11 pancreatic cancer deaths had a latency period of at least 10 years. No excess was found, and no exposure response was examined in the remaining studies: a low-power SMR study conducted in two US plants manufacturing electrical capacitors (8); a nested case-control study in a transformer assembly facility (11) using a plant-specific job exposure matrix for a mix of PCBs and trichlorobenzene; a low-power industrial cohort study in electrical capacitor manufacturing (18); and a proportional study covering a variety of industries (14).

A further excess was observed for employees in chlorohydrin production (one population (7); relative risk = 4.92, 95 percent CI: 1.58, 11.4) (table 10), with a number of concomi-

**TABLE 5. Agent study of tetrachloroethylene, 1969–1998**

Study/country	Study type	Gender	Histologic verification of diagnoses	Industry/exposure	Relative risk	95% CI*	No. of exposed cases	Concomitant exposures
Anttila et al., 1995 (5), Finland	SIR*	M*F*	Yes	Predominantly dry cleaning Exposures verified with biologic monitoring	3.08	0.63, 8.99	3	Trichloroethylene; 1,1,1-trichloroethane

\* CI, confidence interval; SIR, standardized incidence ratio (industrial cohort incidence study with external reference); M, male; F, female.

tant CHC exposures. An increasing risk with increasing duration of employment was found.

There was little evidence for excess risk associated with exposure to tetrachloromethane (carbon tetrachloride) (table 11).

**DISCUSSION**

This study found a significant excess risk of pancreatic cancer associated with occupational exposure to CHC sol-

vents, based on agent studies, and was supported by significant excesses from studies that examined metal degreasing and related jobs and dry cleaning. For individual CHC solvents, indications for weak excesses were seen for trichloroethylene, tetrachloroethylene, methylene chloride, vinyl chloride, PCBs, and chlorohydrin manufacture, but not for carbon tetrachloride.

The internal validity of this meta-analysis needs to be considered from a number of angles. Considering potential selection bias, we selected only published, peer-reviewed studies,

**TABLE 6. Agent studies of dichloromethane (methylene chloride), 1969–1998**

Study/country	Study type	Gender	Histologic verification of diagnoses	Industry/exposure	Relative risk	95% CI*	No. of exposed cases	Concomitant exposures
Hearne et al., 1990 (12), United States	IRR*	M*	No	Photographic film manufacture Exposure levels 140–475 ppm 8-hour TWA* Latency >25 years†	[2.55	1.02, 5.26]‡	7	Methanol, acetone
Lanes et al., 1993 (13), United States	SMR*	MF*	No	Cellulose triacetate fiber production facility† Methylene chloride exposure up to 1,700 ppm (8-hour TWA)	0.83	0.10, 2.99	2	
Gibbs et al., 1996 (10), United States	SMR	MF	No	Cellulose triacetate fiber production facility Methylene chloride exposure up to 250 ppm (8-hour TWA)				Methanol, finishing oils
			Men	High exposure†	0.34	0.01, 1.92	1	
				Low exposure†	0.89	0.11, 3.22	2	
			Women	Low exposure†	0.58	0.01, 3.23	1	
Tomenson et al., 1997 (21) United Kingdom	SMR	M	No	Cellulose triacetate film base production facility ≥20 years since first exposure† 9-year personal average exposure to methylene chloride 19 ppm (8-hour TWA)	[0.99	0.20, 2.90]	3	
Aggregate of †-marked results					1.42	0.80, 2.53		

\* CI, confidence interval; IRR, incidence rate ratio; M, male; TWA, time-weighted average; SMR, standardized mortality ratio (industrial cohort mortality study with external reference); F, female.

† Populations used in calculating meta-relative risks and 95 percent confidence intervals.

‡ Numbers in brackets recovered by us.

**TABLE 7. Exposure-response meta-analysis for dichloromethane (methylene chloride): codings and results, 1969–1999\***

Codings	X: midpoint (ppm-years): (our coding)
Tomenson et al. (21) (cumulative exposure (ppm-years))	
<400	200
400–799	600
≥800	900
Hearne et al. (12) (cumulative exposure (ppm-years))	
<400	200
400–799	600
800–1,199	1,000
≥1,200	1,400
Gibbs et al. (10) (8-hour TWA† (ppm))	
50–100	1,125
350–700	7,875

\* Results:  $\ln(\text{meta-relative risk}) = 0.759 - 0.000211X$ ; 95% confidence interval for slope:  $-0.000529, 0.0001073$ .

† TWA, time-weighted average.

believing that unpublished and unreviewed studies would represent lower quality. Publication bias was not likely, since no small studies addressed occupational exposure to CHCs. As is seen in figures 1 and 2, there was no concentration of small studies (wide confidence intervals) at high relative risks for studies on metal degreasing and dry cleaning. However, some nonpositive findings may have remained unpublished. Extractor bias was minimized by preset extraction rules and central double-checking of the extraction for consistency. Confounding may have been a problem. Its control in pancreatic cancer studies is problematic, since few causes of this malignancy are known. Low or moderate excesses may be particularly prone to confounding. Only two studies (16, 27) controlled for smoking. Occupational exposures to agents other than CHCs may have been confounders. Thus, various metal compounds occurred as concomitant exposures in metal degreasing and related jobs and as nonchlorinated solvents in dry cleaning—a matter of potential confounding and possibly of misclassification of exposure as well. Even within particular CHCs, exposure levels, durations, and cumulative exposures must have varied across studies, adding further uncertainty. We were able to analyze exposure-response for trichloroethylene and methylene chloride, but no trends were seen. Yet another source of potential bias is due to varying

**TABLE 8. Agent studies of vinyl chloride monomer/polyvinyl chloride**

Study/ country	Study type	Gender	Histologic verification of diagnoses	Industry/exposure	Relative risk	95% CI*	No. of exposed cases	Concomitant exposures
Nakamura, 1983 (15), Japan	SMR*	M*	No	25 plants producing VCM* and/or PVC*,†	2.86	[0.57, 8.35]‡	3	
Smulevich et al., 1988 (19), USSR	SMR	MF*	No	VCM/PVC production plant Men† (no cases in women)	1.72	[0.35, 5.03]	3	
Wong et al., 1991 (22), United States	SMR	M	No	37 VCM/PVC plants (11/12 cases from PVC plants)				
				All	0.87	0.50, 1.41	16	
				Latency ≥20 years†	[0.98	0.49, 1.75]	11	
				Length of exposure (years)				
				<10	0.79	[0.34, 1.55]	8	
				10–20	0.78	[0.21, 1.98]	4	
				>20	1.31	[0.35, 3.36]	4	
Simonato et al., 1991 (17), Italy, Norway, Sweden, United Kingdom	SMR, SIR*	M	No	12 plants producing VCM and/or PVC				Butadiene
				SMR	0.83	0.47, 1.35	16	
				SIR (4 plants; improved diagnosis)†	0.70	0.14, 2.03	3	
Chiazze and Ference, 1981 (9), United States	PMR*	MF	No	Employees in 17 PVC fabrication companies				
				Men	1.12	0.78, 1.54	37	
				Women	1.15	0.46, 2.36	7	
Aggregate of †-marked results					1.17	0.71, 1.91		
Aggregate of †-marked results and results of PMR study					1.14	0.87, 1.48		

\* CI, confidence interval; SMR, standardized mortality ratio (industrial cohort mortality study with external reference); M, male; VCM, vinyl chloride monomer; PVC, polyvinyl chloride; F, female; SIR, standardized incidence ratio (industrial cohort incidence study with external reference); PMR, proportional mortality ratio (PMR study).

† Populations used in calculating meta-relative risks and 95 percent confidence intervals.

‡ Numbers in brackets recovered by us.

**TABLE 9. Agent studies of PCBs\*, 1969–1998**

Study/ country	Study type	Gender	Histologic verification of diagnoses	Industry/exposure	Relative risk	95% CI*	No. of exposed cases	Concomitant exposures
Brown, 1987 (8), United States	SMR*	M*F*	No	Capacitor manufacturing Two plants	M†	[0.63 0.01, 3.48]‡	1	
					F†	[0.48 0.01, 2.65]	1	
Yassi et al., 1994 (23), United States	SMR	M	No	Transformer manufacture plant	All	2.92 1.17, 6.01	7	Mineral oil, solvents
				Same, >6 months employment†	4.39 1.51, 10.9	5		
				Assembly only	9.76 2.62, 25.0	4	Same Same	
				Assembly >3 months	12.9 2.59, 37.7	3		
Sinks et al., 1992 (18), United States	SMR	MF	No	Electrical capacitor plant†	0.7	0.1, 2.5	2	Toluene, xylenes, methyl ethyl ketone, trichloro- ethylene, 1,1,1- trichloroethane
Greenland et al., 1994 (11), United States	OR*	M	No	Transformer assembly plant; mix of PCBs and trichlorobenzene†	1.05	0.43, 2.59	NG*	
Magnani et al., 1987 (14), United Kingdom	PMR*	M	No	Various	0.9	0.6, 1.4	NG	
Aggregate of †-marked results					1.37	0.56, 3.31		
Aggregate of †-marked results and results of PMR study					1.22	0.64, 2.35		

\* PCBs, polychlorinated biphenyls; CI, confidence interval; SMR, standardized mortality ratio (industrial cohort mortality study with external reference); M, male; F, female; OR, odds ratio (case-control study); NG, not given; PMR, proportional mortality ratio.

† Populations used in calculating meta-relative risks and 95 percent confidence intervals.

‡ Numbers in brackets recovered by us.

structures of the reference populations between SMR studies, possibly introducing confounding by age.

For assessment of external validity, animal bioassays provide practically no evidence for any CHC exposure and for pancreatic cancer in particular. Animal evidence, which relates to other cancers, may therefore only be taken as an indirect support to the findings of this study.

Experimental cancer studies suggest that environmental PCB mixtures are likely to pose a risk of cancer to humans

(48). Although environmental mixtures have not been tested in cancer assays, this conclusion is supported by several complementary sources of information. Dose-related increased incidences of liver tumors were induced in female rats by Aroclors 1260, 1254, 1242, and 1016 (49). These mixtures contain overlapping groups of congeners that together span the range of congeners most frequently found in environmental mixtures. PCBs give generally negative results in tests of genetic activity, implying that PCBs induce tumors primarily

**TABLE 10. Agent studies of chlorohydrin, 1969–1998**

Study/ country	Study type	Gender	Histologic verification of diagnoses	Industry/exposure	Relative risk	95% CI*	No. of exposed cases	Concomitant exposures
Bensow and Teta, 1993 (7), United States	IRR*	M*	No	Chlorohydrin production All (latencies 26–48 years)†	4.92	1.58, 11.4	8	Ethylene dichloride, propylene dichloride, bis-chloroethyl ether, dichloropropanol, epichlorohydrin
				Duration of employment in chlorohydrin unit (years)				
				2–9	5.56	1.74, 17.7	3	
				10–20	11.2	3.52, 35.8	3	
				>20	17.8	4.31, 73.4	2	
Aggregate of †-marked results					4.92	1.58, 11.4	8	

\* CI, confidence interval; IRR, incidence rate ratio; M, male.

† Populations used in calculating meta-relative risks and 95 percent confidence intervals.

**TABLE 11. Agent studies of tetrachloromethane (carbon tetrachloride), 1969–1998**

Study/country	Study type	Gender	Histologic verification of diagnoses	Industry/exposure	Relative risk	95% CI*	No. of exposed cases	Concomitant exposures
Siemiatycki et al., 1991 (16), Canada	OR*	M*	Yes	Firefighters, metal machinists, electricians, all exposed†	0.9	0.2, 2.6	3	Solvents, PAHs*
				Substantial exposure	0.5	0.0, 2.8	1	
Magnani et al., 1987 (14), United Kingdom	PMR*	M	No	Various	1.1	0.8, 1.5	NG*	
Aggregate of †-marked results					0.9	0.2, 2.6		
Aggregate of †-marked results and results of PMR study					1.09	0.80, 1.48		

\* CI, confidence interval; OR, odds ratio (case-control study); M, male; PAHs, polycyclic aromatic hydrocarbons; PMR, proportional mortality ratio (PMR study); NG, not given.

† Populations used in calculating meta-relative risks and 95 percent confidence intervals.

through modes of action that do not involve gene mutation. Several congeners have dioxin-like activity (50) and may promote tumors by different modes of action (51).

Trichloroethylene is metabolized in rat liver either by oxidation or by glutathione conjugation (52). A metabolite derived from the glutathione-trichloroethylene conjugate can be further metabolically activated to chlorinated thioketones, which have been shown to be mutagenic in bacteria and bind to DNA in vivo (53). Brauch et al. (54) reported a unique mutation spectrum in renal cell cancers of workers exposed to trichloroethylene. This is the first suggestion of a relation between exposure to a defined carcinogen (trichloroethylene) and a specific mutation in renal cell cancer. Trichloroethylene has been also reported to increase the incidence of uncommonly occurring renal-cell tumors in male rats (55)

Methylene chloride increases the incidence of hepatocellular and pulmonary tumors in mice and of benign mammary tumors in both sexes in rats. Methylene chloride is consistently mutagenic in microorganisms, but weaker and less consistent responses are seen in mammalian systems, both in vitro and in vivo (56). Although CHC solvents have often been suspected of acting through a nongenotoxic mechanism of cell proliferation, methylene chloride has been reported to be unable to induce hepatocellular division in mice (57).

Tetrachloromethane (carbon tetrachloride) is not mutagenic in bacterial tests, but it induces hepatic cell proliferation in vivo in rodents (56). It produces liver neoplasms in mice and rats and mammary neoplasms in rats.

As an overall conclusion, this meta-analysis suggests a weak association between exposure to trichloroethylene, PCBs, methylene chloride, and vinyl chloride, but not carbon tetrachloride, and the risk of pancreatic cancer. Unless the results are seriously biased by exposure or by endpoint misclassification or unknown confounders, strong causal associations between CHC compounds and pancreatic cancer can be considered unlikely. However, lifestyle-environment and gene-environment interactions remain a possibility in the induction of pancreatic cancer. Direct animal evidence for CHC compounds and pancreatic cancer is lacking.

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## Submitted

### **Estimating the relative risk of pancreatic cancer associated with exposure agents from job title data with hierarchical Bayesian meta-analysis**

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Running head: “Occupation, pancreatic cancer: meta-analysis”

The number of tables is five and the number of figures is one.

**Objectives.** The study demonstrates an application of hierarchical Bayesian meta-analysis of epidemiological studies that associate pancreatic cancer risk with job titles, using a link (job-exposure) matrix to estimate risks for occupational agents of exposure. A general goal was the evaluation of the applicability of job-exposure matrices in meta-analyses.

**Methods.** We identified 261 studies published from 1969 through 1998 on pancreatic cancer and job titles. Excluding proportional studies, 77 studies were informative of nine selected occupational agents. These studies included more than 3,799 observed pancreatic cancer cases. We used hierarchical Bayesian models for job titles (lower-level data) and agents (higher-level data), the latter from a Finnish job-exposure matrix. Non-Bayesian random effects models were applied for job titles to check consistency with Bayesian results.

**Results.** The results suggest that occupational exposures to chlorinated hydrocarbon compounds may increase the risk of pancreatic cancer.

**Conclusions.** Hierarchical models are applicable in meta-analyses when studies addressing the agent(s) under study are lacking or very few, but several studies address job titles with potential exposure to these agents. A job-exposure matrix or a formal expert assessment system is necessary in these situations.

*Keywords:* Bayesian; hierarchical methods; job-exposure matrix; job titles; MCMC simulation; meta-analysis; occupational exposures; pancreatic neoplasms;

## ***Introduction***

Pancreatic cancer is a highly fatal malignancy whose etiology is mostly unknown. An estimated 216,000 new cases of pancreatic cancer occurred globally in 2000 (1). It represents the fifth leading cause of cancer deaths in developed countries. The only established common risk factors of pancreatic cancer are tobacco smoking and type II diabetes mellitus (2-4). Results of epidemiological studies that have been linked industries and jobs with excess of pancreatic cancer are heterogeneous and inconsistent, and exposures shared by high-risk jobs are hard to identify (5-9). Most of the occupational chemical agents that were associated with excess risk of pancreatic cancer in epidemiological studies emerged in one study only. A previous meta-analysis (10) of studies of occupational agents found significant excesses for chlorinated hydrocarbon solvents and nickel and nickel compounds. After closing this meta-analysis (May 1998), Kernan et al. (7) and Hoppin et al. (11) reported significant excesses for chlorinated hydrocarbon solvents, and Weiderpass et al. (12) for nickel and nickel compounds. Other occupational agents with reported excess risks of pancreatic cancer in at least two epidemiological studies are asbestos, chromium and chromium compounds, ionizing radiation, low frequency electromagnetic fields, pesticides, and polycyclic aromatic hydrocarbons.

McElvenny and colleagues (13) reviewed meta-analyses of occupational epidemiology in general. They identified 66 papers from 1975 to October 2001. Only one study used

Bayesian methods (14). Our literature search from PubMed for the period October 2001 to December 2005 did not identify a single study of Bayesian meta-analysis of occupational epidemiology.

Biggerstaff et al. (14) compared classical and Bayesian meta-analyses in studies of lung cancer and passive smoking in workplace. Tweedie et al. (15) applied Bayesian models to meta-analysis of environmental tobacco smoking and lung cancer studies for nonsmoking women both in workplace and home. Wraith and Mengersen (16) published recently a hierarchical Bayesian meta-analysis of lung cancer and interaction with asbestos and smoking.

Job-exposure matrices (JEMs) were developed to translate job titles to occupational agents. They have been applied in several occupational studies based on individual data, especially if exposure assessment at the individual level is not available. Kauppinen et al. (17) applied a British JEM (18) in a Finnish case-control study of pancreatic cancer. Alguacil et al. (19) used a Finnish JEM (FINJEM, 20) in a Spanish case-control study of pancreatic cancer. Kogevinas et al. (21) used FINJEM in their study combining 11 European case-control studies of bladder cancer. Gilks and Richardson (22) applied JEM and hierarchical Bayesian methods on individual job title data using logistic regression models. Their results from three models, two logistic regression models and one Bayesian logistic regression model, showed that the Bayesian model overestimated the results whereas ecological or aggregated bias on average weaken the relative risks.

Hierarchical models in meta-analysis allow for estimation of both the parameters of the individual studies at the first level, and of aggregated parameters at higher levels. Witte et al. (23-25) applied semi-Bayesian hierarchical regression models in a study of dietary exposures and breast cancer in case-control data. In an analogous manner, we applied hierarchical Bayesian methods in a meta-analysis for job titles and pancreatic cancer, based on studies that addressed job titles only. The second-level agent data were provided by a JEM. We wanted to examine how Bayesian models perform in a meta-analytic setting, compared with conventional methods, using hierarchical data and hierarchical models. We also attempted to evaluate the feasibility of the use of the job-exposure matrices in meta-analyses.

### ***Materials and methods***

We searched cohort, linkage, proportional, and case-control studies in any language with data on job titles, occupational exposures, and pancreatic cancer in Medline, Toxline, and Cancerlit databases for the period January 1969 - May 1998. Reference lists of the identified studies provided additional studies.

Out of 1,902 studies identified, 373 remained after excluding studies that did not report on pancreatic cancer or data for any job title or occupational agent; reviews; reports of earlier than the most recent update; studies with insufficient data for the meta-analysis or

with data contained in another study that was included; and studies on job/agent categories too broad or outside our list of job titles or agents. Out of 373 selected studies 119 were agent specific studies that provided risk estimates directly for one or several of 25 chemical or physical workplace agents. Meta results for these studies have reported elsewhere (10). This paper based on the rest of 261 job title studies that did not provide direct agent data. The list of job titles covered 150 entries in the Finnish social status categories 3, 4, and 5. The upper categories 1 and 2 were excluded from the analyses because of minimal or no exposures.

Standardized data extraction forms covered characteristics of the study (publication year, country, study type, case definition, source of cases, reference population, selection of control subjects, follow-up period, loss to follow-up, response rates, sources of exposure or job data, time reference for exposure or job; risk measure, cohort admission, lag periods, exposure-response, job title coding applied), risk estimates, and numbers of exposed cases. Using the standard form, five epidemiologists extracted relevant estimates of relative risk and the above items. The most unbiased relative risk estimates were sought. Thus, estimates adjusted for social class were preferred over those not adjusted for social class. Estimates adjusted for at least known risk factors for pancreatic cancer (age, gender, diabetes mellitus, tobacco smoking) and those closest to 20-y latency period were chosen, if available. When confidence intervals (CI) were not provided, they were recovered using Byar's approximation (26) for cohort data, and using variance of the log of the odds ratio for case-control data. Two authors double checked all extraction forms and corrected for any inconsistencies.

After excluding from 261 job title studies that did not report on job titles with FIN-JEM-based potential exposure to nine selected occupational agents (aliphatic and alicyclic hydrocarbon solvent [ALHC]; chlorinated hydrocarbon compounds [CHC]; chromium and chromium compounds [CR]; fungicides [FUNG]; insecticides [INSC]; nickel and nickel compounds [NI]; polycyclic aromatic hydrocarbons [PAH]; silica dust [SIL]; wood dust [WOOD]) and proportional studies because of poor quality, 77 studies (27-103) remained, including 27 job titles and more than 3,799 pancreatic cancer cases. This paper is based on the data of 52 cohort studies representing 67 risk estimates, 19 record-linkage studies that are entirely based on linkage of extraneous databases on job titles and occupations (eg, census) and on outcomes (eg, death records) representing 69 risk estimates, and six case-control studies representing 15 risk estimates. (Table 1)

Data for most risk estimates [56] were from Northern Europe, closely followed by North America [48], and less closely by Western [17], Southern [14] and Central Europe [8], and Asia [3], Oceania [3], and mixed Western Europe and North America [2]. There were no studies from Eastern Europe, Central or South America, the Caribbean, or Africa. The annual number of studies increased considerably during 1969-98 (seven risk estimates during 1969-79, 40 risk estimates during 1980-89 and 104 risk estimates during 1990-98).

More than three-fourths of the populations were male. Most studies addressed mortality, death records usually providing the diagnosis.

At the higher level of data, FINJEM provided proportions of exposed workers during the period 1960-85 for the selected nine occupational agents in 27 job titles. Because the proportions exposed to CR and NI were nearly identical, we used means (denoted CR/NI) of them in the hierarchical Bayesian models (Table 2). To reduce misclassification and ecological bias, proportion of exposed workers 20% was used as the cutpoint for exposure (104). Exposure assessment period 1960-85 was selected, assuming that most workers had been exposed during this period. The nine agents represented those with pancreatic cancer meta-relative risks (MRRs) in a previous meta-analysis (10) exceeding 1.1.

We included in the hierarchical Bayesian models five dichotomized covariates: study type (case-control vs. cohort), publication year (cutpoint 1990), diagnosis of pancreatic cancer (histological vs. others), country (Denmark, Finland, Norway and Sweden vs. others) and time reference for job title (longitudinal vs. others).

### *Statistical methods*

DerSimonian and Laird random effects model (105) for meta-analysis without covariates was applied to each of the 27 job titles to compare estimates of job titles against those of hierarchical Bayesian meta-analysis. A  $\chi^2$  test of heterogeneity was performed for each job title. Both Begg's adjusted rank correlation test (106) and Egger's regression asymmetry test (107) were performed to formally test for publication bias.

In the hierarchical Bayesian meta-analyses, we calculated both aggregated estimates of occupational agents using job title estimates from each study and aggregated estimates for job titles themselves. We used Bayesian models for job titles (lower-level, study data) and agents (higher-level FINJEM data). This model is semi-ecological in the sense that the outcome data from the studies are based on individual data, while the agents are assessed at the job title/agent levels (108).

The directed acyclic graph (DAG) in Figure 1 represents equations 1-2 in Appendix. The single boundary squares contain observed data (risk estimates, job titles, covariates, and agents from FINJEM data). The circles represent unknown and must be estimated. The double squares are fixed parameters of prior distributions. The dashed arrows represent functional relationships, and the full arrows stochastic ones. The shaded nodes are normally distributed, represented in the equation 1 in Appendix. The non-shaded circle nodes are gamma distributed with fixed parameters (equation 2 in Appendix). We assumed the prior distributions for precisions  $1/\sigma_\theta^2$  and  $1/\sigma_\beta^2$  are gamma distributions with parameters 0.1 and 0.1 in the first hierarchical Bayesian (HB1) model, implying diffuse priors for the precisions, and with parameters 0.001 and 1 in the second hierarchical Bayesian (HB2) model, implying meaning that the priors for precisions are quite diffuse or reasonable (109, 110). In both HB1 and HB2 models the fixed parameters of prior distributions are  $\mu_\gamma = \mu_\pi = 0$ , and  $\sigma_\gamma^2 = \sigma_\pi^2 = 1$ .

In Bayesian statistics, a Bayesian analogue of a frequentist confidence interval (CI) is called a credible interval (CrI), which is a posterior probability interval (111).

Markov chain Monte Carlo (MCMC) methods were numerically approximated by constructing chains by Gibbs sampling (112). We simulated chains by using the WinBUGS software (113). The convergences of the chains were assessed by examining Monte-Carlo errors and Gelman-Rubin statistics (114). The WinBUGS program version 1.3 being freely available from <http://www.mrc-bsu.cam.ac.uk/bugs> was used in the hierarchical Bayesian models. Stata 8 for Windows was used in the non Bayesian random effects models (115).

## **Results**

The results of the hierarchical Bayesian models for meta-analysis are based on 200,000 iterations with 20,000 burn-in iterations and two chains in both HB1 and HB2 models. We calculated antilog of posterior medians as MRRs, since the posterior median is preferable over posterior mean in preserving the antilog transformation.

The observed study-specific relative risk estimates and the posterior estimates for two job titles, laundry/dry cleaning workers and metal plating workers, based on HB1 and HB2 models are shown in Table 3. Only one observed risk estimate for laundry/dry cleaning workers failed to exceed unity. The study-specific posterior risk estimates for both laundry/dry cleaning and metal plating workers seem to shrink towards the aggregated mean.

**Job title results** of the random effects models and the hierarchical Bayesian models are shown in Table 4. We addressed between-study heterogeneity by using random effects models. Testing heterogeneity with a  $\chi^2$  test by job titles significant heterogeneity was found for studies addressing to asphalt workers, farmers, painters and sawyers. Publication bias was suspected only for studies addressing metal plating workers, using Begg's and Egger's tests for publication bias.

Studies addressing laundry/dry cleaning workers were associated with an excess risk of pancreatic cancer in the random effects (RE) model with MRR 1.41 (95% CI 1.13-1.76), based on eight SIR/SMR risk estimates. In the HB1 and HB2 models MRRs for laundry and dry cleaning were 1.42 and 1.40, and 95% CrIs (1.03-1.93) and (1.12-1.75), respectively. Excesses were found for studies on metal plating workers in the RE model (MRR 2.04, 95% CI 1.17-3.55; 1 OR, 3 SIR/SMR, and 2 RR risk estimates), in the HB1 model (MRR 1.96, 95%; CrI 1.15-3.29), and in the HB2 models (MRR 2.11, 95%; CrI 1.33-3.35). An excess risk for studies on plywood/fiberboard workers was found in RE model (MRR 1.38, 95% CI 0.87-2.17) based only two SMR risk estimates, MRRs in the HB1 and HB2 models were 1.22 and 1.18, respectively. The MRRs for machine/engine mechanics were 1.34, 1.25 and 1.20 in the RE, HB1 and HB2 models, respectively. A decreasing risk was found for bricklayers and construction carpenters in all models but 95% CrIs were wider than 95% CIs.

**Occupational agent results** of the hierarchical Bayesian models are shown in Table 5. Meta relative risks of pancreatic cancer exceeded unity for all agents except fungicides in the HB2 model, and silica and wood dust in both HB models. Credible intervals were mostly narrower in the HB2 model than in the HB1 model. The highest MRRs were found for chlorinated hydrocarbon compounds (CHC) in the HB2 model, MRR and 95% CrI were 2.21 (1.31-3.67) and MRR in HB1 model was 2.03 but 95% CrI (0.99-4.08) was wider than in HB2 model. The second highest MRRs with wide 95% CrIs were found for insecticides, in the HB2 model MRR and 95% CrI were 1.95 (0.45-7.41) and in the HB1 model 1.53 (0.33-7.06).

## ***Discussion***

### *Evidence*

We found excess risks for pancreatic cancer for two job titles that were based on more than two input risk estimates in all models, random effects models and hierarchical Bayesian models: laundry and dry cleaning workers, and metal plating workers. An excess risk was also found for plywood/fiberboard workers (including only two risk estimates) in all models. Laundry and dry cleaning and metal plating workers were likely to have been exposed to chlorinated hydrocarbon compounds, and metal plating workers also to chromium and nickel. Likely agents for plywood/fiberboard workers were fungicides, insecticides, and wood dust.

In a meta-analysis (10) based on agent specific studies, significant excess pancreatic cancer risks were found for occupational exposure to chlorinated hydrocarbon compounds and nickel. In this study we found excess risks for chlorinated hydrocarbon compounds and insecticides in both Bayesian hierarchical models but not occupational exposure to nickel.

### *Publication bias*

Publication bias is not likely in this study, as very few small studies expressly considered the occupational determinants of pancreatic cancer. Publication bias was suspected only for studies addressing metal plating workers (104, 105).

### *Selection of studies*

We used major databases and lists of references of the studies for identifying studies in any language. Unidentified studies were probably of low quality. We did not attempt to identify unpublished studies.

### *Extraction*

We minimized extractor bias by the formal extraction procedure, a group of extractors, and the central checking of extraction. The most relevant risk estimates were extracted.

### *Combinability and heterogeneity*

Results for different exposure levels, time parameters of exposure, study types, methods, time reference for job titles, and diagnostic specificities may not be readily combinable. We calculated all MRRs excluding the lowest quality (proportional) studies. All hierarchical Bayesian models included five covariates (study type, publication year, diagnosis of pancreatic cancer, country, and time reference for job title) to increase combinability by adjustment.

Random effects models addressed between-population heterogeneity. Heterogeneity was found for risk estimates for asphalt workers, farmers, painters, and sawyers. The problem of combining results for different exposure levels and time parameters of exposure remain, as exposure levels remained unknown.

### *Ecological bias*

Ecological or aggregated bias may emerge when using group level data for inferences on the individual level. Because, for instance, whole group of exposed workers exposures as a same proportion to an occupational agent according JEM, it does not take account of the individual deviations. Ecological bias in average weakens relative risks (22).

A simple random effects model for meta-analysis is hierarchical with two levels, between-study heterogeneity representing aggregated or ecological bias, treated as discussed above.

In this study, the hierarchical Bayesian models operated on three levels: risk estimates from studies, job titles, and agents of exposure. Two-level hierarchical Bayesian meta-analysis has been applied for clinical trials, but applications on observational data are rare. Hierarchical Bayesian methods in ecological studies, including ecological bias, have been discussed (108, 110, 115-117). Even a simple meta-analysis involves an ecological bias, as outcomes are not available on the individual level (118). Our meta-analysis involved studies of job titles with external agent data (FINJEM) with unknown extrapolability and unknown exposure levels, hence liable to exposure misclassification. Inclusion of country as a covariate in the hierarchical Bayesian models presumably reduced the misclassification bias.

### *Conclusions*

Summarizing, the results of this meta-analysis suggest that occupational exposures to chlorinated hydrocarbon compounds may increase the risk of pancreatic cancer, a result

obtained in another meta-analysis of independent, agent-specific epidemiological specific studies. Hierarchical models are applicable in meta-analyses when studies addressing the agent(s) under study are lacking or very few, but several studies address job titles with potential exposure to these agents. A job-exposure matrix or a formal expert assessment system is necessary in these situations.

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## Appendix

Let  $i = 1, \dots, M$  denotes the index of relative risk estimates from studies. Let  $j = 1, \dots, N$ ,  $k = 1, \dots, O$ , and  $l = 1, \dots, P$  denote the index of job titles, covariates, and agents, respectively. Let  $RR_i$  denote the observed estimate of the relative risk of pancreatic cancer for job title in the risk estimate  $i$  and  $RR_{L_i}$  and  $RR_{U_i}$  95% lower and upper limits of  $RR_i$ . Outcome variable  $y_i = \log(RR_i)$  and its standard error  $s_i = \log(RR_{L_i} / RR_{U_i}) / 3.92$ . Let  $\theta_i$  and the variance  $\sigma_\theta^2$  represent the true log relative risk for job title in the risk estimate  $i$  and between study variance, respectively.

In the hierarchical Bayesian models  $x_{ij}$  is the element of risk estimates-job  $M \times N$ -matrix with the value of unity when risk estimates ( $RR_i$  and  $s_i$ ) were available for job  $j$  and zero otherwise;  $w_{ik}$  is the element of risk estimates-covariate  $M \times O$ -matrix of 1:s and 0:s; and  $z_{jl}$  is  $s$  element of the job-agent  $N \times P$ -matrix which comes from job-exposure matrix.

Let  $\beta_j$  denote the parameter of job  $j$  representing the mean log of relative risks for job  $j$  for all studies combined and  $\sigma_\beta^2$  the variance of parameter  $\beta_j$ . Let  $\gamma_k$  denote the mean log of relative risks for covariate  $k$  for all studies combined, and  $\mu_\gamma$  and  $\sigma_\gamma^2$  its mean and variance, respectively. Let  $\pi_l$  denote the mean log of relative risks for agent  $l$  for all studies combined and  $\mu_\pi$  and  $\sigma_\pi^2$  its mean and variance, respectively. Let  $N(\mu, \sigma^2)$  denote the normal distribution with mean  $\mu$  and variance  $\sigma^2$ . Let  $\Gamma(a, b)$  denote the gamma distribution with mean  $a/b$  and variance  $a/b^2$ .

In the hierarchical Bayesian model there were following normal distributional assumptions:

$$\begin{aligned} y_i &\sim N(\theta_i, s_i^2) \\ \theta_i &\sim N(\sum_j x_{ij} \beta_j + \sum_k w_{ik} \gamma_k, \sigma_\theta^2) \\ \beta_j &\sim N(\sum_l z_{jl} \pi_l, \sigma_\beta^2) \\ &\text{and prior distributions for } \gamma_k \text{ and } \mu_\pi \\ \gamma_k &\sim N(\mu_\gamma, \sigma_\gamma^2) \\ \pi_l &\sim N(\mu_\pi, \sigma_\pi^2), \end{aligned} \quad (\text{equation 1})$$

where  $i = 1, 2, \dots, M$ ,  $j = 1, 2, \dots, N$ ,  $k = 1, 2, \dots, O$ , and  $l = 1, 2, \dots, P$

Additionally the prior gamma distributions for the precisions  $1/\sigma_\theta^2$  and  $1/\sigma_{\beta_j}^2$  are

$$\begin{aligned} 1/\sigma_\theta^2 &\sim \Gamma(a_\theta, b_\theta) \\ 1/\sigma_{\beta_j}^2 &\sim \Gamma(a_\beta, b_\beta), \end{aligned} \quad (\text{equation 2})$$

where  $j = 1, 2, \dots, N$ .

**Table 1.** Characteristics of pancreatic cancer studies and risk estimates included by job titles. (C-C = case-control study, COH = cohort study; R-L = record-linkage study; OR = odds ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio; RR = rate ratio)

Job title	Number and type of studies included	Number and risk measure of risk estimates included
Asphalt workers (27-29)	2 COH; 1 R-L	3 SIRs
Bench carpenters (28)	1 COH	1 SMR
Bricklayers (27, 28, 30, 31)	1 COH; 3 R-L	2 SIRs; 1 SMR; 1 RR
Cabinetmakers (31, 32)	1 COH; 1 R-L	1 SMR; 1 RR
Concrete mixers (28, 34)	2 COH	2 SIRs
Concrete shutterers (28, 34)	2 R-L	1 SIR; 1 SMR
Construction carpenters (27, 28, 31, 32)	2 COH; 2 R-L	2 SIRs; 1 SMR; 1 RR
Construction workers (28, 35-37)	2 C-C; 1 COH; 1 R-L	2 ORs; 2 SIRs; 1 RR
Electric machine operators (31, 38)	2 R-L	1 SIR; 1 RR
Farmers (28, 31, 36, 37, 39-49)	4 C-C; 3 COH; 8 R-L	6 ORs; 9 SIRs; 4 SMRs; 2 RRs
Fitters/assemblers (28)	1 R-L	1 SIR
Foundry workers (50-55)	5 COH; 1 R-L	1 SIR; 7 SMRs
Laundry/dry cleaning workers (28, 31, 34, 56-59)	3 COH; 4 R-L	3 SIRs; 4 SMRs; 1 RR
Machine /engine mechanics (31, 47, 50, 60, 61)	1 C-C; 1 COH; 3 R-L	1 OR; 2 SMRs; 2 RRs
Metal plating workers (28, 31, 35, 36, 62, 63)	1 C-C; 2 COH; 3 R-L	1 OR; 1 SIR; 2 SMRs; 2 RR
Metal smelting furnacemen (28, 35, 50, 64-77)	15 COH; 2 R-L	6 SIRs; 9 SMRs; 2 RRs
Miners (28, 31, 35, 78-89)	12 COH; 3 R-L	1 SIR; 12 SMRs; 2 RRs
Painters (27, 28, 30, 31, 34, 50, 90-92)	1 C-C; 2 COH; 6 R-L	1 OR; 4 SIRs; 4 SMRs; 1 RR
Plywood/fiberboard workers (28, 93)	1 COH; 1 R-L	1 SIR; 1 SMR
Printers/pressmen (28, 30, 31, 35, 37, 94-98)	1 C-C; 4 COH; 5 R-L	1 OR; 5 SIRs; 4 SMRs; 2 RRs
Sawyers (52, 99)	1 COH; 1 R-L	1 SIR; 1 SMR
Sheet metal workers (27, 28, 31)	1 COH; 2 R-L	2 SIRs; 1 RR
Smiths (31)	1 R-L	1 RR
Stone cutters (27)	1 COH	1 SIR
Timbermen/lumbermen (28, 36)	1 C-C; 1 R-L	1 OR; 1 SIR
Turners/toolmakers (28, 31, 50, 100)	1 COH; 3 R-L	1 SIR; 2 SMRs; 1 RR
Wood working machine operators (28, 34, 35, 37, 93, 101-103)	2 C-C; 4 COH; 2 R-L	2 ORs; 2 SIRs; 3 SMRs; 1 RR

**Table 2.** Part of a job exposure matrix (FINJEM, ref. 20) used in the hierarchical Bayesian models 1 and 2. (ALHC = aliphatic and alicyclic hydrocarbon solvents, CHC = chlorinated hydrocarbon compounds, FUNG = fungicides, INSC = insecticides, NI= nickel and nickel compounds CR = chromium and chromium compounds, PAH = polycyclic aromatic hydrocarbons, SIL = silica dust, WOOD = wood dust).

Job title	Proportion exposed to chemical agent							
	ALHC	CHC	FUNG	INSC	NI/CR	PAH	SIL	WOOD
Construction carpenters	- <sup>a</sup>	-	-	-	-	-	0.76	1
Electric machine operators	-	-	-	-	-	-	0.29	-
Farmers	-	-	0.25	-	-	-	-	-
Fitters/assemblers	-	-	-	-	0.42	-	-	-
Foundry workers	-	-	-	-	0.25	-	0.44	-
Laundry/dry cleaning workers	-	0.39	-	-	-	-	-	-
Machine/engine mechanics	-	-	-	-	0.33	1	-	-
Metal plating workers	-	0.92	-	-	0.46	-	-	-
Metal smelting furnacemen	-	-	-	-	0.41	1	1	-
Painters	0.98	-	-	-	-	-	-	-
Plywood/fiberboard workers	-	-	0.33	0.33	-	-	-	0.66
Printers/pressmen	0.33	0.20	-	-	-	-	-	-
Sawyers	-	-	0.45	-	-	-	-	1
Sheet metal workers	-	-	-	-	0.38	-	-	-
Stone cutters	-	-	-	-	-	-	0.87	-
Timbermen/lumbermen	-	-	-	-	-	-	-	0.56

<sup>a</sup> Proportion exposed to agent is zero

**Table 3.** Results of risk estimates for laundry/dry cleaning and metal plating workers. (NEC = number of exposed cases, RR = observed relative risk, CI = confidence interval, RR<sub>HB1</sub> = posterior relative risk of hierarchical Bayesian model 1, CrI = credible interval, RR<sub>HB2</sub> = posterior relative risk of hierarchical Bayesian model 2).

Job title Study	Observed risk estimates			Posterior risk estimates			
	NEC	RR	95% CI	RR <sub>HB1</sub>	95% CI	RR <sub>HB2</sub>	95% CI
<b>Laundry/dry cleaning workers:</b>							
33	6	1.11	0.41-2.42	1.41	0.91-2.17	1.40	1.00-1.95
36	1	1.10	0.01-6.12	1.43	0.88-1.43	1.41	0.99-2.01
39	16	1.0	0.6-1.5	1.21	0.86-1.70	1.27	0.94-1.69
61	13	1.40	0.74-2.39	1.29	0.88-1.88	1.24	0.91-1.69
61	9	2.37	1.08-4.50	1.46	0.97-2.20	1.31	0.96-1.84
62	12	2.03	1.1-3.5	1.60	1.09-2.36	1.49	1.09-2.06
63	15	1.2	0.7-1.9	1.34	0.93-1.90	1.36	1.01-1.82
64	11	1.72	0.86-3.10	1.66	1.11-2.46	1.63	1.19-2.23
<i>Aggregated risk estimates</i>				<i>1.42</i>	<i>1.05-1.93</i>	<i>1.40</i>	<i>1.12-1.73</i>
<b>Metal plating workers:</b>							
33	12	3.54	1.83-6.19	2.41	1.20-3.89	2.35	1.53-3.65
36	1	1.2	0.02-6.68	1.95	1.05-3.59	2.13	1.29-3.47
40	7	1.6	0.6-4.3	2.14	1.22-3.70	2.37	1.47-3.77
41	5	1.23	0.34-4.40	2.05	1.11-3.73	2.31	1.38-3.84
67	1	0.91	0.02-5.09	1.94	1.04-3.56	2.12	1.28-3.46
68	1	0.37	0.01-2.08	1.90	1.01-3.50	2.10	1.27-3.42
<i>Aggregated risk estimates</i>				<i>1.96</i>	<i>1.15-3.29</i>	<i>2.11</i>	<i>1.33-3.35</i>

**Table 4.** The results of random effects (RE) models and hierarchical Bayesian (HB) models 1 and 2 for job titles included more than two observed risk estimates (NEC = number of exposed cases,  $MRR_{RE}$  = meta-relative risk in the RE-models, 95% CI = 95% confidence interval,  $MRR_{HB1}$  = meta-relative risk in th HB model 1, 95% CrI = 95% credible interval,  $MRR_{HB2}$  = meta-relative risk in th HB model 2).

Job title	Aggregated estimates						
	RE-models			HB-models			
	NEC	$MRR_{RE}$	95% CI	$MRR_{HB1}$	95% CrI	$MRR_{HB2}$	95% CrI
Asphalt workers	50	1.25	0.69-2.26 <sup>a</sup>	1.17	0.83-1.66	1.14	0.91-1.43
Bricklayers	32	0.64	0.44-0.93	0.77	0.52-1.13	0.85	0.64-1.10
Construction							
carpenters	174	0.81	0.67-0.97	0.84	0.61-1.16	0.86	0.67-1.09
Construction workers	116	1.11	0.89-1.38	1.00	0.75-1.32	0.99	0.84-1.19
Farmers	> 1746 <sup>b</sup>	0.88	0.77-1.01 <sup>c</sup>	0.89	0.72-1.10	0.90	0.77-1.05
Foundry workers	> 90 <sup>d</sup>	1.02	0.81-1.27	1.01	0.72-1.40	0.99	0.79-1.23
Laundry/dry							
cleaning workes	83	1.41	1.13-1.76	1.42	1.05-1.93	1.40	1.12-1.75
Machine/engine							
mechanics	95	1.34	0.92-1.94	1.25	0.89-1.77	1.20	0.95-1.53
Metal plating workers	27	2.04	1.17-3.55	1.96	1.15-3.29	2.11	1.33-3.35
Metal smelting							
furnacemen	214	1.15	0.99-1.33	1.10	0.81-1.49	1.07	0.84-1.37
Miners	156	1.07	0.89-1.28	1.02	0.73-1.39	1.01	0.79-1.30
Painters	255	1.13	0.87-1.48 <sup>e</sup>	1.11	0.83-1.50	1.10	0.87-1.39
Printers/pressmen	183	1.19	0.97-1.46	1.21	0.91-1.60	1.21	0.99-1.48
Sheet metal workers	17	1.03	0.61-1.74	1.00	0.65-1.54	1.02	0.77-1.33
Turners/toolmakers	21	0.69	0.44-1.08	0.93	0.58-1.46	1.08	0.77-1.46
Wood working							
machine operators	241	0.98	0.85-1.13	0.95	0.71-1.26	0.95	0.77-1.16

<sup>a</sup> Test of heterogeneity:  $p = 0.061$

<sup>b</sup> Missing from two studies

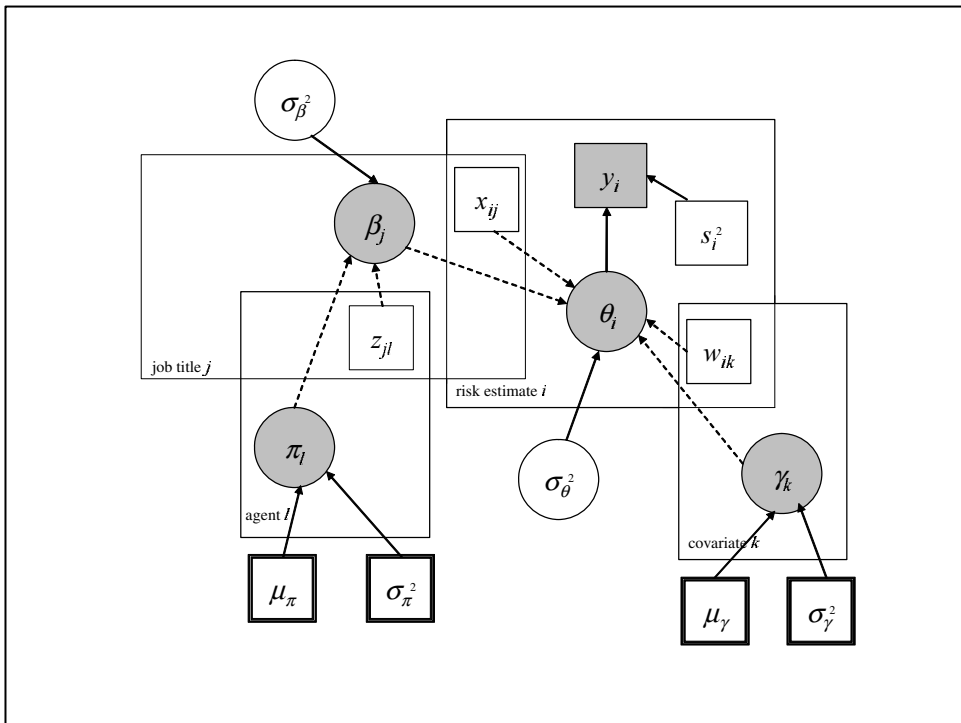
<sup>c</sup> Test of heterogeneity:  $p < 0.001$

<sup>d</sup> Missing from one studiy

<sup>e</sup> Test of heterogeneity:  $p = 0.002$

**Table 5.** The results of hierarchical Bayesian hierarchical models 1 and 2 for occupational agents (MRR<sub>HB1</sub> = meta relative risk in the hierarchical Bayesian model 1, CrI = credible interval, MRR<sub>HB2</sub> = meta relative risk in the hierarchical Bayesian model 2)

Agent	MRR <sub>HB1</sub>	95% CrI	MRR <sub>HB2</sub>	95% CrI
Aliphatic and alicyclic hydrocarbon solvent	1.11	0.65-1.92	1.10	0.80-1.51
Chlorinated hydrocarbon compounds	2.03	0.99-4.08	2.21	1.31-3.67
Fungicides	1.09	0.37-3.24	0.91	0.45-1.93
Insecticides	1.53	0.33-7.06	1.95	0.51-7.41
Nickel and nickel / chromium and chromium compounds	1.03	0.46-2.27	1.05	0.61-1.81
Polycyclic aromatic hydrocarbons	1.13	0.78-1.63	1.14	0.89-1.45
Silica dust	0.90	0.65-1.24	0.90	0.72-1.11
Wood dust	0.97	0.69-1.33	0.96	0.78-1.17



**Figure 1.** A directed acyclic graph for hierarchical Bayesian meta-analysis with data from FINJEM: equations (1)-(2) in Appendix.