

Aarne Laakkonen

# Occupational exposure to organic dusts and cancer among Finnish workers: special emphasis on the food industry and agriculture



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Acta Electronica Universitatis Tamperensis 782  
ISBN 978-951-44-7500-9 (pdf)  
ISSN 1456-954X  
<http://acta.uta.fi>

**Cover design** Tiina Vaahtera  
**Cover picture** Corbis / Lehtikuva  
**ISBN** 978-951-802-851-5 (paperback)  
978-951-802-852-2 (PDF)  
**ISSN** 1237-6183  
**Press** Tampereen Yliopistopaino Oy – Juvenes Print, Tampere 2008

# **Occupational exposure to organic dusts and cancer among Finnish workers: special emphasis on the food industry and agriculture**

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**People and Work  
Research Reports 84**

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# CONTENTS

1. LIST OF ORIGINAL ARTICLES .....	5
2. ABBREVIATIONS.....	6
3. ABSTRACT .....	8
4. TIIVISTELMÄ (ABSTRACT IN FINNISH) .....	12
5. INTRODUCTION.....	16
6. REVIEW OF THE LITERATURE .....	18
6.1. Organic dusts and their health effects .....	18
6.1.1. What are organic dusts? .....	18
6.1.2. Exposure to organic dusts in Finland.....	24
6.1.3. Health effects of organic dusts.....	25
6.1.4. Occupational diseases caused by organic dusts in Finland .....	26
6.2. Organic dusts and cancer.....	27
6.2.1. Animal dust.....	27
6.2.2. Bacterial dust .....	27
6.2.3. Flour dust .....	29
6.2.4. Leather dust.....	29
6.2.5. Mould dust.....	30
6.2.6. Pulp and paper dust .....	32
6.2.7. Plant dust .....	33
6.2.8. Synthetic polymer dust.....	33
6.2.9. Textile dust .....	34
6.2.10. Wood dust.....	35
6.3. Job-exposure matrix (JEM).....	37
6.3.1. What is a job-exposure matrix? .....	37
6.3.2. Validity of a JEM .....	37
6.4. Cancer in Finland .....	38
6.4.1. Cancer in men and women .....	38
6.4.2. Occupational cancers.....	41
7. AIMS OF THE STUDY .....	42

## CONTENTS

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8. MATERIALS AND METHODS .....	44
8.1. Study design .....	44
8.1.1. Census-based cohort study .....	44
8.1.2. Finnish Cancer Registry.....	45
8.2. Occupational exposures in this study .....	45
8.2.1. Finnish National Job-Exposure Matrix (FINJEM).....	45
8.2.2. Division of the cohort into those exposed and not exposed .....	46
8.2.3. Application of FINJEM .....	47
8.3. Statistical analyses .....	48
9. SUMMARY OF THE RESULTS .....	51
9.1. Cancer among food industry workers (I) and farmers (IV).....	51
9.2. Organic dust exposure and cancer (II and III) .....	54
10. DISCUSSION .....	58
10.1. Methods.....	58
10.2. Findings.....	63
11. SUMMARY AND CONCLUSIONS .....	69
12. ACKNOWLEDGEMENTS .....	70
13. REFERENCES .....	72
14. ORIGINAL ARTICLES .....	85

## **1. LIST OF ORIGINAL ARTICLES**

This thesis is based on the following original articles which are referred to by their Roman numerals:

- I Laakkonen A, Kauppinen T, Pukkala E (2006): Cancer risk among Finnish food industry workers. *International Journal of Cancer* 118:2567–2571.
- II Laakkonen A, Kyyrönen P, Kauppinen T, Pukkala E (2006): Occupational exposure to eight organic dusts and respiratory cancer among Finns. *Occupational and Environmental Medicine* 63:726–733.
- III Laakkonen A, Verkasalo P, Nevalainen A, Kauppinen T, Kyyrönen P, Pukkala E (2008): Moulds, bacteria and cancer among Finns: an occupational cohort study. *Occupational and Environmental Medicine* 65:489–493.
- IV Laakkonen A, Pukkala E (2008): Cancer incidence among Finnish farmers, 1995–2005. *Scandinavian Journal of Work, Environment and Health* 34:73–79.

## 2. ABBREVIATIONS

BMI	Body mass index
CAREX	International Information System on Occupational Exposure to Carcinogens, (CARcinogen EXposure)
CE	Cumulative exposure
CFU	Colony-forming unit
CI	Confidence interval
CLL	Chronic lymphatic leukaemia
E	Expected number of cases
EU15	European Union with 15 member states
EU25	European Union with 25 member states
FAII	Federation of Accident Insurance Institutions
FCR	Finnish Cancer Registry
FINJEM	Finnish National Job-Exposure Matrix
FIOH	Finnish Institute of Occupational Health
FROD	Finnish Registry of Occupational Diseases
GPJEM	General population job-exposure matrix
HR	Hazards ratio
IARC	International Agency for Research on Cancer
ILO	International Labour Organisation
ISCO	International Standard Classification of Occupations
ISJEM	Industry-specific job-exposure matrix
JEM	Job-exposure matrix
L	Level of average exposure among the exposed persons
LAL	Limulus amoebocyte lysate assay
MELA	Farmers' Social Insurance Institution (in Finnish)
MMOF	Man-made organic fibre
N	Number of persons

## 2. ABBREVIATIONS

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O	Observed number of cases
ODTS	Organic dust toxic syndrome
OEL	Occupational exposure limit
P	Proportion of exposed persons
PAH	Polycyclic aromatic hydrocarbons
PID	Personal identification code
PPM	Parts per million
PRR	Pooled relative risk
RR	Relative risk
SAS	Statistical analysis software by SAS Institute Inc.
SES	Socioeconomic status
SIR	Standardized incidence ratio

### **3. ABSTRACT**

Organic dusts of vegetable, animal or microbial origin are major causes of occupational diseases of the respiratory tract. There is inconclusive evidence concerning the risk of cancer from organic dusts, and only limited knowledge on inhalatory exposure to some organic dusts and cancer, e.g., bacteria and moulds. The food industry and agriculture have significant occupational organic dust exposure.

The aims of the present study were:

1. To study the risk of respiratory cancer among workers in the food industry and agriculture, whose exposure is mainly inhalatory.
2. To generate a hypothesis concerning other cancers among food industry workers and agricultural workers, and to discover new associations between occupational agents and cancer.
3. To describe the cancer risk pattern of Finnish farmers and to define the type of farm as a potential determinant of the observed risk ratios.
4. To study whether changes in the type of farm account for alterations in lung cancer risk. A low prevalence of cancer has been associated especially with dairy farming; discontinuing dairy farming might thus increase the risk of lung cancer.
5. To assess the association between cancer and occupational exposure to bacteria and moulds in Finland. The presumption was that exposure to biological dust dominated by moulds and Gram-positive bacteria increases the risk of respiratory cancer due to mycotoxin and bacterial exotoxin, and that, conversely, exposure dominated by Gram-negative bacteria decreases respiratory cancer risk due to the presence of endotoxin.

### 3. ABSTRACT

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6. To study whether inhalatory exposure to moulds increases the risk of cancers of the liver, oesophagus, upper respiratory tract, and urinary tract.

The computerized registries of Statistics Finland (census, occupations, and death certificates), Finnish Cancer Registry (cancer cases), Finnish Institute of Occupational Health (Finnish Job-Exposure Matrix (FINJEM)), Finnish National Public Health Institute (life-style data) and Farm Registry of Finland (farm data) were linked based on either individual or group level key variables.

The cohort in the studies utilizing FINJEM comprised all economically active Finns born between 1 January 1906 and 31 December 1945 who participated in the national population census on 31 December 1970 (667,121 men; 513,110 women). Statistics Finland maintains and updates the census files for vital status to allow exact person-year calculation. Data on the main occupation in 1970 were obtained from the Population Census records (Statistics Finland 1974). The socioeconomic status (SES) of each subject was based on the subject's occupation. In our analyses, the SES was categorized as follows: farmers, higher white-collar, clerical, skilled blue-collar, and unskilled workers. The occupational exposures of the cohort were estimated by using a job-exposure matrix, FINJEM. FINJEM covers the major occupational exposures in Finland from 1945 onwards by occupation and calendar time. FINJEM characterizes exposure by the proportion of exposed persons (P) and the average level of exposure (L) among the exposed persons in each occupation. The estimates are based on exposure measurements, hazard surveys, and the assessments of occupational hygienists. P and L are assessed in FINJEM quantitatively for chemical, biological and physical agents. Major changes in exposure over time are taken into account enabling estimations of cumulative exposure (CE). FINJEM also includes estimates of alcohol consumption and smoking prevalence by occupation.

The Finnish Cancer Registry (FCR) has collected data on cancer cases diagnosed in Finland since 1953. All physicians, hospitals and other institutions, and all pathologic, cytological and haematological laboratories in the country must notify the FCR of all cancer cases that come to their attention. In addition, Statistics Finland annually provides a computerized file on all death certificates in which cancer is mentioned.

### 3. ABSTRACT

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The expected number of cancer cases was calculated by multiplying the number of person-years lived by persons in that occupation (or in exposure) with the cancer incidence rate of the referent population (or un-exposed population). Exposure for each birth cohort was assumed to start in the year when the average age of the birth cohort was 20, and to end in the mid-year of the observation period, or at 65 years of age, whichever came first. In internal comparison within an occupation, the employees within an occupation were divided into groups of cumulative exposure of un-exposed (none) and exposed (low, medium, high) using time, and P and L data as the base for grouping. In selected cancers, regression analysis was performed adjusting for smoking, social class, and alcohol consumption (laryngeal cancer), asbestos and quartz dust (lung cancer).

A total of 2,526 incident cancer cases were found among Finnish food industry workers. Among male food industry workers, elevated risks were observed for pancreatic cancer (standardized incidence ratio (SIR) 1.5, 95% confidence interval (CI) 1.1–2.0) and kidney cancer (SIR 1.5, CI 1.2–1.9). There was an excess of lung cancer among female bakers (SIR 1.4, CI 1.0–1.9) and laryngeal cancer among male grain millers (SIR 2.6, CI 1.1–5.4).

A total of 20,426 incident cases of respiratory cancer were found among employees exposed to one or more types of eight organic dusts. A slightly elevated risk of nasal cancer (SIR 1.4, CI 0.8–2.4) was observed among men exposed to wood dust. Men exposed to plant dust (mainly grain millers) had an elevated SIR of laryngeal cancer in the high exposure class (SIR 3.6, CI 1.3–7.7). Men exposed to wood dust had an elevated SIR for lung cancer, but only in the low exposure class (SIR 1.1, CI 1.0–1.2). Women exposed to wood dust had an elevated SIR for mesotheliomas in the low exposure class (SIR 4.6, CI 1.3–11.7) and some excess in the medium exposure category.

Men with the highest occupational exposure to moulds and bacteria had a reduced relative risk for lung cancer (risk ratio (RR) 0.7, 95% confidence interval 0.6–0.9 for moulds and RR 0.9 (CI 0.8–1.0) for bacteria) as compared with non-exposed men. Women in the highest mould and bacteria exposure category had RRs of 3.1 (CI 1.0–9.2) and 2.6 (CI 1.5–4.7) for cervical cancer, respectively. The respective RRs for

### 3. ABSTRACT

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lip cancer in the highest mould and bacteria exposure category among men and women combined were 2.4 (CI 1.2–5.1) and 1.6 (CI 1.2–2.2).

The farmer study cohort comprised all farmers on 31 December 1978, who were included in the Finnish Farm Registry. The continuation of farming activity was checked from the 1990 and 1994 Farm Registry data. The overall cancer incidence among farmers was lower than in the general population. The only significantly elevated SIR was that for lip cancer. The lowest rates among farmers who continued farming were in mesothelioma and cancers of the liver, larynx, lung, nose, oesophagus and urinary bladder. Permanent beef and dairy farmers had the lowest SIRs for overall cancer. Those dairy farmers who had changed over to crop farming had a slightly higher overall cancer incidence than those who continued dairy farming.

Occupational exposure is unlikely to be a major risk factor for cancer among Finnish food industry workers. Exposure to organic dusts is unlikely to be a major risk factor of respiratory cancer, with the possible exception of wood dust in the causation of nasal cancer. Some evidence that exposure to grain dust might elevate the risk of laryngeal cancer was found. Exposure to either moulds or bacteria is unlikely to be a major risk factor of cancer, even though increased risk was observed for some cancer types. The cancer incidence of Finnish farmers was significantly below the national average. The hypothesis that exposure to textile dust and plant and animal dust might decrease the risk of lung cancer was supported. The finding that lung cancer risk was low among dairy farmers but increased along with a change to other types of farming offers some support to the hypothesis that endotoxin exposure may decrease cancer risk. Both the present results as well as earlier ones related to lung cancer need to be interpreted with caution, because even after adjustment for the strongest confounding factor, i.e., smoking, there is a possibility of residual confounding.

## 4. TIIVISTELMÄ (ABSTRACT IN FINNISH)

Orgaaniset pölyt ovat kasvi-, eläin- tai mikrobiperäisiä pölyjä, ja ne ovat yleisiä työperäisten hengityselinsairauksien aiheuttajia. Orgaanisten pölyjen mahdollisesti aiheuttamasta lisääntyneestä syöpäriskistä ei ole varmaa tietoa ja esimerkiksi bakteereille ja homeille hengitysteiden kautta tapahtuvan altistumisen mahdollisesta vaikutuksesta syöpäriskiin ei ole juuri mitään julkaistua tietoa. Elintarviketeollisuudessa ja maanviljelystyössä orgaanisille pölyille altistuminen on yleistä.

Tutkimuksen tavoitteet olivat:

1. Selvittää hengityselinten syöpäriskiä elintarviketyöntekijöillä ja maanviljelijöillä.
2. Selvittää muiden syöpien riskiä edellä mainituilla aloilla työskentelevillä ja etsiä mahdollisia uusia viitteitä työn altisteiden ja syövän välisistä yhteyksistä.
3. Selvittää suomalaisten maanviljelijöiden syöpäriskiä ja tuotantosuunnan vaikutusta havaittuihin riskeihin.
4. Selvittää tuotantosuunnan muutoksen vaikutusta riskiin saada keuhkosyöpä. Erityisesti karjataloudessa työskentelevillä maanviljelijöillä on aiemmin havaittu muuta väestöä alhaisempi keuhkosyöpäriski, joten karjataloudesta luopuminen saattaa kasvattaa keuhkosyöpäriskiä.
5. Selvittää työssä bakteereille ja homeille altistumisen ja syövän välisiä yhteyksiä. Oletuksena oli, että altistuminen homeita ja Gram-positiivisia bakteereita sisältävälle pölylle lisää hengityselinten syövän riskiä homeiden mykotoksiinien ja bakteerien eksotoksiinien vuoksi ja että pääasiallisesti Gram-negatiivisia bakteereja sisältävälle pölylle

## 4. TIIVISTELMÄ

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altistuminen vähentää hengityselinten syövän riskiä sisältämänsä endotoksiinin vuoksi.

6. Selvittää, lisääkö altistuminen homeille hengitysteiden kautta riskiä saada maksan, ruokatorven, ylähengitysteiden ja virtsateiden syöpä.

Tilastokeskuksen (väestölaskenta- ja ammattitiedot, kuolintodistukset), Suomen Syöpärekisterin (syöpätapaukset), Työterveyslaitoksen (työaltistematriisi (FINJEM)), Kansanterveyslaitoksen (elintapatiedot) ja Maatilarekisterin (maatilatiedot) ATK-pohjaiset rekisterit yhdistettiin joko yksilö- tai ryhmätason tunnistetiedoilla.

Työaltistematriisia hyödyntävän tutkimuksen kohorttiin kuuluivat kaikki työlliset 1906–1945 syntyneet suomalaiset, jotka osallistuivat väestölaskentaan 31.12.1970 (667 121 miestä, 513 110 naista). Tilastorekisteri ylläpitää ja päivittää väestön elintiedot mahdollistaen tarkan henkilövuosien laskennan. Vuoden 1970 pääasiallisen ammatin tiedot saatiin väestölaskentatiedoista. Kunkin henkilön sosiaaliluokka perustui kunkin omaan ammattiin. Sosiaaliluokat jaettiin maanviljelijöihin, ylempiin toimihenkilöihin, toimihenkilöihin, ammattityöntekijöihin ja työntekijöihin. FINJEM sisältää eri ammattien pääasialliset altistetiedot vuodesta 1945 alkaen ajanjaksottain. Kunkin ammatin altistekohtainen altistuneiden osuus (P (proportion)) ja altistuneiden keskimääräinen altistumisen taso (L (level)) on arvioitu FINJEM:ssä. Luvut perustuvat työhygienisiin mittauksiin, riskiarvioihin ja työhygienikkojen arvioihin. P ja L on esitetty määrällisinä arvoina kemiallisille, biologisille ja fyysikaalisille tekijöille ja merkittävät altistumisen muutokset eri aikakausina on huomioitu mahdollistaen altistumisen kertymisen (CE (cumulative exposure)) arvioinnin. FINJEM:ssä on myös ammattikohtaisia tietoja alkoholin kulutuksesta ja tupakoinnin yleisyydestä.

Suomen Syöpärekisterissä on tiedot syöpätapauksista Suomessa vuodesta 1953 alkaen. Kaikkien lääkäreiden, sairaaloiden ja laboratorioden on ilmoitettava syöpärekisterille toteamansa syöpätapaukset. Tilastokeskus toimittaa vuosittain tiedot vainajista, joiden kuolintodistuksessa on syöpädiagnoosi.

Ennustettu syöpätapausten lukumäärä laskettiin kertomalla tietyn ammatin (altistuneet) henkilöiden henkilövuosien lukumäärä syövän ilmaantumisluvulla verrokkiväestössä (altistumattomat). Jokaisen synty-

#### 4. TIIVISTELMÄ

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mävuosikohortin altistumisen katsottiin alkavan syntymävuosikohortin iän keskiarvon ollessa 20 vuotta ja päättyvän seuranta-ajan päättymisvuoden keskellä tai 65 vuoden iässä riippuen siitä, kumpi raja täyttyy ensin. Ammatin sisäisessä vertailussa (II ja III) työntekijät jaettiin P- ja L-arvojen perusteella kumulatiivisen altistumisen luokkiin, jotka olivat altistumaton, matala, keskimääräinen ja suuri altistuminen. Valituissa syövässä tehtiin regressioanalyysi vakioimalla tupakointi, sosiaaliluokka, alkoholinkulutus (kurkkusyöpä), asbesti ja kvartsipöly (keuhkosyöpä).

Suomalaisilla elintarviketyöntekijöillä todettiin 2 526 syöpätapausta. Miespuolisilla elintarviketyöntekijöillä todettiin suurentunut riski haimasyövälle (vakioitu ilmaantuvuussuhde SIR (standardized incidence ratio) 1,5; 95 %:n luottamusväli CI (confidence interval) 1,1–2,0) ja munuaissyövälle (SIR 1,5; CI 1,2–1,9). Keuhkosyövän riski oli suurentunut naispuolisilla leipureilla (SIR 1,4; CI 1,0–1,9) ja kurkkusyövän riski miespuolisilla mylläreillä (SIR 2,6; CI 1,1–5,4).

Työntekijöillä, jotka olivat altistuneet yhdelle tai useammalle kahdeksasta orgaanisesta pölystä, todettiin 20 426 syöpää. Puupölylle altistuneilla todettiin hieman suurentunut SIR (1,4; CI 0,8–2,4) nenäsyövälle. Kasvipölylle altistuneilla (suurin osa mylläreitä) oli suurentunut kurkkusyövän riski korkeimmassa altistumisen luokassa (SIR 3,6; CI 1,3–7,7). Puupölylle altistuneilla miehillä oli kohonnut keuhkosyövän riski, mutta vain alhaisimmassa altistumisen luokassa (SIR 1,1; CI 1,0–1,2). Puupölylle altistuneilla naisilla oli suurentunut mesoteliooman riski alhaisimmassa altistumisen luokassa (SIR 4,6; CI 1,3–11,7) ja jonkin verran suurentunut riski keskimääräisen altistumisen luokassa.

Keuhkosyövän riskisuhde oli alentunut suurimman homeille ja bakteereille altistumisen luokassa (risk ratio (RR) 0,7; CI 0,6–0,9 homeille ja RR 0,9; CI 0,8–1,0 bakteereille altistuneilla) altistumattomiin miehiin verrattuna. Naisilla oli suurentunut kohdunkaulansyövän riskisuhde (RR 3,1; CI 1,0–9,2 homeille ja RR 2,6; CI 1,5–4,7 bakteereille altistuneilla). Huulisyövän riskisuhde (molemmat sukupuolet yhdessä) oli suurimman altistumisen luokassa kohonnut (RR 2,4; CI 1,2–5,1 homeille ja RR 1,6; CI 1,2–2,2 bakteereille altistuneilla).

Maanviljelijätutkimuksessa kohorttina olivat kaikki Maatilarekisterissä 31.12.1978 kirjattuna olevat maanviljelijät. Maanviljelijän ammatissa jatkaminen tarkistettiin vuoden 1990 ja 1994 Maatilarekisteristä. Maanviljelijöiden yleinen syövän ilmaantuvuus oli muuta väestöä alhaisempi.

#### 4. TIIVISTELMÄ

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Huulisyöpä oli ainoa, jolla oli merkittävästi suurempi SIR kuin muussa väestössä. Alhaisimmat SIR-arvot maanviljelijän ammatissa jatkavilla olivat mesoteliomalle ja maksan, kurkunpään, keuhkojen, nenän, ruokatorven ja virtsarakon syöville. Lihan- ja maidontuottajilla oli alhaisin yleinen syöpäriski. Vuoden 1978 maidontuottajilla, jotka olivat vaihtaneet tuotantosuuntaa viljanviljelyyn, oli hieman korkeampi yleinen syöpäriski kuin maidontuottajina jatkaneilla.

Työn altisteet ovat tuskin merkittävä syövän riskitekijä suomalaisessa elintarviketeollisuudessa työskenteleville. Altistuminen orgaanisille pölyille ei vaikuta olevan merkittävä hengityselinten syövän riskitekijä poikkeuksena mahdollisesti puupölyn nenäsyövän riskiä lisäävä vaikutus. Tutkimuksessa saatiin viitteitä viljapölyn kurkunpään syövän riskiä kasvattavasta vaikutuksesta. Homeille tai bakteereille altistuminen ei vaikuta olevan merkittävä syövän riskitekijä, vaikka viitteitä joidenkin syöpien lisääntyneestä riskistä saatiinkin. Suomalaisten maanviljelijöiden syövän ilmaantuvuus oli merkittävästi väestön keskimääräistä alhaisempi. Tutkimuksen tulokset tukevat jonkin verran hypoteesia, jonka mukaan altistuminen tekstiili-, kasvi- ja eläinpölyille vähentää keuhkosyövän riskiä. Maidontuottajien alhainen syöpäriski ja riskin lisääntyminen maidontuottajan vaihtaessa tuotantosuuntaa tukee jonkin verran hypoteesia, jonka mukaan altistuminen endotoksiineille voi alentaa syöpäriskiä. Keuhkosyöpää koskevat tulokset, sekä tässä että aikaisemmissa tutkimuksissa julkaistut, on syytä tulkita varauksella, koska tärkeimmän sekoittavan tekijän tupakoinnin vakiointi voi jäädä vaillinaiseksi.

## **5. INTRODUCTION**

Most of the diseases that can be due to occupational exposure, also have non-occupational causes. Chronic occupational diseases, such as cancer, usually have a long latency period between the start of occupational exposure and the occurrence of clinical disease. The first suggestions of the carcinogenicity of some substances (e.g., asbestos and benzene) were found in epidemiological studies (Hernberg 1992). Epidemiological studies have also given hints of excess cancer risks in some industries, and the causes have been recognized only later.

The availability of exposure data is often problematic in large-scale studies. The job-exposure matrix is a tool that translates information on jobs into information on occupational risk factors. Register-based linkage studies offer a method to utilize a large quantity of collected data. The Finnish Cancer Registry collects and combines all data available on the primary site, histology and behaviour of the cancer to a nationwide database with unique high compliance and data quality.

Organic dusts are derived from living material and have always been inherent in the environment. They include dusts or aerosols containing live or dead microbes (e.g., viruses, bacteria, moulds, spores), and dusts arising from organic compounds (e.g., wood, leather, flour). Dust from synthetic polymers (e.g., plastic, synthetic textiles or leather, synthetic dyes and binders of paints) is also included in organic dusts in this thesis.

Symptoms and diseases are mainly initiated by irritation and inflammatory responses and allergic reactions. Exposure to organic dusts in the occupational environment is associated with a wide range of health effects having a major public health impact, including infectious diseases, acute toxic effects, allergies and cancer. Respiratory symptoms

## 5. INTRODUCTION

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and lung function impairment are among the most important health effects associated with exposure to organic dust (Douwes et al. 2003). Systemic effects on the liver, kidneys, joints, peripheral nerves, skin and gut, as well as fever and fatigue have also been reported (Rylander and Jacobs 1997).

There is very limited knowledge on the cancer risks of organic dust exposure. There are sporadic observations of elevated risk of sinonasal cancer, lung cancer, liver cancer, bladder cancer, lymphatic and haematopoietic malignancies, pancreatic cancer, salivary gland tumours and multiple myeloma related to organic dusts (Rylander and Jacobs 1997). Some studies suggest that exposure to organic dust leads to lower rates of lung cancer (Mastrangelo et al. 2002, Mastrangelo et al. 2005).

The numerous unanswered questions related to the association between organic dust and plausible biological mechanisms present a challenging and relevant research target. The Finnish comprehensive databases offer the best possible tools to resolve this question by means of epidemiological research.

## **6. REVIEW OF THE LITERATURE**

### **6.1. Organic dusts and their health effects**

#### **6.1.1. What are organic dusts?**

Dusts are solid particles suspended in a gaseous medium. Dusts result from the mechanical disintegration of materials by the action of e.g., grinding, with enough mechanical energy to propel particles into the air. Airborne dust particles vary greatly in size, ranging from approximately 50 $\mu\text{m}$  to less than 1 $\mu\text{m}$ . Most dusts produced by industrial operations as well as non-industrial operations such as construction or demolition consist of particles of various sizes, the small particles greatly outnumbering the large ones.

Inhalation is the primary route of exposure for dusts. Particle size determines the site of deposition within the respiratory system. Total dust includes all airborne particles, regardless of size or composition. Inhalable dust is the size fraction of dust which enters the body, but is trapped in the nose, throat, and upper respiratory tract. The median aerodynamic diameter of this dust is about 10  $\mu\text{m}$ . The dust concentrations known to be harmful are defined as the inhalable fractions in Finland (STM (Ministry of Social Affairs and Health) 2007). Respirable dust is airborne material which is capable of penetrating to the gas-exchange region (alveoli) of the lungs (U.S. Occupational Safety and Health Administration, [www.osha.gov](http://www.osha.gov)). Particles with a diameter between 1 and 8  $\mu\text{m}$  may enter the lung alveoli (Rylander and Jacobs 1997, Herrick and Dement 2005)

There are also other respirable particles besides dusts, e.g., fumes and smoke formed when materials are burnt or metal is heated above its boiling point and its vapours condense into very fine particles.

## 6. REVIEW OF THE LITERATURE

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Organic dust, as defined by the Committee on Organic Dust of the International Commission on Occupational Health, is dust of vegetable, animal or microbial origin (Rylander and Jacobs 1997). Bioaerosols are usually defined as aerosols or particulate matter of microbial, plant or animal origin that is often used synonymously with organic dust (Douwes, et al. 2003). Examples of organic dusts are pollen, the dust from plants, cellulose, textiles, sugar, wood, pulp and paper, flour, mould, bacteria, enzymes, fur, animal epithelia, raw coffee, flax, cotton, fish powder, yeast feed, raw tea, spices and milk powder. Synthetic polymers are produced from organic substances and their dust can be included in organic dusts although they are not directly derived from natural materials.

Organic dusts occur in numerous occupations, including agricultural work; the textile industry, especially cotton processing; flour milling and bakeries; and the wood industry, particularly sawmills, carpentry, and wood processing. Many of these occupations, especially in agriculture, also have the potential for concurrent exposure to other substances that affect respiratory health, e.g., metals, gases, fibres and chemicals (Omland 2002). The sources of exposure to organic dusts derive from occupational or domestic activities or the environment at work or at home. Examples of sources of exposure to organic dusts are presented in Table 1.

Several edible plants belonging to the grass family, including wheat, rye, barley, oats, corn, rice, sorghum and millet, are valuable agricultural commodities. Three major grains produced for their oil, i.e. oilseeds, are soybean, rapeseed and sunflower (Rylander and Schilling 1998). Grain dust is produced by abrasion and attrition of grain kernels and emitted whenever grain is handled. Grain dusts are a complex mixture of materials deriving primarily from cereal grains and vegetation, but contain natural contaminants and human additives as well. The biological activity of the dust depends on the composition, which varies with the region, climate, the source of the product, the state of decomposition, temperature, etc.

Stored grains or silage contain high concentrations of *Aspergillus* and *Penicillium* species. Thermoactinomycetes grow best in stored grain heated above 50°C during decomposition. In grain elevators, bacteria are the most prevalent micro-organisms in airborne dust. In addition to the plant-derived particles and micro-organisms, grain dust contains

## 6. REVIEW OF THE LITERATURE

**Table 1. Environments and occupations that expose to organic dusts (Dutkiewicz et al. 1988, Rylander and Jacobs 1997, Louhelainen 2005).**

<b>Environment</b>	<b>Source of exposure or process</b>	<b>Occupation involving exposure</b>
Agriculture	handling of grain, field crops, and hay; animals (breeding/livestock), greenhouses, dairy farming, animal confinement buildings (swine, poultry, cattle); transportation and storage of livestock and agricultural products	farmers, farm substitutes, veterinarians
Food industry	grain stores, mills, bakeries, feed factory, slaughter and meat processing facilities, spice production	grain handlers, process workers, grain millers, bakers, char workers, butchers, dairy workers
Wood industry	wood processing (cutting, production, manufacturing)	process workers, carpenters, char workers, timbermen, sawyers, plywood and fibreboard workers, renovators
Pulp and paper industry	pulp and paper production	process workers, packers and labellers, char workers
Textile industry	preparation of plant fibres (cotton, flax, soft hemp), preparation of animal fibres (wool, mohair)	fibre processors, spinning machine operators, weaving machine operators, textile machine setter operators, knitting machine operators, textile finishers, dyers, tailors, pattern makers and cutters, industrial sewers
Leather industry	leather clothing and shoe manufacture	furriers, pattern makers and cutters, last makers and sole fitters, leather sewers, tanners, fell mongers and pelt dressers
Pharmaceutical industry	pharmaceutical work, handling of laboratory animals (research)	process workers, laboratory animal caretakers
Biotechnology	biotechnology (recombinant DNA, tissue culture, vaccine production, enzyme production), fermentation processes	process workers, researchers
Energy production	peat and wood chip production	peat workers, energy plant workers
Waste processing	sewage treatment, composting, household garbage	sewage and compost workers, garbage truck drivers
Processing contamination	cutting fluids	process workers
Office buildings and residences	contaminated humidifiers, mould in structures, ventilation ducts, etc.	any occupation

## 6. REVIEW OF THE LITERATURE

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endotoxin, glucans, mycotoxins, proteases, animal hairs, feathers, insect and mite particles (grain weevils, storage mites), fertilizers, ammonia and pesticide residues, and silica. Grain dust is a mixture of many materials, including various types of grain and their disintegration products, as well as pollens, fungi, insects, and mites. It also contains silicon dioxide in varying amounts, and is contaminated by the excretions of rodents and pigeons (Rylander and Jacobs 1997). Vegetable dusts may also contain constituents of weeds that contaminate the plant crop; these may be irritants or sensitizers in themselves (Merchant 2005).

Cotton is generally harvested using machines, and therefore the contamination with branches, leaves, soil, and other contaminants can be up to 42% of the total weight (Rylander and Jacobs 1997). The by-products of processing sugar from sugar cane are stalks, bagasse, rum and molasses. Thermophilic actinomycetes grow in stored, mouldy bagasse (Rylander 1998).

Wheat flour is a complex mixture of substances containing peptides and saccharides, which may be considered potential allergens that may induce specific IgE-sensitization after inhalation. Cereal amylases are present in cereal flour in its native form. Cereal amylases should be distinguished from fungal amylases that are added as dough improvers (Houba et al. 1998).

The process of preparing paper from wood separates the lignin bonds between the cellulose fibres of the wood, freeing the cellulose fibres to be compressed into paper. This is done by using chemical or physical means or a combination of both. When the cellulose has been released from the wood, it is dried and rolled; during this process small particles of airborne paper are produced. Furthermore, there is potential co-exposure to asbestos and welding fumes in the paper industry (Korhonen et al. 2004). Other pollutants in the pulp and paper industry are wood dust, hydrogen sulphide, sulphur dioxide, chlorine, chlorine dioxide, and various mercaptans (Jäppinen 1987). The airborne particles can act as a vehicle which carries the chemicals into the lungs.

The formation of minute dust particles cannot be avoided in the production and processing of wood-based materials. Natural wood components, materials used in working and processing wood, metabolites of wood fungi, pyrolysis products from processing, or simple mechanical irritation may be potential health hazards. Wood components, particularly

## 6. REVIEW OF THE LITERATURE

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those of hard deciduous woods, have been suggested to be mutagenic and carcinogenic (Wittmann and Wolf 1996).

The possible health effects of wood dust differ according to the species of wood. The etiological agent in western red cedar asthma is plicatic acid (Rylander and Jacobs 1997). The polyphenol content in wood may be a useful chemical surrogate for detecting species with carcinogenic properties (Bianco and Savolainen 1994). The etiologic agents which cause hypersensitivity pneumonitis and organic dust toxic syndrome (ODTS) in workers exposed to wood dust have all been fungi which are contaminants of the wood. Wood dust also contains other contaminants such as bacterial endotoxins, but these have not been proven to be the etiological agents causing the respiratory conditions resulting from wood dust exposure. A number of chemical contaminants, most notably anti-sap stain agents or fungicides and impregnation agents, may also be encountered by workers exposed to wood dust.

Examples of dusts originating from animals are epithelial dust and leather dust. The epithelia and excretions of animals constitute the main health hazards of animal dust. They are carried by airborne dust particles and are consequently inhaled by the workers (Rylander and Jacobs 1997). The animal dust is heterogeneous, containing mainly pure fur in some occupations and biological matter and endotoxins in others. Leather dust contains numerous chemicals acquired during the tanning and finishing of leather (chromium salts, vegetable dye extracts, mineral oils), which may contribute to the carcinogenic effect.

Microbial dust originates mainly from bacteria and moulds. The micro-flora of organic dusts depends on the micro-flora of the source material, which depends on the substrate composition, pH, aeration, the availability of water, and temperature (Rylander and Jacobs 1997). In many occupations, the workers are exposed to filamentous fungi and bacteria. Moulds are used in many industrial processes, e.g., in the preparation of wine, beer, bread, milk products, enzymes, chemotherapeutic agents and other pharmaceutical products (Stanier et al. 1989). High airborne levels of endotoxins, bacteria, fungi and mycotoxins have been measured in the agricultural environment (Merchant and Reynolds 2000). Elevated exposure levels are also present in occupations in which organic materials are handled, e.g. in biotechnical industries and in water and waste treatment (Louhelainen 2005).

## 6. REVIEW OF THE LITERATURE

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Previous studies have shown that endotoxins and other microbial products are inherent elements in farm dusts, particularly in cowsheds, where faeces of animals contaminate organic dusts on which bacteria and fungi adhere and grow (Rask-Andersen et al. 1989, Olenchock et al. 1990). There is very limited published data on endotoxin exposure in jobs exposing to animal dust, except in the case of farmers (Rask-Andersen et al. 1989, Reif et al. 1989, Olenchock et al. 1990, Mastrangelo et al. 1996). There is less endotoxin exposure in fur farming than in agriculture in general (Schimberg et al. 1992, Lange 2000). Furriers and veterinarians are less exposed to endotoxins than farm workers in general (Rylander and Jacobs 1997). Some studies have suggested that exposure to endotoxins in early life, and possibly in the occupational environment, also protects against allergy and/or asthma. This has been commonly called the hygiene hypothesis (Lange et al. 2003c).

Microbial toxins are toxic secondary metabolites of many fungi and bacteria. Mycotoxins typically enter the human body via the oral route, but additional exposure may occur by inhaling airborne particles containing mycotoxins, including dust and fungal components and fragments (Reijula and Tuomi 2003, Gorny 2004). The spores of many important fungi are less than 5  $\mu\text{m}$  in aerodynamic diameter, and are therefore able to enter the lungs. They may contain significant amounts of mycotoxins (Sorenson 1999). The inhalation of mycotoxins or mould particles can thus represent additional exposure to ingested mycotoxins (Iavicoli et al. 2002).

The organic dusts in the textile and clothing industry may be of plant, animal, microbial or synthetic origin. Dust is produced during fibre and textile processing. It is generally agreed that cotton fibres do not cause the various effects induced by exposure to cotton dust (Rylander and Jacobs 1997). The contamination by cotton lint causes some of the biological effects. The amount of contaminants in cotton dust varies due to the different sources of cotton fibre. Bacterial endotoxin has also been suggested to be an important etiological factor (Castellan et al. 1987). Cotton dust also contains proteases, which may contribute to disease processes (Milton and Chawla 1986).

Synthetic polymer dust is defined in FINJEM as dust from synthetic polymers (e.g., plastic, synthetic textiles or leather, synthetic dyes and binders of paints). Examples of polymers are polyacrylates, polyamides

## 6. REVIEW OF THE LITERATURE

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(nylon, aramid), polyesters, polyolefins (polyethylene, polypropylene), polyvinyls and polyurethans. Some types of synthetic polymer dust originate from man-made organic fibres (MMOF). Polymeric MMOFs are synthesized from organic polymers that are manufactured from petroleum-derived chemicals. The petroleum-based polymeric MMOFs have been used to make textiles and upholstery. They have traditionally been manufactured in diameters too thick to be inhaled into the lungs. However, new developments in the MMOF industry have resulted in the production of increasingly fine-diameter fibres for special applications (moisture-resistant, insulating clothing), and certain post-manufacturing processes (e.g., chopping) generate respirable-sized MMOF dust particles (Warheit et al. 2001).

### 6.1.2. Exposure to organic dusts in Finland

The largest group of workers exposed to flour dust in Finland consists of about 6,500 bakers and confectioners. The second most exposed occupations are cooks and pantry workers (about 1,000), packers (about 800), grain millers (about 400) and cleaners (about 400). In bakeries, health hazards may also arise from bread processors, enzymes, spices, additives, and contaminants such as microbes, insects and mites. Exposure levels exceeding 50% of the occupational exposure limit (OEL) are found especially in bakeries. Exposure levels have been high also in grain mills. The average total dust concentrations in the breathing zone have been 3–30mg/m<sup>3</sup> among millers, 2–30mg/m<sup>3</sup> among packers, 4–35mg/m<sup>3</sup> among sackers and 2–40mg/m<sup>3</sup> among cleaners (Louhelainen 2005).

The highest exposure to plant dust in Finland takes place in agriculture and involves about 70,000 farmers and 4,000 holiday assistants. According to estimates of the Finnish Institute of Occupational Health, the majority of the exposures are less than 10% of the OEL of 5mg/m<sup>3</sup> for organic dusts, although levels exceeding the OEL occur on pig farms and in poultry houses (Louhelainen 2005).

Farmers who keep animals are exposed mainly to animal dust. Practitioners of horse management, veterinarians and laboratory animal keepers are also exposed to animal dusts. About 11,000 persons are exposed to textile dust. Seamstresses are the largest group in the textile industry; the next largest groups are tailors, dressmakers and upholster-

## 6. REVIEW OF THE LITERATURE

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ers. About 8,000 workers, over half of whom are paper and cardboard workers, are exposed to pulp and paper dust. In addition, about 1,000 workers in the printing business are exposed to paper dust. The workers exposed to leather dust are shoemakers and cobblers (about 250), leather cutters (below 200) and leather seamstresses (about 100). The workers in peat production and peat burning power plants used to be exposed to concentrations higher than 5mg/m<sup>3</sup> of peat dust, but modern harvesting methods have reduced the exposure. About 3,000 workers are exposed to organic dusts in garbage handling, a half of whom are engaged in garbage transport and the rest in waste disposal plants (Louhelainen 2005).

### **6.1.3. Health effects of organic dusts**

The hazard associated with airborne particulate matter is a function of: (1) the biologic activity of the material, (2) concentration of the airborne material, and (3) size of the airborne particles (Herrick and Dement 2005). Organic dusts contain a multitude of substances with potential biological effects. The major agents are tannins, histamine, plicatic acid, alkaloids (e.g., nicotine) and cytochalasins of plant origin; proteins, and enzymes of animal origin; and endotoxins, (1→3)- $\beta$ -D-glucans, proteases and mycotoxins of microbial origin (Rylander and Schilling 1998).

The relative role of each of these substances, alone or in combination with others, for the development of disease, is mostly unknown. The acute reaction to inhaled organic dusts is inflammation in the airways resulting in increased airway responsiveness (Rylander 1994). The symptoms and diseases induced by organic dusts may develop through irritative, toxic, allergic or carcinogenic mechanisms. Most of the persons with symptoms from organic dust exposure suffer from non-allergic inflammation (Rylander 2004). The inflammation causes symptoms such as irritation, swelling, mucus secretion, and coughing (Rylander 2004).

The major diseases induced by exposure to organic dusts are toxic pneumonitis (inhalation fever, organic dust toxic syndrome ODTS), airway inflammation (mucous membrane inflammation), chronic bronchitis, hypersensitivity pneumonitis (allergic alveolitis), asthma, rhinitis and conjunctivitis (Rylander and Schilling 1998). It is well established

## 6. REVIEW OF THE LITERATURE

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that endotoxin is an inflammagenic agent, and that it is the likely cause of serious respiratory disease among those exposed to organic dusts (Rylander and Jacobs 1997). Endotoxins increase the counts of cytotoxic T lymphocyte precursors, induce the secretion of various cytokines, and activate immune cells that infiltrate tumours (Pance et al. 2002). Endotoxins, as well as dust containing endotoxins, may enhance the production of anticancer mediating factors and cells that have been suggested to be responsible for the observed reduced lung cancer rates (Lange 2000, Lange et al. 2003b).

Inorganic fibrous materials such as chrysotile and crocidolite asbestos are known to cause cancer. Synthetic organic fibres were traditionally manufactured in diameters too thick to be respired into the lower lung. However, a unique form of interstitial lung disease has been reported in nylon flock workers, and respirable sized nylon shreds were identified in the workplace air samples (Warheit et al. 2001).

In addition to health effects in the respiratory tract, systemic effects may also occur. The mechanism involved seems to be a local inflammation at the target site, i.e. the lung, and a subsequent release of cytokines either with systemic effects (Dunn 1992, Michel et al. 1995, Rylander 2004) or an effect on the epithelium in the gut (Axmacher et al. 1991). Non-respiratory clinical symptoms are fever, joint pains, neurosensory effects, skin problems, intestinal disease, fatigue and headache.

A worker who has a disease due to organic dust exposure, often presents with a combination of different disease entities. One person may have airway inflammation for a number of years, suddenly develop asthma, and in addition have symptoms of toxic pneumonitis during particularly heavy exposure. Another person may have subclinical hypersensitivity pneumonitis with lymphocytosis in the airways and develop toxic pneumonitis during particularly heavy exposure.

### **6.1.4. Occupational diseases caused by organic dusts in Finland**

The Finnish Registry of Occupational Diseases (FROD) was established in 1964. In addition to cases diagnosed in wage earners, the statistics also cover farmers and some other entrepreneurs.

Incident cases of occupational diseases (diagnosed or suspected) are notified to the FROD by the Federation of Accident Insurance Institu-

## 6. REVIEW OF THE LITERATURE

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tions (FAII) and the Farmers' Social Insurance Institution – MELA. In 2005 a total of 6,774 cases of occupational disease (28 cases per 10,000 employed were notified to the FROD (Laakkonen et al. 2007).

Altogether 1,097 disease cases caused by organic dust exposure were notified. The main causes were exposure to mould dust (412), flour dust (122), animal dust (115), wood dust (53) and plant dust (39). The most common respiratory diseases were asthma and allergic rhinitis. The most common occupational diseases caused by organic dusts were asthma from flour dust (38) and from animal epithelia (33). The incidence of notified occupational diseases caused by organic dusts was highest in agriculture and food processing. There were 191 occupational skin diseases caused by organic dusts. The most common skin diseases were protein contact dermatitis and contact urticaria caused by animal epithelia (43) and flours (15) (Laakkonen et al. 2007).

### **6.2. Organic dusts and cancer**

#### **6.2.1. Animal dust**

Animal dust is usually not considered a cause of cancer. It has been suggested that microbial dust of animal origin may increase the risk of lung cancer among farmers (Blair and Zahm 1995). A reduced risk of lung cancer has been found among dairy farmers but not among crop/orchard farmers (Reif et al. 1989, Mastrangelo et al. 1996). No excess cancer risk was found in the fur industry (Guay and Siemiatycki 1987). Exposure to animal dust and microbial dust of animal origin has been reported to increase the risk of lung cancer among butchers in some studies (Boffetta et al. 2000) but not in all (De Stefani et al. 2005). Endometrial cancer has been associated with exposure to animal dust (Weiderpass et al. 2001).

#### **6.2.2. Bacterial dust**

The influence of exposure to bacteria on cancer risk is probably mediated by endotoxins through immunological mechanisms (Lange 2000). In a study on a cohort of female textile workers in Shanghai, China, cumulative exposure to endotoxin was inversely related to the risk of both oesophageal cancer ( $p$ -trend = 0.01) and stomach cancer ( $p$ -trend

## 6. REVIEW OF THE LITERATURE

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< 0.001) when the exposures were lagged 20 years (Wernli et al. 2006). Analysis of endotoxin exposure and liver cancer risk in the same cohort also revealed a protective effect (adjusted hazards ratio (HR) = 0.60; 95% CI 0.41–0.88) (Chang et al. 2006). A decreasing trend in the incidence of cancer of the rectum was observed for increasing cumulative cotton dust or endotoxin exposure, when the exposures were lagged by 20 years (De Roos et al. 2005).

Farmers have a reduced risk of lung cancer; this may be due to the protective effect of endotoxin exposure (Mastrangelo et al. 1996, Rylander 2002, Mastrangelo et al. 2005). In a study of lung cancer mortality by type of farming, the relative risk of lung cancer was 0.80 (CI 0.78–0.81) in crop farmers and 0.70 (CI 0.67–0.73) in livestock farmers (Lange et al. 2003a). In a case control study nested in a cohort of Italian farmers, there was evidence of an exposure-dependent reduction of lung cancer risk in farmers who had ceased working on dairy farms less than 15 years previously, but not among those who had ceased working more than 15 years ago. The protection afforded by exposure to endotoxin-containing organic dust thus diminishes over time after the exposure discontinues (Mastrangelo et al. 2005).

A reduced risk for cancer, particularly lung cancer, has also been shown in occupational populations exposed to cotton dust containing endotoxin (Merchant and Ortmeier 1981, Mastrangelo et al. 2002). The lung cancer risk of cotton workers in the textile industry was around 0.4 in the first study published in 1936, around 0.7 in subsequent studies, published mostly in the 1970s and 1980s, and around 1.0 in studies published in the 1990s. The recent findings could be due to the reduced dust and endotoxin concentrations in the workplaces (Mastrangelo et al. 2002). Recent levels of endotoxins in different occupational environments are presented in Table 2.

## 6. REVIEW OF THE LITERATURE

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**Table 2. Concentrations of airborne endotoxins (ng/m<sup>3</sup>) in different work environments in Finland (Laitinen et al. 2001) and Sweden (Rylander et al. 1999) analysed by the LAL<sup>1</sup> assay.**

Environment	Mean or median	Range
Slaughterhouse	190	0.02–940
Grain/vegetable storage	17,000	1,700–38,000
Animal feed industry	6.5	0.3–20
Garbage-handling plant	120	0.9–1,400
Wood industry	3.3	0.1–51
Cotton mill	11	1.9–223
Printing house	0.05	0.03–0.1
Metal working industry	6.7	1.6–27
Bark cleaning unit	97.7	23–220
Paper recycling plant	18.2	4–45
Recycled paper storage	2.0	0–5

<sup>1</sup>LAL = Limulus ameocyte lysate assay

### 6.2.3. Flour dust

Sensitization and work-related symptoms are common among bakery workers exposed to flour dusts (Houba et al. 1998). No associations were seen between exposure to flour dust and laryngeal cancer (Laforest et al. 2000) or lung cancer (Siemiatycki et al. 1986). In a population-based case-control study in Italy, male bakers had an excess risk of lung cancer, whereas women had a decreased risk (Richiardi et al. 2004).

### 6.2.4. Leather dust

Employment in the leather goods industry has been associated with an increased risk of stomach cancer among men (Krstev et al. 2005). A significant association between exposure to leather dust and pancreatic cancer was found in a case-control study within a cohort of Swedish leather tannery workers (Mikoczy et al. 1996). Exposure to leather dust

## 6. REVIEW OF THE LITERATURE

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may increase the risk of cancer of the nose and paranasal sinuses (IARC 1981, Merler et al. 1986, Fu et al. 1996, 't Mannetje et al. 1999). An association between lung cancer and leather dust from vegetable tanning has been reported in Swedish leather tanneries (Mikoczy et al. 1996). An association between bladder cancer and work in the leather industry is supported by a number of studies (IARC 1981). Indications of an elevated risk of ovarian cancer among employees exposed to leather dust were found in a previous study using FINJEM (Vasama-Neuvonen et al. 1999). There was no association between leather dust exposure and bladder cancer in a Canadian case-control study (Siemiatycki et al. 1994).

### 6.2.5. Mould dust

The International Agency for Research on Cancer (IARC) has classified some fungal mycotoxins as carcinogenic to humans (IARC group 1) or as probably (2B) or possibly (3) carcinogenic to humans (IARC 1993, IARC 2002). The known carcinogenic effects have been found mainly in studies on ingested mycotoxins, but airborne exposure can result in raised mycotoxin levels in the serum (Autrup et al. 1993, Iavicoli et al. 2002). Information on suspected carcinogenic effects of mycotoxins is given in Table 3.

Swedish grain millers have been reported to have a significantly elevated risk of liver cancer potentially associated with metabolic products of fungal contaminants (e.g., aflatoxins) (Alavanja et al. 1987a). Dutch oil-press workers exposed to aflatoxins primarily via the respiratory route had an elevated risk of lung cancer (Hayes et al. 1984). Danish male employees exposed to aflatoxins in livestock feed production had elevated risks for liver cancer and cancer of the biliary tract (Olsen et al. 1988). Inhaled aflatoxins are also suspected to enhance the risk of urinary tract cancer (Hendry and Cole 1993). A moderate association between increasing levels of fungal forecasts and lip cancer has been found among Norwegian farmers (Nordby et al. 2004).

Mould cell wall components, particularly (1→3)-beta-D-glucans, are often present in connection with bacterial endotoxins (Rylander 2002), and this may influence the risk for cancer after environmental exposure.

## 6. REVIEW OF THE LITERATURE

**Table 3. Known and suspected carcinogenic effects of ingested mycotoxins (Betina 1984, IARC 1993, Pitt 2000, El-Serag 2002, IARC 2002, Pfohl-Leskowicz et al. 2002, Schwartz 2002, van der Westhuizen et al. 2003, Williams et al. 2004).**

<b>Mycotoxin</b>	<b>IARC group</b>	<b>Causative agent</b>	<b>Source</b>	<b>Cancer site</b>
naturally occurring aflatoxins	1	<i>Aspergillus flavus</i> , <i>A. parasiticus</i>	peanuts, maize, other nuts, oilseeds	liver
aflatoxin M1	2B	-	milk	-
ochratoxin A	2B	<i>Penicillium verrucosum</i> <i>A. carbonarius</i> <i>A. ochraceus</i>	cereal grains grapes, wines coffee beans, pork	urinary tract, testis
fumonisin B1 and B2, fusarin C	2B	<i>Fusarium moniliforme</i> , <i>F. proliferatum</i>	maize	oesophagus
sterigmatocystin	2B	<i>A. versicolor</i> , <i>A. flavus</i> , <i>A. nidulans</i> , <i>A. rugulosus</i> , <i>A. unguis</i>	food grains	-
actinomycin D	3	-	-	-
zearalenone, deoxynivalenol, nivalenol, fusarenone X	3	<i>F. graminearum</i> , <i>F. culmorum</i> , <i>F. crookwellense</i>	wheat, barley, maize	-
T-2 toxin	3	<i>F. sporotrichioides</i>	wheat, maize	-

### 6.2.6. Pulp and paper dust

An IARC monograph stated that epidemiological data are not sufficient to assess definitively the cancer risk of work in the pulp and paper industry (IARC 1981). An increased risk of lung cancer and pleural mesothelioma has been found in the pulp and paper industry in Norway. The authors believed that almost all of the increased risk for lung cancer could be explained by a combination of smoking habits and asbestos use, even though the effects of sulphur and chloride compounds and wood dust could not be excluded (Langseth and Andersen 2000). An excess of lung cancer has been associated with paper dust exposure among maintenance workers in paper mills in Sweden (Toren et al. 1991). An increased risk of lung cancer has been found in paperboard workers (Jäppinen et al. 1987). However, there are also studies that have found no excess risk of respiratory cancer among pulp mill workers (Andersson et al. 1998) or paper mill workers (IARC 1999). Occupational exposure to high concentrations of dust containing silica has been considered a factor increasing lung cancer risk among Polish male workers in the pulp and paper industry. Of the organic dusts, only wood dust increased, albeit non-significantly, the risk of lung cancer in the afore-mentioned Polish case-control study (Szadkowska-Stanczyk and Szymczak 2001).

An excess risk of ovarian cancer was shown among women working in the Norwegian pulp and paper industry (Langseth and Andersen 1999). A further evaluation of the same cohort did not show an association between ovarian cancer and exposure to asbestos, talc, and total dust (Langseth and Kjaerheim 2004). An elevated risk of prostate cancer has been demonstrated among workers exposed to paper dust (Siemiatycki et al. 1986).

The results among male pulp and paper workers in Norway showed an increased risk for malignant melanoma (Langseth and Andersen 2000). An increased mortality from brain tumours among sulphite mill workers has been found (Andersson et al. 1998). In a literature review on the work environment in pulp and paper mills, Toren et al. (1996) constantly found an increased risk for malignant lymphomas in both sulphite and sulphate pulp mills. An increased risk for leukaemia was also found in many studies (Toren et al. 1996).

### **6.2.7. Plant dust**

An elevated risk for colon cancer was found among employees exposed to grain dust in a case-control study in Canada (Siemiatycki et al. 1986). An excess of primary liver cancer was shown among men employed in grain mills in Sweden (McLaughlin et al. 1987). No excess of respiratory cancers among those exposed to grain dust was found in Canada, but an excess of prostate cancer was found (Siemiatycki et al. 1986).

Farmers have multiple exposures, for example, to dusts from plants and animals. Farmers nevertheless have significantly less lung cancer than expected (Pukkala and Notkola 1997). An excess of cancers of the lymphatic and haematopoietic systems, other neoplasms of lymphoid tissue, and multiple myeloma have been found among grain millers (Alavanja et al. 1987b). In a mortality study in the USA, Caucasian workers in the corn wet-milling industry exposed to grain dust had an elevated risk for bladder cancer and lymphatic and haematopoietic malignancies, whereas black workers had an elevated risk for pancreatic cancer (Thomas et al. 1985).

### **6.2.8. Synthetic polymer dust**

The risk of cancers of the digestive system has been shown to be elevated among textile workers who are exposed to synthetic fibres (Mastrangelo et al. 2002). An elevated risk of colorectal cancer was found among patients exposed to synthetic fibres in a multi-factor case-control study in Canada (Siemiatycki et al. 1986). Rayon fibres were associated with an elevated risk of rectum cancer in a population-based case control study in Canada (Dumas et al. 2000). Lung cancer PRRs did not significantly deviate from 1.0 in textile workers who handle synthetic fibres (Mastrangelo et al. 2002). Synthetic polymers in paints have not been shown to cause cancers of the respiratory tract (IARC 1989). An elevated risk of bladder cancer was also found in the case-control study in Canada (Siemiatycki et al. 1986).

### 6.2.9. Textile dust

The textile industry has been classified as possibly carcinogenic to humans (group 2B) by the IARC. This evaluation was based mainly on findings of bladder cancer among dyers (possibly due to exposure to dyes) and among weavers (possibly due to exposure to dusts from fibres and yarns) and of cancer of the nasal cavity among weavers (possibly due to exposure to dusts from fibres and yarns), and among other textile workers (IARC 1990). Cotton dust and wool fibres have been associated with an elevated risk of rectum cancer (Dumas et al. 2000). A study of colorectal cancer incidence among female textile workers in Shanghai showed an increased risk of colon cancer associated with dyes and dye intermediates, and cancer of the rectum associated with exposure to metals (De Roos et al. 2005). A decreased risk of rectal cancer was associated with exposure to natural fibres such as cotton, and a decreasing trend of rectal cancer incidence was observed by category of cumulative quantitative cotton dust or endotoxin exposure, when the exposures were lagged by 20 years (De Roos et al. 2005). Recently, in a study of female textile workers in China, the case-cohort analysis revealed a protective effect of prolonged cotton fibre exposure or endotoxin exposure for liver cancer (Chang et al. 2006) and pancreatic cancer (Li et al. 2006b). The risk of cancers of the digestive system has been shown to be elevated among textile workers who handle silk (Mastrangelo et al. 2002).

Exposure to textile dust (cotton, wool, synthetic fibres) may increase the risk of sinonasal cancer according to some studies (Luce et al. 1997, Teschke et al. 1997, Li et al. 2006a) but not according to others (Hernberg et al. 1983, Yu et al. 1990, Magnani et al. 1993). In a pooled analysis of case-control studies, exposure to textile dust was associated with non-significantly elevated risk of sinonasal adenocarcinoma, but among women only (Luce et al. 2002). Excess laryngeal cancer associated with cotton dust exposure has been found among textile workers (Elci et al. 2001, 2002). Mortality from lung cancer, on the other hand, has been found to be lower than expected among textile industry workers. It has been assumed that exposure to cotton dust may reduce the risk of lung cancer (Levin et al. 1987, Hodgson and Jones 1990, Wu-Williams et al. 1993). Studies published in the 1970s and 1980s showed reduced risk estimates for lung cancer among workers exposed to cotton

## 6. REVIEW OF THE LITERATURE

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(pooled relative risk PRR = 0.77; CI = 0.69-0.86) and wool dust (0.71; 0.50-0.92) (Mastrangelo et al. 2002). However, an increased risk of lung cancer among men exposed to linen dust was shown in a study in Russia (Baccarelli et al. 2006). Lung cancer PRRs did not deviate significantly from 1.0 in silk textile workers (Mastrangelo et al. 2002). No significant excess of lung cancer has been found among glass fibre textile workers (Shannon et al. 1990).

A significant exposure-response trend of testicular cancer (mainly seminoma) has been shown among Finnish men exposed to textile dust (Guo et al. 2005). Hodgkin's lymphoma has been associated with exposure to textile dust and non-Hodgkin lymphoma with textile-related exposure (Fritschi and Siemiatycki 1996). The handling or processing of wool has been associated with an increased risk of brain tumours (Gold et al. 2006).

### **6.2.10. Wood dust**

IARC has concluded that there is sufficient evidence for the carcinogenicity of furniture and cabinet making to humans. There is limited evidence for the carcinogenicity of carpentry and joinery, and there is inadequate evidence for the carcinogenicity of lumber and sawmill work and pulp and paper manufacturing (IARC 1987).

Wood dust has been classified as carcinogenic to humans (group 1) by the IARC, mainly based on evidence of nasal cancer in workers exposed predominantly to hardwood dusts (IARC 1995). There is some evidence that specifically beech and oak dust increase the risk of nasal adenocarcinoma, but IARC nevertheless recommends recognition of nasal carcinomas as occupational diseases regardless of the species of wood in question and tumour histology (IARC 1981, Jansing et al. 2003). Exposure to both formaldehyde and wood dust may increase the risk of nasal adenocarcinoma, compared with the risk from wood dust alone (Luce et al. 1993). The associations between wood dust exposure and cancer are presented in Table 4.

## 6. REVIEW OF THE LITERATURE

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**Table 4. Known or suspected associations between wood dust exposure and cancer.**

Primary site	Reference	
	Elevated risk	Risk not elevated or reduced
Oral cavity and pharynx	Arias Bahia et al. 2005, Vlainac et al. 2006	Gustavsson et al. 1998
Oesophagus	-	Gustavsson et al. 1998
Stomach	Siemiatycki et al. 1986, Arias Bahia et al. 2005, Jansson et al. 2005	Cocco et al. 1999
Colon	Innos et al. 2000	Simpson et al. 1998
Rectum	Innos et al. 2000	-
Liver	Arias Bahia et al. 2005	-
Nose and sinuses	Demers et al. 1995, IARC 1995, Andersen et al. 1999, 't Mannetje et al. 1999, Hildesheim et al. 2001, Luce et al. 2002	-
Larynx	Elci et al. 2002, Berrino et al. 2003	Gustavsson et al. 1998, Laforest et al. 2000
Lung	Siemiatycki et al. 1986, Stellman et al. 1998, Barcenás et al. 2005	Kauppinen et al. 1993
Cervix	Weiderpass et al. 2001	-
Prostate	Stellman et al. 1998	-
Brain	Pan et al. 2005	-
Soft tissue sarcoma	Briggs et al. 2003	-
Hodgkin's lymphoma	Briggs et al. 2003, Arias Bahia et al. 2005	-
Non-Hodgkin lymphoma	Cartwright et al. 1988, Mao et al. 2000, Fritschi et al. 2005	-

### **6.3. Job-exposure matrix (JEM)**

#### **6.3.1. What is a job-exposure matrix?**

A job-exposure matrix (JEM) in its simplest form is a cross-classification of a list of job titles with a list of agents to which the persons doing those jobs are potentially exposed. All JEMs have at least a “job axis” and an “exposure axis”. Other dimensions, such as calendar time, industrial branch and the workers’ gender may also be incorporated to increase the validity of the JEM. Numerous work-related factors, such as chemical, physical, microbiological, physiological, ergonomic, psychosocial and lifestyle factors may be included in a JEM. JEMs may be classified into general population JEMs (GPJEMs) and industry-specific JEMs (ISJEMs). A GPJEM is nationwide and usually covers all occupations in all industries using a general job classification. An ISJEM covers one or several industries, occupations, workplaces, etc. The job classifications and exposure assessments in ISJEMs are often too detailed to be applicable in general population studies. Thus, in the following, the abbreviation JEM is used to refer to a GPJEM.

The exposure classification in JEMs ranges from dichotomous, semi-quantitative to quantitative. Quantitative exposure scores make it possible to supply estimations on cumulative exposures based on the quantitative level of exposure and proportion of the exposed persons with time dimensions (Kauppinen et al. 1998). JEM-based analyses are economical and assess the subjects consistently irrespective of the outcome. JEM is a valuable tool for studying rare cancers based on retrospective job histories.

#### **6.3.2. Validity of a JEM**

The main weakness of JEMs is the possible misclassification of exposure due to the variability of exposures within the same occupation or job. There may also be over- and underestimation of exposures originating from data collection, data interpretation, expert judgment, or coding during the construction of a JEM. The inherent misclassification of the general JEM approach has been diminished by incorporating the time, and even the industrial unit dimensions to the JEMs, but an increase in

## 6. REVIEW OF THE LITERATURE

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accuracy is often followed by a decrease in general applicability (Kauppinen et al. 1992).

Most chemical exposures have low prevalence (<10%) in the general population. However, if the population to be studied is large, the problems of low numbers of exposed subjects and non-differential misclassification (i.e., misclassification that does not differ among the diseased and non-diseased subjects) can be reduced by using the cumulative exposure (CE) based on the product of prevalence and level of exposure as the exposure metric. In principle, this metric provides an unbiased exposure estimate for worker groups, including both exposed and unexposed workers (Kauppinen et al. 1992).

JEMs have been compared with the self-reporting of exposures and expert judgements of work histories. Each method of exposure assessment has its limitations (Kauppinen 1994). Self-reported exposure assessment may have differential misclassification caused by reporting bias. Estimation by experts based on individual data can reduce exposure misclassification in comparison to a JEM when it contains information on tasks with a time dimension and not only job titles. The validity of FINJEM was evaluated by comparing it with self-report and a panel of occupational hygienists (Benke et al. 2001). In this study, FINJEM outperformed the self-report assessments and showed moderate agreement with the experts' panel.

### **6.4. Cancer in Finland**

#### **6.4.1. Cancer in men and women**

According to the 2006 report of FCR, men's prostate cancer is the most common cancer among Finns, with an incidence of 97.8/100,000 (Table 5) ([www.cancerregistry.fi/eng/statistics](http://www.cancerregistry.fi/eng/statistics)). The incidence of prostate cancer has increased partly due to the increase in the number of people in the oldest age categories, as well as improved diagnostics.

Lung cancer is the second most common cancer among Finnish men. In 2006, 1,537 new cases were diagnosed among men and 613 cases among women (Tables 5 and 6). Despite the decreasing lung cancer incidence among men, lung cancer still causes more deaths (mortality rate 29.2/100,000 among men and 8.2/100,000 among women) than

## 6. REVIEW OF THE LITERATURE

any other cancer. The number of lung cancer deaths among women has been rising, but lung cancer has not overtaken breast cancer as a leading cause of cancer mortality, as happened e.g., in Denmark and Iceland in the late 1990s.

Cancer incidence is highest in the age groups of 65–79-year-old men and 70–84-year-old women. The incidence of prostate and lung cancer is highest in 65–79-year-old men, and of breast cancer in 50–64-year-old women. There is a major difference in cancer incidence between urban

**Table 5. Leading primary sites of cancer among Finnish men in 2006. (¹ Adjusted for age to the “world standard population”. ² Excludes basal cell carcinomas of the skin.)**

Primary site	No. of cases	Percentage distribution	Incidence per 100,000 <sup>1</sup>
Prostate	4,642	33.6	97.8
Lung, trachea	1,537	11.1	31.5
Colon	736	5.3	15.8
Bladder, ureter, urethra	659	4.8	13.6
Non-Hodgkin lymphoma	581	4.2	13.4
Rectum, rectosigmoid, anus	535	3.9	11.5
Skin, non-melanoma <sup>2</sup>	510	3.7	10.0
Melanoma of the skin	491	3.6	11.7
Kidney	437	3.2	9.7
Pancreas	426	3.1	9.2
Stomach	398	2.9	8.4
Brain, central nervous system	394	2.9	11.4
Leukaemia	338	2.4	9.0
Liver	264	1.9	5.7
Multiple myeloma	179	1.3	3.8
Oesophagus	159	1.2	3.6
Larynx, epiglottis	115	0.8	2.7
Testis	103	0.7	4.1
All sites <sup>2</sup>	13,803	100.0	304.0

## 6. REVIEW OF THE LITERATURE

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and rural areas of Finland. Lip cancer is markedly more common in rural areas, among both men and women. All other cancers are more common in urban areas. The relative difference is greatest in cancers of the liver, larynx and prostate among men, and lung, breast and liver among women (Pukkala 2004).

**Table 6. Leading primary sites of cancer among Finnish women in 2006. ( <sup>1</sup> Adjusted for age to the "world standard population".  
<sup>2</sup> Excludes basal cell carcinomas of the skin.)**

Primary site	No. of cases	Percentage distribution	Incidence per 100,000 <sup>1</sup>
Breast	4,075	31.1	86.5
Colon	794	6.1	12.5
Corpus uteri	789	6.0	14.6
Lung, trachea	613	4.7	10.1
Brain, central nervous system	572	4.4	14.0
Skin, non-melanoma <sup>2</sup>	563	4.3	6.3
Non-Hodgkin lymphoma	557	4.3	10.1
Pancreas	484	3.7	6.6
Ovary	455	3.5	9.0
Melanoma of the skin	435	3.3	9.4
Rectum, rectosigmoid, anus	433	3.3	7.3
Kidney	365	2.8	6.5
Stomach	332	2.5	5.3
Leukaemia	271	2.1	6.1
Thyroid gland	267	2.0	7.1
Bladder, ureter, urethra	205	1.6	2.8
Multiple myeloma	165	1.3	2.5
Cervix uteri	158	1.2	3.9
Liver	151	1.2	2.0
Gall bladder, bile ducts	148	1.1	1.9
All sites <sup>2</sup>	13,084	100.0	247.2

### **6.4.2. Occupational cancers**

In 2005, 149 occupational cancers (diagnosed or suspected) were reported. All but eight cases were asbestos-related. The majority of patients with occupational cancer were over 60 years old. There were five reported cases of occupational cancer among women. 41 cases of mesothelioma and 92 cases of lung cancer caused by asbestos exposure were reported (Laakkonen et al. 2007).

The general estimate of the proportion of work-related cancers of all cancers is 4%. The lower than expected numbers of reported occupational cancer cases is due to difficulties in recognizing work-related cancer. Occupational cancers are usually manifest after a long latency period when the employee has already retired. In the case of lung cancer, smoking confounds occupational exposure (Laakkonen et al. 2007).

The Finnish Institute of Occupational Health also maintains a registry of workers at risk of exposure to carcinogenic substances and processes. In 2005, a total of 28,028 such workers were registered, 40 % of whom were women. Workers in the hotel and restaurant business comprised the biggest group (9,486). All those registered were exposed to environmental tobacco smoke. In relation to the number of people employed in the occupation, exposure was most common in metal ore quarrying. Nearly 28% of the workers in the sector were exposed to carcinogenic substances. The most common sources of cancer risk were asbestos, arsenic and nickel compounds, and polycyclic aromatic hydrocarbons in the exhaust fumes of mining machines. The most prevalent sources of cancer risk were tobacco smoke (11,424), chromium (VI) compounds (7,278) and nickel and its inorganic compounds (6,729) (Saalo et al. 2007).

As regards organic dusts, 957 workers were exposed to oak and beech dust. The only other agent in the registry associated with organic dust exposure was aflatoxin with 15 exposed workers (Saalo et al. 2007).

## **7. AIMS OF THE STUDY**

This study is an independent part of a large project that evaluates risks of occupational cancers among Finnish workers. The study covers material obtained from FINJEM, cancer registry data, databases of the Population Census 1970, and survey data on life-styles and other cancer-related co-factors. Exposure to organic dusts is a major cause of occupational diseases of the respiratory tract. Specific carcinogens in organic dusts and/or chronic inflammation may cause cancer. There is inconclusive evidence concerning the cancer risk of organic dusts, and very limited knowledge on inhalatory exposure to some organic dusts, e.g., bacteria and moulds, and their association with cancer.

The aims of the present study were:

1. To study the risk of respiratory cancer among food industry and agricultural workers with mainly inhalatory exposure.
2. To generate a hypothesis concerning other cancers among food industry workers and agricultural workers, and to explore new associations between occupational exposures and cancer.
3. To determine the cancer risk pattern of Finnish farmers and to define the type of farm as a potential determinant of the observed risk ratios.
4. To study whether changes in the type of farm account for altered lung cancer risk. A low cancer rate has been associated especially with dairy farming; quitting dairy farming might therefore increase the risk of lung cancer.
5. To assess the association between cancer and occupational exposure to bacteria and moulds in Finland. The presumption was that exposure to biological dust dominated by moulds and Gram-positive

## 7. AIMS OF THE STUDY

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bacteria increases the risk of respiratory cancer due to exposure to mycotoxins and bacterial exotoxins, and that exposure dominated by Gram-negative bacteria decreases the risk of respiratory cancer due to exposure to endotoxins.

6. To study whether inhalatory exposure to moulds increases the risk of cancer of the liver, oesophagus, upper respiratory tract, and urinary tract, associated with ingestion of mycotoxins.

## **8. MATERIALS AND METHODS**

### **8.1. Study design**

#### **8.1.1. Census-based cohort study**

In epidemiology, a cohort is defined most broadly as "any designated group of individuals who are followed or traced over a period of time" (Last 1995). The study cohort (I–III) comprised all economically active Finns born between 1 January 1906 and 31 December 1945 who participated in the national population census on 31 December 1970 (667,121 men; 513,110 women). The census files are maintained at Statistics Finland and updated for vital status to allow exact person-year calculation. Data on the occupation held for the longest period in 1970 were obtained from the Population Census records (Statistics Finland 1974). The socioeconomic status (SES) for each subject was based on the subject's own occupation. In our analyses, the SES was categorized as farmers, higher white-collar, clerical, skilled blue-collar and unskilled workers.

The study cohort in Study IV comprised all farmers on 31 December 1978 who were registered in the Finnish Farm Registry. A person's occupational status as a farmer was controlled from the 1990 and 1994 Farm Registry data. All persons or corporations owning a farm of at least one hectare (ha) of cultivated land (field or garden) are included in the registry.

The cohort was comprised of subjects in a census registry of Statistics Finland in Studies I–III, and the Farm Registry of Finland in Study IV, on a certain date in the past. The cohorts were thus closed and the study design retrospective. These cohorts were linked with the computerized registers of Statistics Finland (death certificates) and the

## 8. MATERIALS AND METHODS

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Finnish Cancer Registry (cancer cases) based on the unique 11-digit personal identification code (PID) assigned to every person residing in Finland since 1967.

### **8.1.2. Finnish Cancer Registry**

The Finnish Cancer Registry (FCR) has collected data on all cancer cases diagnosed in Finland since 1953. All physicians, hospitals and other institutions, and all pathologic, cytological and haematological laboratories in the country must notify the FCR of all cancer cases that come to their attention. In addition, Statistics Finland annually provides a computerized file on death certificates in which cancer is mentioned. The Cancer Registry requests additional data from hospitals if the first diagnosis is based on a laboratory notification or death certificate (FCR 2007). The FCR coverage is virtually complete and the data accuracy high (Teppo et al. 1994, Korhonen et al. 2002).

All main cancer sites, including 34 main categories of cancer, were investigated in Studies I, III and IV. The cancer sites (ICD-7 code) were: lip (140), oral cavity (143, 144), pharynx (145, 147, 148), oesophagus (150), stomach (151), colon (153), rectum (154), liver (155.0), gall bladder and biliary tract (155.1), pancreas (157), nose (160), larynx (161), lung (162.0-1), pleurae (mesothelioma) (162.2, 164), breast (170), cervix (171), corpus uteri (172), ovary (175), prostate (177), testis (178), kidney (180); bladder, urether and urethra (181), skin melanoma (190), non-melanoma skin cancer (191), eye (192), brain and nervous system (193), thyroid (194), other endocrine glands (195), bone (196), soft tissue (197), non-Hodgkin lymphoma (200, 202), Hodgkin's lymphoma (201), multiple myeloma (203) and leukaemia (204). Study II covered nasal, laryngeal and lung cancer.

## **8.2. Occupational exposures in this study**

### **8.2.1. Finnish National Job-Exposure Matrix (FINJEM)**

The occupational exposures of the cohort (II and III) were assessed by using FINJEM (Kauppinen et al. 1998, Pukkala et al. 2005). FINJEM was

## 8. MATERIALS AND METHODS

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constructed by the Finnish Institute of Occupational Health in the 1990s for epidemiological research, hazard surveillance and risk assessment. FINJEM covers the major occupational exposures in Finland since 1945 by occupation and calendar time (Figure 1). Exposure is characterized by the proportion of exposed persons (P) and the average level of exposure (L) among the exposed persons in each occupation. The estimation periods are 1945–59, 1960–84, 1985–94, 1995–97, 1998–2000, 2001–03 until now. The estimates are based on exposure measurements, hazard surveys and the assessments of occupational hygienists. The estimates were generated for all agent-occupation combinations in which P was suspected to have exceeded 5% at any time after the year 1945. In the present study, the exposure estimates for 1945–59 and 1960–84 were used. FINJEM contains a selection of 74 exposure agents including chemical, biological, physical, physiological, ergonomic and psychosocial factors. P and L are assessed in FINJEM quantitatively for chemical, biological and physical agents; major changes in exposure over time are taken into account enabling estimations of CE. FINJEM also includes data on alcohol consumption (g/week) and smoking (daily smokers) by occupation. These data were obtained from annual surveys carried out on the health behaviour of the Finnish adult population by the Finnish National Public Health Institute during 1978–91 (Helakorpi et al. 2003). For rare occupations in which the number of respondents in the surveys was below 20, the values were estimated by using the data on larger proxy occupations. The version of FINJEM used in the present study included 311 occupational categories with 3 digit codes based on the Nordic Classification of Occupations, which is compiled on the basis of the International Standard Classification of Occupations (ISCO) published in 1958 by the International Labour Organisation (ILO) (Statistics Finland 1981).

### **8.2.2. Division of the cohort into those exposed and not exposed**

The estimates of occupational exposure in this study were based on the Census 1970 occupations and FINJEM (Studies I–III) and on the 1978 Farm Registry occupation in Study IV. In internal comparison (Studies II and III) the employees were stratified into groups of cumulative ex-

## 8. MATERIALS AND METHODS

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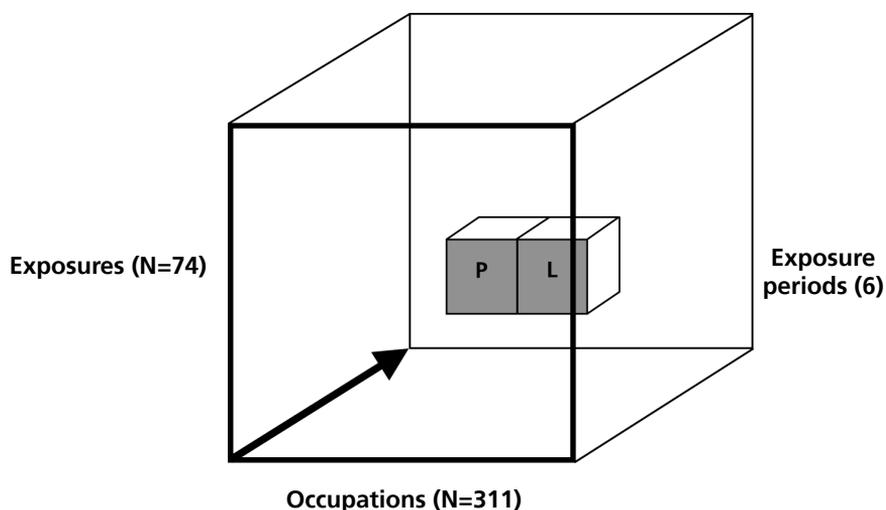


Figure 1. Dimensions of the Finnish Job-Exposure Matrix (FINJEM). Variables P (proportion of exposed persons) and L (mean level of exposure among those exposed, e.g., in ppm) are defined for each stratum. Exposure periods: 1945–59, 1960–84, 1985–94, 1995–97, 1998–00, 2001–03 (Kauppinen et al. 1998, Guo 2005).

posure of non-exposed (exposure category “none”) and exposed (low, medium, high) using time, P and L data as the base for grouping. The same person may produce person-time to several exposure categories along with increasing cumulative exposure over age.

### 8.2.3. Application of FINJEM

The study focused on 10 organic dusts and biological exposures in FINJEM. When cancer risk was investigated among Finnish food industry workers (Study I), information on exposure to organic dust was acquired from FINJEM as background information. When studying cancer and exposure to organic dusts, and mould and bacteria (Studies II and III) all basic dimensions of exposure assessment of FINJEM were utilized, i.e., occupations, exposure agents and calendar periods. Data from FINJEM on alcohol consumption, smoking, exposure to quartz dust and asbestos was also utilized in regression modelling.

### 8.3. Statistical analyses

The statistical analyses were performed by a statistician and epidemiologist utilizing the SAS-program. In Studies I–III the observed and expected numbers of cancer cases for every occupation were calculated for each five-year birth cohort (1906–10, ..., 1941–45) and five-year calendar period of observation (1971–75, ..., 1991–95) (Figure 2). Agent-specific cumulative exposure (CE) estimates were calculated for every five-year birth cohort and every five-year calendar period of observation. Exposure for each birth cohort was assumed to start in the year when the average age of the birth cohort was 20, and to end in the mid-year of the observation period, or at 65 years of age, whichever came first. If the exposure took place before 1960, we used the FINJEM estimates for the period 1945–59; otherwise the estimates for the period 1960–84 were applied in the analyses. A lag period was incorporated into the CE by omitting exposure years before the mid-point of the observation period. A 10- or 20-year lag period was applied depending on the cancer site and study setting (indicated in the studies). For instance, when studying cancer risk in 1971–75, only exposures until 1953 were taken into account. The expected number in each stratum was calculated by multiplying the number of person-years lived by persons in that occupation with the cancer incidence rate of the entire economically active Finnish population in the respective stratum. The SIR was defined as the ratio of observed to expected numbers of cases. The 95% CI was calculated for the SIR.

Confounding was controlled by stratifying data by occupation, cancer site and gender (I–IV) and CE class of exposure agent, cancer site and gender (II, III). The data were standardized by age, gender, observation period and social class. Poisson regression analysis of the stratum-specific observed numbers of cases and person-years at risk was used in internal comparison to study exposure-response patterns. The most prevalent and significant occupational and non-occupational carcinogens were incorporated into the models. The unexposed strata were used as the reference category for estimates of RR. The 95% CI was calculated for the RR. In the regression models, the agents/confounders were adjusted by each other, age, social class, and exposure period (II, III).

## 8. MATERIALS AND METHODS

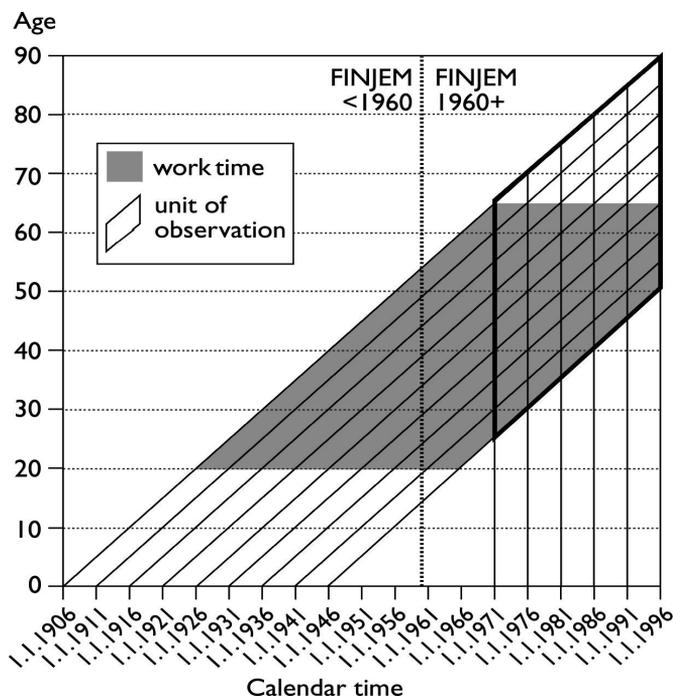


Figure 2. Setting of the census-based studies (I–III). The thick vertical lines indicate the beginning of follow-up in the occupational cancer risk for each birth cohort of the entire population (Guo 2005).

In Study IV all persons who were farmers on 31 December 1978 and alive on 1 January 1995 were included in the cohort (Figure 3). Data on continuing as a farmer and the type of farming were collected from the 31 December 1990 and 1994 farm registries. The follow-up started on 1 January 1995 and ended at emigration or death or on 31 December 2005, whichever came first. The numbers of observed cases and person-years at risk were counted by gender and 5-year age groups. The expected numbers of cases were calculated by multiplying the number of person-years in each 5-year age group by the corresponding average gender-specific cancer incidence in the overall Finnish population during the period of observation.

## 8. MATERIALS AND METHODS

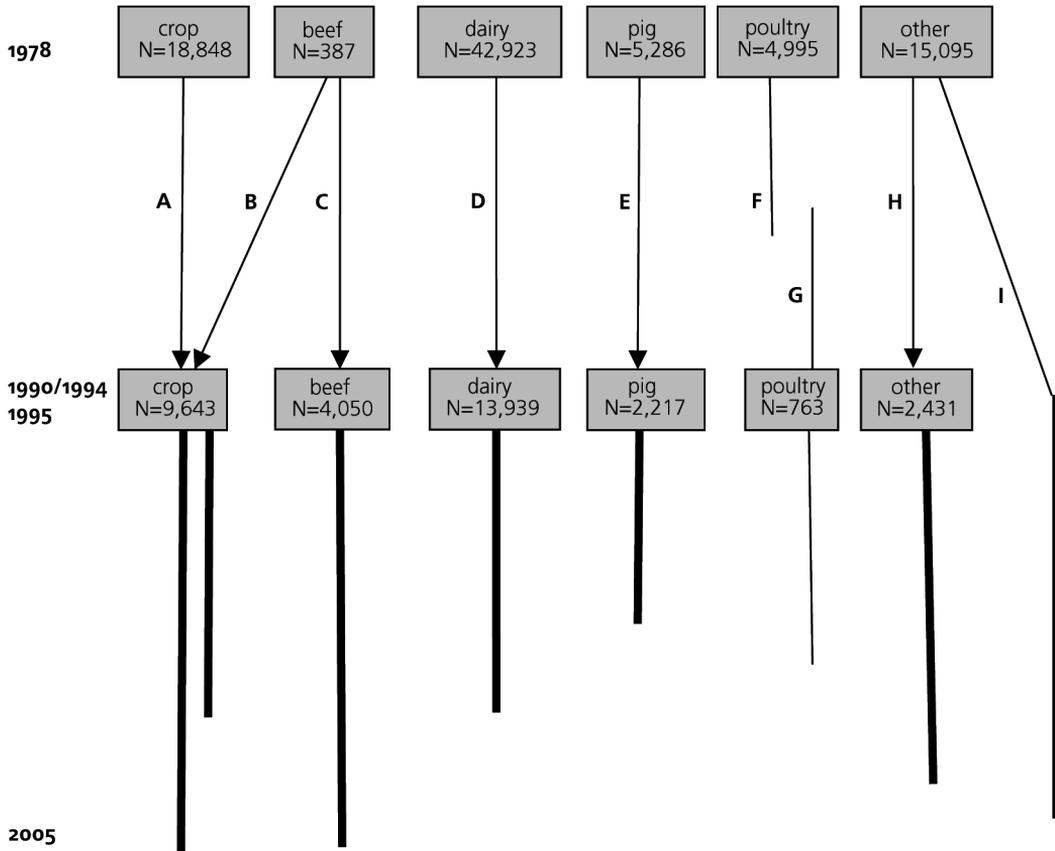


Figure 3. Setting of the farmer study (IV) showing examples of different types of single farmers (A-I) and their contribution to the follow-up time (1995–2005). The arrows indicate continuing as a farmer, the narrow lines stopping farming before 1995 (F not alive 1995) or starting farming after 1978 (G) or quitting farming by 1994 and alive (I). The bold lines show the follow-up time. A large proportion of the persons who were farmers in 1978 had quit farming by 1990/1994. Retirement age was the major reason for quitting farming.

## **9. SUMMARY OF THE RESULTS**

### **9.1. Cancer among food industry workers (I) and farmers (IV)**

There were 989 observed cases (O) of cancer among the male and 1,537 cases among the female food industry workers of the cohort (I). The SIR for all cancers was 1.02 (CI 0.96–1.09) for men and 0.97 (CI 0.93–1.02) for women. There was an excess of pancreatic cancer (O 55, SIR 1.50, CI 1.13–1.96) and kidney cancer (O 62, SIR 1.51, CI 1.16–1.94) among male food industry workers, but no statistically significant excess among female food industry workers.

Among specific occupations in the food industry, the only significant excess in overall cancer incidence (O 55, SIR 1.35, CI 1.02–1.76) was found in men (but not in women) belonging to ‘other occupations’ in the food industry. This class covers jobs in the processing of margarine, yeast, cocoa, coffee, spices, macaroni, fish and poultry products, and refrigeration employees. An excess of kidney cancer (O 7, SIR 4.20, CI 1.69–8.65) was noted among men.

There was an excess of lung cancer among female bakers (O 45, SIR 1.38, CI 1.01–1.85) but not among male bakers (Table 7). The only other significantly elevated SIR in respiratory tract cancers was the one for laryngeal cancer among male grain millers (O 7, SIR 2.60, CI 1.05–5.36).

Of the cancers not related to the respiratory tract, pancreatic, urinary tract, skin melanoma, and leukaemias showed elevated SIRs in certain occupations. We found no statistically significantly elevated SIRs among chocolate and confectionery workers, cannery workers and food-processing workers.

## 9. SUMMARY OF THE RESULTS

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A total of 19,640 incident cases of cancer were found among the farmers of the cohort (IV). For most of the cancer sites, the SIRs were below 1.0. The lowest rates among farmers who were still continuing farming were in mesothelioma (O 6, SIR 0.29, CI 0.11–0.62) and in cancers of the liver (O 24, SIR 0.40, CI 0.26–0.59), larynx (O 19, SIR 0.51, CI 0.30–0.79), lung (O 352, SIR 0.60, CI 0.54–0.66), nose and nasal sinuses (O 4, SIR 0.62, CI 0.17–1.58), oesophagus (O 32, SIR 0.65, CI 0.44–0.91) and urinary bladder (O 147, SIR 0.69, CI 0.58–0.80). The only significantly elevated SIR was for lip cancer (O 43, SIR 1.39, CI 1.00–1.86). The SIRs for all these cancers were higher among those farmers who finished farming before 1990. The only cancer that showed a markedly lower SIR among those who finished farming was cervical cancer (O 46, SIR 0.67, CI 0.49–0.88).

Among the more homogeneous farm types (the group other farmers contains many different smaller groups) and farmers keeping the same type of farm (production), beef and dairy farmers had the lowest SIRs for overall cancer. The lowest SIRs among dairy farmers continuing farming as dairy farmers were in cancers of the liver (O 6, SIR 0.32, CI 0.12–0.70), bladder (O 30, SIR 0.47, CI 0.32–0.67), breast (O 11, SIR 0.48, CI 0.24–0.85), lung (O 94, SIR 0.51, CI 0.42–0.62), and colon (O 41, SIR 0.60, CI 0.43–0.82) (Table 7). The only significantly elevated SIR was the one for lip cancer among dairy farmers (O 20, SIR 2.17, CI 1.32–3.34). Crop and pig farmers also had elevated SIRs of lip cancer.

The dairy farmers of 1978 who had changed their production type to crop farming had increased their risk for overall cancer from the SIR 0.82 to 0.92. The SIRs for cancers of the colon, lung and bladder were elevated by more than 0.2 among the most common cancers. A similarly increasing risk was shown among dairy farmers who had switched their production type to raising beef cattle.

The SIR of lung cancer varied from 0.51 (O 94, CI 0.42–0.62) among those who had continued as dairy farmers to 0.73 (O 40, CI 0.52–0.99) among those who had switched to crop and 0.87 (O 33, CI 0.60–1.21) among those who had switched to raising beef cattle. Lip cancer risk showed an opposite falling trend among dairy farmers who had switched farm type or quit farming.

## 9. SUMMARY OF THE RESULTS

**Table 7. Standardized incidence ratios (SIR) of lung cancer by gender among all occupations (1970) in the food industry in 1971-95 and among different farm types (1978) keeping the same farm type (1990/1994) in 1995-2005 (I, IV). SIRs adjusted for age and social class, exposure lag period 20 years. O=observed number of cases, CI=confidence interval**

Occupation	Site	Men			Women		
		O	SIR	95% CI	O	SIR	95% CI
Grain millers	lung	41	1.05	0.75-1.42	-	0	0.00-10.2
Bakers	lung	53	0.96	0.72-1.25	45	1.38	1.01-1.85
Chocolate and confectionery workers	lung	6	0.90	0.33-1.95	4	0.91	0.25-2.33
Brewers, beverage makers and kiln men	lung	12	0.88	0.46-1.54	3	0.99	0.20-2.88
Cannery workers	lung	6	0.57	0.21-1.24	7	1.99	0.80-4.10
Butchers and sausage makers	lung	65	1.00	0.77-1.27	9	1.47	0.67-2.79
Dairy workers	lung	23	0.71	0.45-1.07	7	0.50	0.20-1.04
Food-processing workers	lung	2	1.51	0.18-5.46	2	0.62	0.07-2.24
Sugar-processing workers	lung	10	0.84	0.40-1.54	2	3.51	0.42-12.7
Other occupations in the food industry	lung	13	1.19	0.63-2.03	1	0.55	0.01-3.04
Crop farmer	lung	40	0.54	0.38-0.73	-	0	0.00-2.46
Beef farmer	lung	-	0	0.00-2.52	-	0	0.00-187
Dairy farmer	lung	92	0.51	0.14-0.62	2	0.65	0.08-2.33
Pig farmer	lung	13	0.73	0.39-1.24	-	0	0.00-16.4
Poultry farmer	lung	4	0.47	0.13-1.21	1	4.62	0.12-25.7
Other farmer	lung	7	0.51	0.20-1.05	1	1.17	0.03-6.49

### **9.2. Organic dust exposure and cancer (II and III)**

A total of 20,426 incident cases of respiratory cancer were observed among employees exposed to one or more of eight organic dusts (II). Men exposed to wood dust had an elevated SIR for nasal cancer; the SIR for all exposed men was 1.42 (O 33, CI 0.79–2.44). The other organic dusts did not show significant differences from the entire economically active Finnish population for nasal cancer, although SIRs related to exposure to flour dust tended to be above 1.0.

As regards laryngeal cancer, men exposed to plant dust had a statistically elevated SIR in the highest exposure class (O 6, SIR 3.55, CI 1.30–7.72). Women did not show elevated SIRs for plant dust and laryngeal cancer. The most exposed men were mainly grain millers. Flour dust was suggestive of an exposure response trend among men. Textile dust also showed some indication of a similar trend.

Men exposed to wood dust had a significantly elevated SIR for lung cancer, but only in the low exposure class (O 936, SIR 1.11, CI 1.04–1.18) (Table 8). No other organic dust showed elevated SIRs for lung cancer. On the other hand, numerous worker groups with dust exposure had a lung cancer incidence that was significantly below the national average.

Women exposed to wood dust showed a significantly elevated SIR for mesotheliomas in the low exposure class (O 4, SIR 4.57, CI 1.25–11.7) and some excess in the middle exposure category.

Some of the suggestive findings were analysed further by Poisson regression modelling. The significance of exposure to plant dust as a risk factor for laryngeal cancer remained in the high exposure class in a Poisson regression analysis, when smoking habits and alcohol consumption were added to the model.

A total of 37,969 incident cases of cancer were observed among employees exposed to moulds and bacteria (III). In the highest CE category to moulds there were 0.6% of the cancer cases and in the highest CE category to bacteria were 2.1% of the cancer cases. The overall cancer risk among men and among women was similar irrespective of mould exposure. A significantly reduced risk for lung cancer was observed among men with low mould exposure (O 7,456, SIR 0.92, CI 0.90–0.94).

## 9. SUMMARY OF THE RESULTS

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As for other cancer types, there was a slightly elevated risk of lip cancer among both men and women. In addition, statistically non-significant increases among the highest mould exposure category were observed in women for cancers of the lung and pancreas, and for leukaemia.

Men exposed to bacteria had a lower incidence of overall cancer than non-exposed men. This resulted mainly from the reduced SIR for lung cancer (Table 8). The SIRs among women with highest CE to bacteria were non-significantly elevated for oral cancer and cervical cancer.

We analysed further the suggestive finding of a reduced risk of lung cancer by Poisson regression modelling. The exposure to moulds and bacteria significantly decreased lung cancer, even after adding exposure to asbestos, quartz dust, smoking and social class to the model. In women, the adjusted risk estimates from Poisson models were increased for the high exposure categories.

Cancer of the cervix showed slightly elevated SIRs responding to increasing cumulative exposure. The elevated risk among women exposed to moulds and bacteria remained in a Poisson regression analysis, when smoking habits and social class were added to the model.

## 9. SUMMARY OF THE RESULTS

**Table 8. Standardized incidence ratio (SIR) of lung cancer in 1971-95 by gender and cumulative exposure (CE) to 10 organic dusts among economically active Finns born in 1906-45. O=observed number of cases, CI=confidence interval, CFU=colony-forming unit. SIRs adjusted for age and social class, exposure lag period 20 years.**

Exposure agent	CE class	Men			Women		
		O	SIR	95% CI	O	SIR	95% CI
Wood dust	none (0)	27,309	1.00	0.98-1.01	3,446	1.00	0.97-1.03
	low (<3mg/m <sup>3</sup> -y)	936	1.11	1.04-1.18	21	0.92	0.57-1.41
	medium (3-50mg/m <sup>3</sup> -y)	1,784	1.02	0.97-1.06	48	1.03	0.76-1.37
	high (>50mg/m <sup>3</sup> -y)	108	0.85	0.70-1.02	12	0.95	0.49-1.66
Pulp or paper dust	none (0)	29,933	1.00	0.99-1.01	3,477	1.00	0.97-1.04
	low (<10mg/m <sup>3</sup> -y)	102	0.82	0.67-1.00	25	0.97	0.62-1.43
	medium (10-15mg/m <sup>3</sup> -y)	100	0.82	0.66-0.99	23	0.71	0.45-1.07
	high (>15mg/m <sup>3</sup> -y)	2	1.22	0.15-4.42	2	1.08	0.13-3.89
Flour dust	none (0)	29,944	1.00	0.99-1.01	3,116	1.00	0.97-1.04
	low (<5mg/m <sup>3</sup> -y)	54	0.86	0.65-1.13	350	0.97	0.87-1.07
	medium (5-50mg/m <sup>3</sup> -y)	50	0.89	0.66-1.18	17	0.68	0.40-1.10
	high (>50mg/m <sup>3</sup> -y)	89	0.95	0.77-1.18	44	1.20	0.87-1.61
Plant dust	none (0)	23,211	1.03	1.02-1.05	2,684	1.00	0.97-1.04
	low (<10mg/m <sup>3</sup> -y)	2,555	0.86	0.82-0.89	495	0.99	0.90-1.08
	medium (10-40mg/m <sup>3</sup> -y)	4,340	0.93	0.90-0.96	347	0.98	0.88-1.09
	high (>40mg/m <sup>3</sup> -y)	31	1.06	0.72-1.51	1	0.55	0.01-3.05
Textile dust	none (0)	29,867	1.00	0.99-1.01	3,288	1.01	0.98-1.05
	low (<5mg/m <sup>3</sup> -y)	162	1.08	0.92-1.26	95	0.99	0.80-1.21
	medium (5-20mg/m <sup>3</sup> -y)	82	0.87	0.69-1.08	125	0.79	0.66-0.95
	high (>20mg/m <sup>3</sup> -y)	26	0.66	0.43-0.97	19	0.60	0.36-0.94

continues...

## 9. SUMMARY OF THE RESULTS

**Table 8. continues...**

Exposure agent	CE class	Men			Women		
		O	SIR	95% CI	O	SIR	95% CI
Leather dust	none (0)	30,069	1.00	0.99-1.01	3,511	1.00	0.97-1.04
	low (<5mg/m <sup>3</sup> -y)	47	0.85	0.62-1.13	12	0.66	0.34-1.15
	medium (5-20mg/m <sup>3</sup> -y)	20	0.88	0.54-1.36	4	0.90	0.24-2.30
	high (>20mg/m <sup>3</sup> -y)	1	1.00	0.03-5.55	0	0.00	0.00-28.1
Animal dust	none (0)	24,237	1.03	1.01-1.04	3,105	1.01	0.97-1.05
	low (<0.5mg/m <sup>3</sup> -y)	4,519	0.89	0.87-0.92	136	0.95	0.79-1.12
	medium (0.5-1.5mg/m <sup>3</sup> -y)	1,321	0.92	0.87-0.97	284	0.93	0.83-1.05
	high (>1.5mg/m <sup>3</sup> -y)	60	1.22	0.93-1.57	2	0.46	0.06-1.65
Synthetic polymer dust	none (0)	29,877	1.00	0.99-1.01	3,392	1.01	0.98-1.04
	low (<5mg/m <sup>3</sup> -y)	204	0.94	0.82-1.08	135	0.81	0.68-0.96
	medium (5-20mg/m <sup>3</sup> -y)	46	0.68	0.49-0.90	0	0.00	0.00
	high (>20mg/m <sup>3</sup> -y)	10	1.23	0.59-2.26	0	0.00	0.00
Mould dust	none (0)	22,214	1.03	1.02-1.05	3,315	1.00	0.96-1.03
	low (<1.3 million cfu/ m <sup>3</sup> -y)	7,456	0.92	0.90-0.94	189	1.05	0.91-1.21
	medium (1.3-1.5 million cfu/ m <sup>3</sup> -y)	380	0.95	0.85-1.05	15	1.08	0.61-1.79
Bacterial dust	high (> 1.5 million cfu/ m <sup>3</sup> -y)	87	0.88	0.70-1.08	8	1.51	0.65-2.98
	none (0)	22,214	1.03	1.02-1.05	3,315	1.00	0.96-1.03
	low (≤ 2.1 million cfu/ m <sup>3</sup> -y)	7,468	0.92	0.90-0.94	189	1.05	0.91-1.21
	high (> 2.1 million cfu/ m <sup>3</sup> -y)	455	0.93	0.85-1.02	23	1.22	0.77-1.83

## **10. DISCUSSION**

### **10.1. Methods**

Occupational epidemiology attempts to reveal the causal connections between occupational exposure and a non-specific disease. The disease is usually multi-factorial and the work-related exposure factor is only one of several causes, which means that it is typically not a sufficient explanation. Etiologic epidemiologic research is often carried out to test a hypothesis which suggests that some factor causes a particular disease. Epidemiologic research can also be carried out without a prior hypothesis, e.g., different disorders caused by a certain exposure (Hernberg 1992). These studies are descriptive. Both hypothesis testing and hypothesis generating approaches were applied in the present study.

Registries are a useful practical source of data for epidemiologic research. The comprehensiveness and accuracy of the Finnish Cancer Registry are very high. Various check-ups have shown that the Registry covers more than 99% of all malignant solid tumours diagnosed in Finland, and that false positive diagnoses are not registered as cancers. The registration of some haematological malignancies is slow (Teppo et al. 1994). There are also problems in the registration of benign brain tumours (under-coverage almost 20%). The under-coverage is not likely to be strongly associated with social class or occupation, and the possible bias is thus minimal. Errors in personal identification codes are rare and do not have an effect on the observed cancer risk estimates (Pukkala 1992). The coverage and accuracy of the annual death and emigration files at Statistics Finland are known to be high; thus the bias in the numbers of person-years caused by lack of follow-up information is not significant.

## 10. DISCUSSION

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Retrospective exposure evaluation is often problematic. Experienced hygienists can assess past exposure by combining data on present measurements, earlier measurements, cumulative use of chemicals, and data on major changes in an industry. Job-exposure matrices are useful tools for assessing exposure indirectly. Their most important use lies in the screening of large materials. If the JEM method reveals elevated risks, the finding should be scrutinized further by means of more refined exposure assessments (Hernberg 1992). FINJEM based analyses have been found accurate enough to reveal established occupational cancer risks (Benke et al. 2001, Pukkala et al. 2005). One of the most difficult problems in exposure assessment is the simultaneous occurrence of multiple exposures. Etiologic studies may often fail to pinpoint the specific agent causing the disease of interest. Exposure to multiple organic dusts is common in many of the occupations in our study, so the significance of a single exposure is in many cases impossible to estimate. The occurrence relation between one exposure and several diseases can be investigated in a cohort-based census study at the same time (Hernberg 1992).

The health of an employee affects job selection, and later deteriorations in the health state may lead to selection during the course of employment. This kind of selection leads to underestimation of the exposure-related health effects because many of those who should have been classified as "diseased" may have been exposed for a short period only before leaving their job permanently. The economically active population was used as the reference (I-III), and this reduces the healthy worker effect. Using the JEM method improves the validity of the exposure histories compared to potential recall bias in case-referent studies.

The under-coverage of the 1970 population census in the age range of the study was 2.3% (Pukkala 1995). A random sample of cancer patients missing from the 1970 population census was studied by using the information on occupations in the Cancer Registry records, and the distribution was similar to that of the general population (Pukkala et al. 1983). The under-coverage of the census thus does not have any major effect on the observed occupational risk pattern. The highest percentages of missing census data were obtained among persons who later developed cancers associated with alcohol use.

## 10. DISCUSSION

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The occupational status of a person was assessed before his or her cancer had been diagnosed, i.e., the bias caused by a downward shift in the social hierarchy as a result of disease (Wilkinson 1986) should thus have been avoided. The accuracy of the occupational codes in Finnish population censuses has been evaluated and was proven to be high (Kolari 1989). The occupational stability between the censuses of 1975 and 1980, and between those of 1980 and 1985, was 85-86% in both sexes (Kolari 1989). It can be assumed that in occupations with a professional or vocational training, the occupational category of the 1970 population census usually represents relatively well the the person's life-long occupational history, whereas in less specialized occupations there is more heterogeneity.

The methods used for controlling confounding in the present study were restriction of age-groups and periods, standardization, stratification, and modelling. Controlling of confounding using information on social class is even at its best incomplete because of the intermixing of confounding factors throughout the social strata. On the other hand, in many studies social class has been considered as a risk determinant of cancer even when no specific aetiological factors can be pointed out. Historically, occupation has been selected as a principal indicator of social class. Occupation-based classifications of social class most often have two main problems: the classifications are too rigid and do not take into account the changes in society, and the occupational groups are too heterogeneous in income and education (Liberatos et al. 1988). The classification used in the 1970 population census of Finland was not a mechanical one, but rather used results from sociological studies on social class and occupation in Finland.

Because the cohorts used in this study are very large, rare forms of cancer can also be studied. Most of the known occupational causes of cancer have been identified through epidemiological observations with subsequent confirmation by clinical studies. In the case of rare types of cancer in communities with a high prevalence of a specific risk factor, occupational carcinogens can be first identified from clinical observations. The risk of mesothelioma caused by asbestos is a typical example of this kind of approach (Decouflé 1982). If the disease is more common or the causal factor more evenly spread throughout the population, a systematic surveillance system may be the only way to generate clues

## 10. DISCUSSION

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for causal risk associations. The present study includes components of systematic surveillance, e.g., limited exposure (flour dust) and common cancer (lung cancer).

Most of the studies on social and occupational variation in cancer risk are based on mortality. However, there are some problems which may bias the mortality pattern. First, the principles in defining the underlying cause of death may vary by time, by period, and even by social class or occupation. Secondly, the mortality from competing causes of death may vary in these subgroups. For example in Finland mortality from all main disease categories and also from violent causes of death in 1971-85 has been greatest in the lowest social classes (Valkonen et al. 1990). Finally, the survival of cancer patients in different social classes varies, because of both stage distribution and better treatment (Karjalainen and Pukkala 1990, Auvinen et al. 1995). In Finland the reliability of official causes of death is high, and thus the error caused by misclassification of cancer deaths is minimal. In the most fatal cancers there is almost no difference between incidence and mortality patterns, whereas mortality-based studies of the cancers with a high relative survival rate are seldom valid to demonstrate differences in aetiology (Pukkala 1995). The present study used only incidence as a measure of cancer risk.

In most countries it is impossible to conduct large cohort studies like the present one because of lack of linkable population-based registries or because of too restrictive legislation. Even the largest case-control occupational studies have significantly less cases, and thus wider confidence intervals, compared with this cohort study. The occupational exposure and confounder data might be somewhat less exact in cancer surveys based on population-based registries in comparison with large-scale case-control studies. This is nevertheless compensated by the greater number and better coverage of cancers, and by lower costs of the study.

Criticism of the surveillance systems based on registries has been raised, because the inconsistencies, e.g., in occupational classifications, tend to diminish the real risk differences. However, the risk estimates provided by specific studies and by the present study method are in most instances almost equal, e.g., exposure to crystalline silica and lung cancer (Pukkala et al. 2005). The diluting effect in the general surveillance approach thus does not seem to be essentially more disturbing than in specific studies on occupational cancer risks.

## 10. DISCUSSION

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It is difficult to conclude which of the excess risks are merely chance findings and which ones are true. The number of observed statistically significant SIRs compared with the corresponding expected number may tell whether or not the occupational variation for a certain cancer site is larger than by pure chance. There should be about 2.5% of the occupation-specific SIRs significantly both below and above 1.0 at the 95% significance level. The justification of whether or not an observed association is likely to be true should not be based on statistical significance only. Other knowledge about the meaningfulness of the association, such as similar earlier observations and theories of possible causal mechanisms, should be taken into account. If this evaluation is done properly, it should actually not make any difference whether the risk estimate stems from a multiple test system or from a specific study designed to investigate specifically that association (Rothman 1990). In reality there are less significantly reduced risk ratios, because the expected number of cases is often so small that even no observed cases would not give a statistically significant result (Pukkala 1995).

The age range of the study subjects (I–III) is close to what has been considered optimal in occupational cancer studies (Siemiatycki 1991). Cancers, solid tumours in particular, diagnosed before 35 years of age are not likely to be associated with occupational exposure, since the minimum latency between the first exposure and the onset of cancer is at least five years, with a large proportion of cases appearing after 10 to 30 years of exposure. In the older age groups other factors than occupational ones become so dominant that the possible occupational component may be non-identifiable (Simonato 1992). There are, however, some carcinogenic agents with long inducing times. Asbestos-related mesotheliomas may appear more than 40 years after the first exposure (Meurman et al. 1994).

Although the occupational cancer risks caused by exposures at work tend to decrease strongly some decades after the carcinogenicity of the exposures becomes known, new occupation-related risk factors can come up. Repeatable surveillance systems are therefore of great value.

### 10.2. Findings

The overall cancer incidence of farmers has been lower than the incidence of the general population in many studies (Blair and Zahm 1991, Pukkala and Notkola 1997, Andersen et al. 1999). The cancer incidence of Finnish farmers was significantly below the national average also in the present study (IV).

Farmers have been found to have elevated rates of lip cancer (Lindqvist 1979, Blair and Zahm 1991, Blair and Zahm 1995, Wiklund and Dich 1995, Khuder 1999). Elevated risks of lip cancer were also found predominantly among crop and dairy farmers (IV). Lip cancer risk was also elevated in occupations that expose the workers to bacteria and moulds (III). The estimated risk increased after adjusting for previous suspected causes smoking and UV-radiation (III). Exposure to moulds and bacteria combined with smoking and ultraviolet radiation may be the cause of the elevated risk of lip cancer shown in previous studies (Lindqvist 1979, Nordby et al. 2004).

Farmers have displayed lower mortality risks for colon cancer (Blair and Zahm 1991, Hanrahan et al. 1996, Wang et al. 2002). The risk of liver cancer has been below unity in many studies (Blair and Zahm 1991). Significantly reduced risks of cancers of the colon and liver were found (IV). The risks of the farmers who had changed production type from dairy farming to crop farming, or had quit farming, increased towards the risk of the general population. The farmers who changed their production type were somewhat older than those who kept the same production type, and this difference could explain a part of the difference in relative risk. A significantly reduced risk for breast cancer was also found (IV). This could be attributable to the greater number of children among farmers and the protective effect of physical activity (Rintala et al. 2002).

The exposure of farmers to organic dust is similar to that in the refining industries, as the raw materials of animal and plant origin from agriculture and forestry are similar in both occupations (Figure 4). The major inhalatory exposures in the food industry are flour and plant dust. Bacteria and moulds present a significant exposure hazard in certain occupations in the food-processing industry. The major inhalatory exposure to organic dusts originates from leather dust, plant dust

## 10. DISCUSSION

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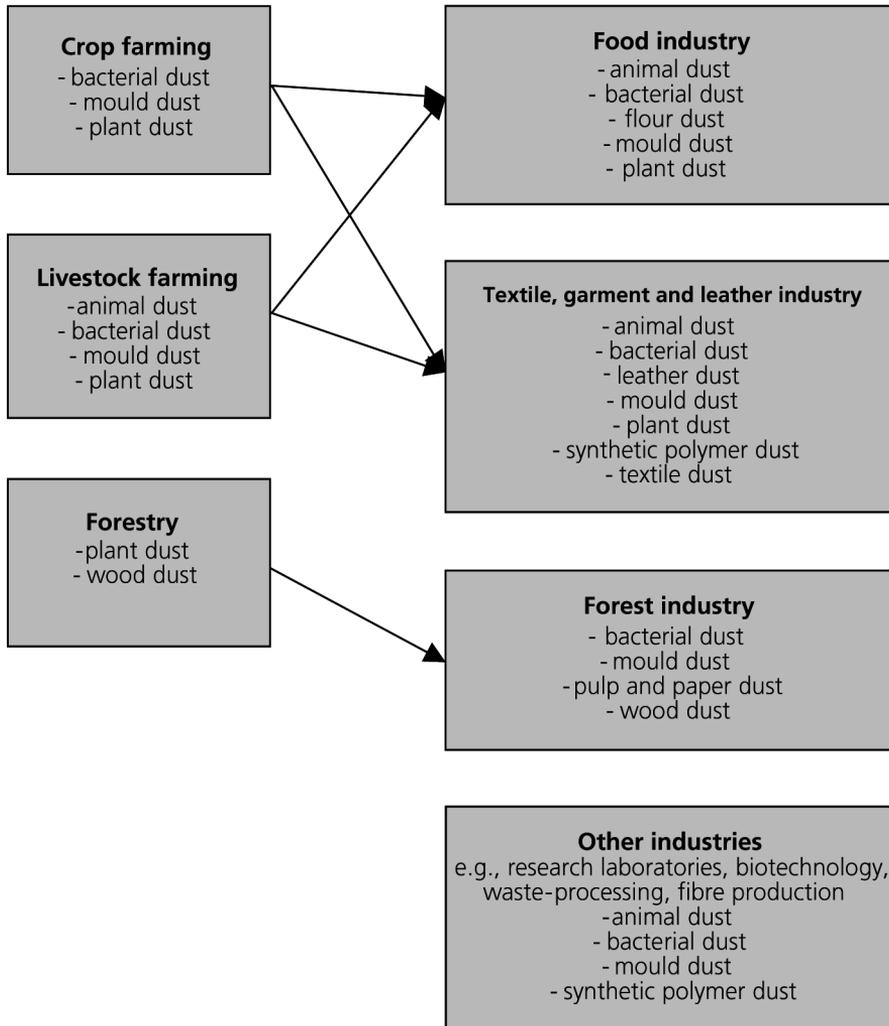


Figure 4. Industries involving exposure to different kinds of organic dust, and the chain of raw materials and organic dusts from agriculture and forestry to industry. (Other substances and contaminants of organic dusts are not mentioned)

## 10. DISCUSSION

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and textile dust in the textile and leather industry, and wood dust in the forest industry.

Reduced lung cancer rates have been found among agricultural workers in numerous studies (Blair and Zahm 1991). Exposure to endotoxins in agricultural work has been suggested as the reason for this finding (Lange 2000). Also in the present study the incidence of lung cancer was significantly reduced (IV). Lung cancer risk was lowest among dairy farmers and increased if the dairy farmer quit farming or changed to some other type of farming. It is also known that Finnish farmers, and particularly women in the countryside, especially in earlier times, smoked less than Finns on the average (Berg et al. 1992). Farmers who leave dairy farming may possibly engage in a more urban life-style. Significantly reduced lung cancer SIRs among those exposed to plant dust and animal dust (predominantly farmers) were found (II). The mortality from lung cancer has been found to be lower than expected among cotton industry workers. It has been assumed that exposure to cotton dust and the endotoxins contaminating it may reduce the risk of lung cancer (Hodgson and Jones 1990). A significantly decreased risk of lung cancer in the high exposure category was observed (II). In addition, a decreased lung cancer risk among men, but not women, who were exposed to moulds and bacteria was found (III). This kind of decrease has previously been hypothesized to result from the cancer-protective effects of bacterial endotoxins predominantly in dairy farming (Mastrangelo et al. 2005) and in the cotton industry (Mastrangelo et al. 2002).

An excess of larynx cancer among male grain millers was noted (I). An elevated risk for larynx cancer among grain millers has not been reported earlier. Men in the high cumulative exposure class of plant dust showed an excess of laryngeal cancer (II). The majority in the heavily exposed group were grain millers, whereas farmers were the majority in the lower exposure categories. Bakers have shown an increased risk of lung cancer (Richiardi et al. 2004), and the present study also revealed an excess of lung cancer among female bakers (I).

There is considerable evidence of the connection between wood dust exposure and sinonasal cancer (Hernberg et al. 1983, Magnani et al. 1993, Nylander and Dement 1993, 't Mannetje et al. 1999, Hildesheim et al. 2001, Luce et al. 2002). Exposure to wood dust has been reported to increase the risk of lung cancer as well (Siemiatycki et al. 1986). A slight

## 10. DISCUSSION

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excess of nasal cancer among men exposed to wood dust was found (II). In Finland the exposure to wood dust is mainly to softwood dust (pine, spruce), which may explain the smaller risk than that described in many other studies (Andersen et al. 1999). This may be due to the low concentrations of polyphenols in domestic tree species, compared to imported wood from more southern regions (Mämmelä 2001). A suggestion of an increased risk of lung cancer among men was found in the low exposure class comprised mainly of carpenters (II). However, the excess was small, and may possibly be due to the slightly higher prevalence of smoking among carpenters as compared to all economically active men.

Moulds are used in many industrial processes, e.g., in the preparation of wine, beer, bread, milk products, enzymes, chemotherapeutic agents and other pharmaceutical products (Stanier et al. 1989). Some of these are intentionally cultivated and are necessary in the preparation process, while others are a disadvantage. The inhalation of fungal spores may cause cancer (Sorenson 1999). Elevated risks of liver cancer have been found associated with fungal contaminants among livestock feed producers (Olsen et al. 1988) and grain millers (Alavanja et al. 1987a). Workers exposed to aflatoxins primarily via the respiratory route have shown an elevated risk of lung cancer (Hayes et al. 1984) and cancers of the urinary tract (Hendry and Cole 1993). No statistically significant excess of cancers of the liver or urinary tract was found (III). Exposure to moulds is generally concurrent with bacterial exposure, and thus the effects are difficult to distinguish from each other. Therefore, the results for cumulative exposure to moulds and bacteria were also very similar, and proper distinguishing between the effects of the two was not possible (III).

The assumption of a linear relationship between cumulative exposure and tissue dose has been shown to be violated in a pharmacokinetic study among test subjects. The findings provide a possible explanation for the common observation of a disproportionately high risk of pulmonary effects for workers with relatively short, intense dust exposures, and for the finding that workers exposed to metabolically activated organic agents have a risk that is related to years of exposure but not to intensity (Smith 1992).

## 10. DISCUSSION

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Many cancers, especially lung cancer, are associated with carcinogenic exposures at the workplace, and tobacco smoking is a dominant risk factor. It is estimated that an increase in the proportion of current smokers by 0.1 unit (10 percentage points) increases the lung cancer incidence by about 26%. The smoking adjusted SIR of lung cancer among Norwegian food-processing workers was 1.29, and 0.93 among farmers (Haldorsen et al. 2004) compared to 1.20 and 0.42 respectively of the same cohort without adjusting for smoking (Andersen et al. 1999).

A key issue in investigating the effect of organic dusts is the difficult problem of disentangling the separate effects of concurrent and multiple exposures (Table 9). Exposure to benzene and other solvents and glue is also associated with cancer risk in the leather industry (Fu et al. 1996). Pesticides are associated with cancer risk among workers who handle materials of plant origin (Alavanja et al. 1987a). Suspected carcinogens in bakeries include polycyclic aromatic hydrocarbons (PAH), reaction products of PAH, free radicals, n-nitrosodimethylamine, aflatoxin, sterigmatocystin, and zearalenone (Tuchsen and Nordholm 1986). Further study of the interaction between aflatoxin B1 and hepatitis B virus and the role of both factors in hepatocarcinogenesis is needed (IARC 2002).

The exposures in the food industry have remained the same, whereas the proportion of persons exposed and the level of exposure have decreased slightly in some occupations in the Finnish food industry according to FINJEM data. This change has taken place mainly in the 1990s and later. The results of this study do not fully apply to the present conditions. The risks in the present working conditions are not overestimated. The number of employees in the Finnish food industry has decreased due to developing process automation mainly in the 1990s and thereafter.

The benefits of organic dust exposure in reducing cancer should be considered a real effect. There is a likely interrelationship between this anti-cancer activity and inflammation. A risk of non-malignant occupational disease from exposure to endotoxins and organic dusts nevertheless exists, and this risk has been suggested to outweigh any benefits associated with reduced cancer rates (Boffetta 2007). To date there is no paradigm providing a base from which the protective effects afforded by an exposure can be confirmed.

## 10. DISCUSSION

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**Table 9. Major concurrent exposures occurring with organic dusts.**

Wood dust	moulds, formaldehyde, fungicides, impregnation agents
Paper dust	pigments (e.g., kaolin, calcium carbonate, titanium dioxide), adhesives, additives (e.g., dyes, synthetic polymers)
Pulp dust (chemical or mechanical pulp)	different components of wood (mechanical pulp), chemical residuals (chemical pulp), non-human bacteria, moulds
Flour dust	plant dust
Plant dust	flour dust, textile dust, animal dust, non-human bacteria, moulds, fertilizers, pesticides, silica
Textile dust	plant dust, textile dyes
Leather dust	tanning agents (e.g., chromium salts, vegetable tannins), leather dyes, organic solvents
Animal dust	plant dust, moulds, non-human bacteria
Synthetic polymer dust	formaldehyde, aromatic hydrocarbons, other organic solvents, resins and dyes

Occupational exposure to organic dusts is unlikely to be a major risk factor of cancer in Finland. Occupational exposure does not seem to be a major causative factor of cancer in typical food industry occupations in Finland. The finding that exposure to plant and animal dust (mainly among farmers) and textile dust decreases the risk of lung cancer was supported by the results of the present study.

## **11. SUMMARY AND CONCLUSIONS**

Biologically active agents in organic dusts when deposited in the respiratory system, and their effects, determine the pathogenesis of the work-related symptoms and diseases in people exposed to organic dust. The causative agents identified are bacterial endotoxins, moulds, and different allergens. There is substantial evidence to suggest that of the many agents present in organic dusts, bacterial endotoxins are a major causative agent for inflammation of the airways. The type of inflammatory response and immunomodulatory effect may affect the risk of lung cancer, and the dissemination of cytokines from the cells in the lungs into the blood and entire body may affect cancer risk in other organs as well.

Occupational exposure is unlikely to be a major risk factor for cancer among Finnish food industry workers (I) or farmers (IV). The cancer incidence of Finnish farmers was significantly below the national average (IV). The only significantly elevated risk among farmers was that for lip cancer (IV). The finding that lung cancer risk was low among dairy farmers but increased with change to some other type of farm production gives some support to the hypothesis that exposure to endotoxins may lower cancer risk (IV).

Exposure to organic dusts is unlikely to be a major risk factor of respiratory cancer (II, III). Exposure to grain dust may, however, increase the risk of laryngeal cancer (I, II). Exposure to textile dust (mainly cotton), and to plant and animal dust (agricultural dusts) may decrease the risk of lung cancer (II, III, IV). Cumulative exposure to bio-aerosols (mould and bacteria dust) appears to be associated with a reduced risk of lung cancer (III, IV).

## 12. ACKNOWLEDGEMENTS

This work was carried out at the Finnish Institute of Occupational Health, Helsinki. I wish to thank professors Helena Taskinen, MD, PhD, Hilikka Riihimäki, MD, PhD, and Kari Reijula, MD, PhD, and Risto Sankila, MD, PhD, for introducing this interesting study topic and encouraging me to pursue it. I express my gratitude to docent Timo Kauppinen, PhD, my supervisor and co-author, for giving me ideas and options for the study, and for his advice and patient support. I owe my warmest thanks to professor Eero Pukkala, PhD, my other supervisor and co-author, for his expertise, guidance and admirable skill in showing how to keep to essential issues. I would like to offer my sincere thanks to Mr. Pentti Kyyrönen, my co-author, for excellent and rapid statistical services. In addition, I wish to express my gratitude to my other co-authors: docent Aino Nevalainen, PhD, and docent Pia Verkasalo, MD, PhD.

I am grateful to Sirpa Laitinen, PhD, for her expertise in occupational hygiene measurements and bioaerosols. I wish to thank my colleagues Timo Hannu, MD, PhD, and Johannes Guo, MD, PhD, for introducing me to this study and supporting me throughout this project. I wish to thank professor Elsebeth Lynge and professor Paavo Jäppinen for their critical review of the manuscript. I owe my sincere thanks to Mrs Lea Palo for keeping my study-related affairs organized at the Finnish Institute of Occupational Health. I am grateful to Mrs Luanne Siliämaa and Terttu Kaustia, MA, for the linguistic revision of the manuscript.

The work was supported financially by the Finnish Work Environment Fund and The Finnish Cancer Foundation, which I acknowledge gratefully.

I am grateful to my manager Lasse Lintilä at Valio Ltd for granting me study leave from my main occupation. I thank the kind staff of the

## 12. ACKNOWLEDGEMENTS

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occupational health unit at Valio Ltd, Helsinki, Mrs Tuula Engberg, Mrs Johanna Haavisto, Mrs Teija Heiskanen, Mrs Minna Hietala and Mrs Riitta Pippuri for their support, patience and flexibility during my study leaves.

Finally, I owe my most heartfelt thanks to my wife Marja-Liisa and our children Anni and Johanna, and my parents Anneli and Einar for their love and constant support during this study.

Helsinki, 4th of August, 2008

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## **14. ORIGINAL ARTICLES I–IV**



Organic dusts are the major cause of occupational diseases of the respiratory tract. The evidence on the risk of cancer from organic dusts is inconclusive, however. The food industry and agriculture are significant sources of occupational exposure to organic dust.

The computerized registries of Statistics Finland, the Finnish Cancer Registry, the Finnish Institute of Occupational Health, the Finnish National Public Health Institute and the Finnish Farm Registry were linked, based on either individual or group-level key variables.

The cohort in the studies on the food industry and organic dust comprised all economically active Finns born in 1906 to 1945 who participated in the national population census in 1970 (1.2 million persons). Data on their main occupation in 1970 were obtained from the Population Census records. The occupational exposures of the cohort were estimated by using the Finnish National Job-Exposure Matrix (FINJEM).

The cohort in the farmer study comprised all farmers in 1978 registered in the Finnish Farm Registry (160,000 persons).

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ISBN 978-951-802-851-5 (paperback)  
978-951-802-852-2 (PDF)  
ISSN 1237-6183

Cover picture: Corbis / Lehtikuva

ISBN 978-951-802-851-5

