Epidemiology and occupational health: the need for a coordinated approach

Manolis Kogevinas, MD, PhD
Barcelona Institute for Global Health (ISGlobal)

OMEGA-NET, 28 March 2022

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Outline

- The importance of epidemiology for occupational health
- The development of occupational epidemiology and current trends
- Why we need coordination

Occupational exposures

	Involuntary	Voluntary
Preventable	Occupation	Tobacco
No Preventable	Genetics	Reproductive factors

Involuntary + Preventable ➔ High priority for public health

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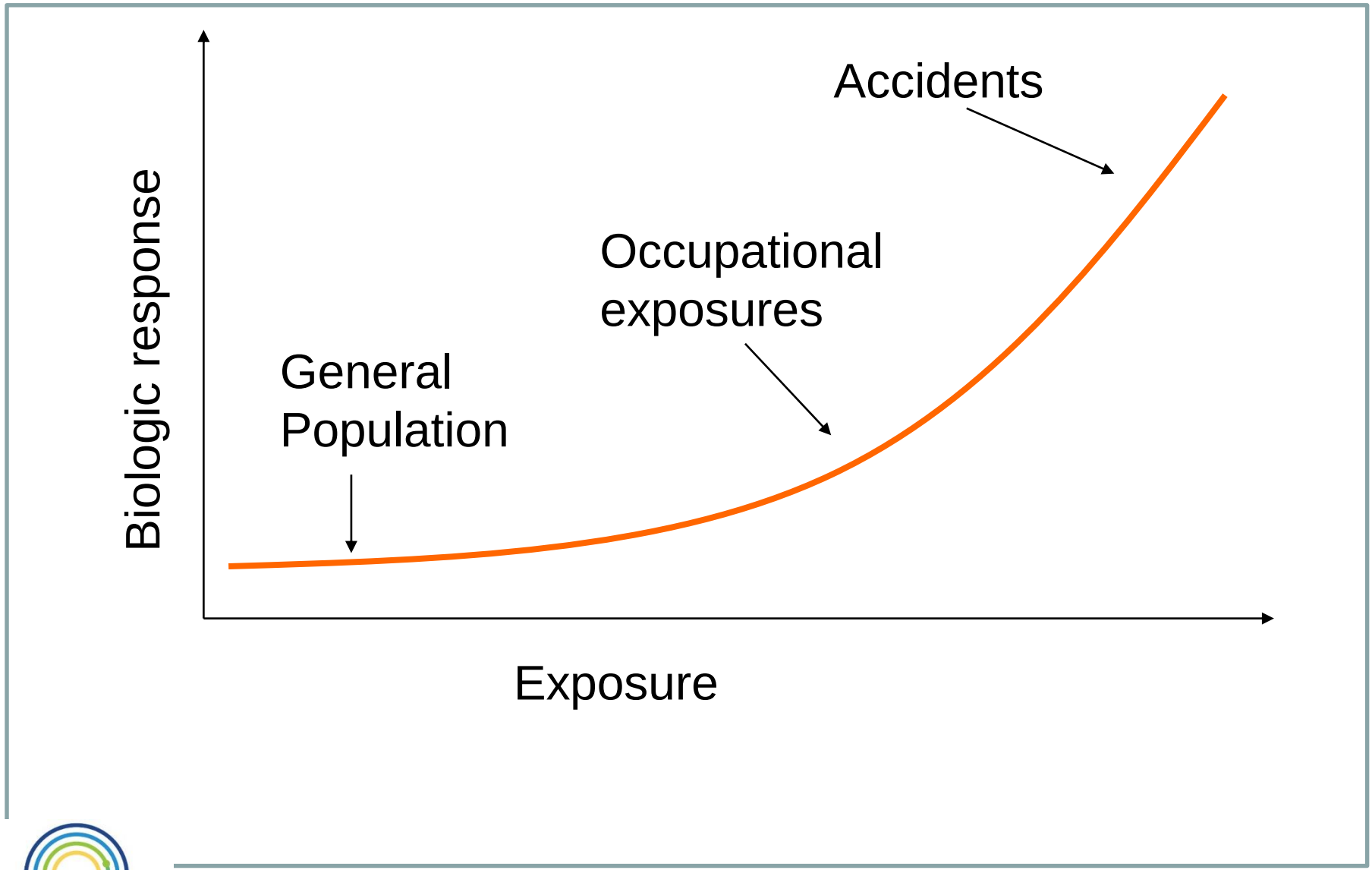

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THE LANCET

Vol 338 Saturday 26 October 1991 No 8774

ORIGINAL ARTICLES

In 1997 dioxins were classified as human carcinogens and prevention measures for workers and the general population were implemented

RODOLFO SARACCI MANOLIS KOGEVINAS PIER-ALBERTO BERTAZZI
BAS H. BUENO DE MESQUITA DAVID COGGON
LOIS M. GREEN TIMO KAUPPINEN KRISTAN A. L'ABBÉ
MARGARETA LITTORIN ELSEBETH LYNGE JOHN D. MATHEWS
MANFRED NEUBERGER JOHN OSMAN NEIL PEARCE
REGINA WINKELMANN

Occupational Human carcinogens (Group 1- IARC)

- **118** agents in Group 1
- **57** are occupational or also occur in the occupational environment (e.g. aflatoxins, SHS, radiations etc)
- Of those, **36** were identified as Group 1 before the year 2000, and **21** after the year 2000

(numbers of occupational carcinogens identified until 2018)

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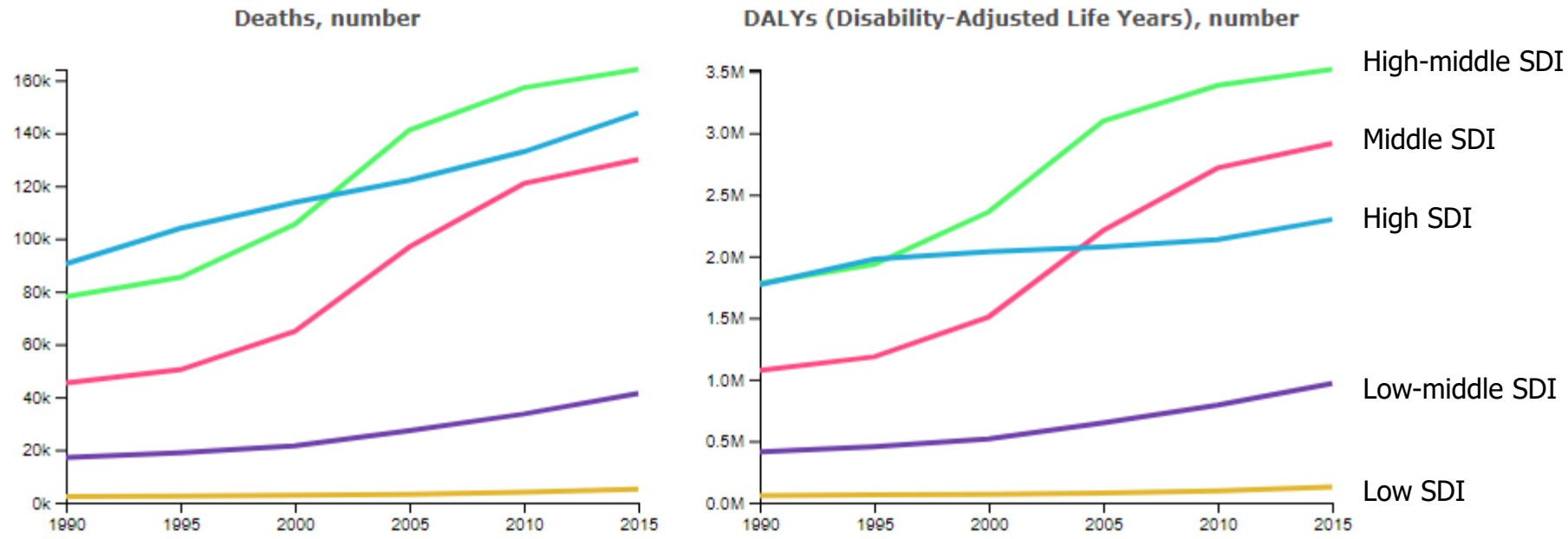
Global Burden of Disease – Deaths and DALYs from occupational carcinogens by Social Development Index (SDI)



(http://ghdx.healthdata.org/gbd-results-tool)

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The Development of Occupational Epidemiology

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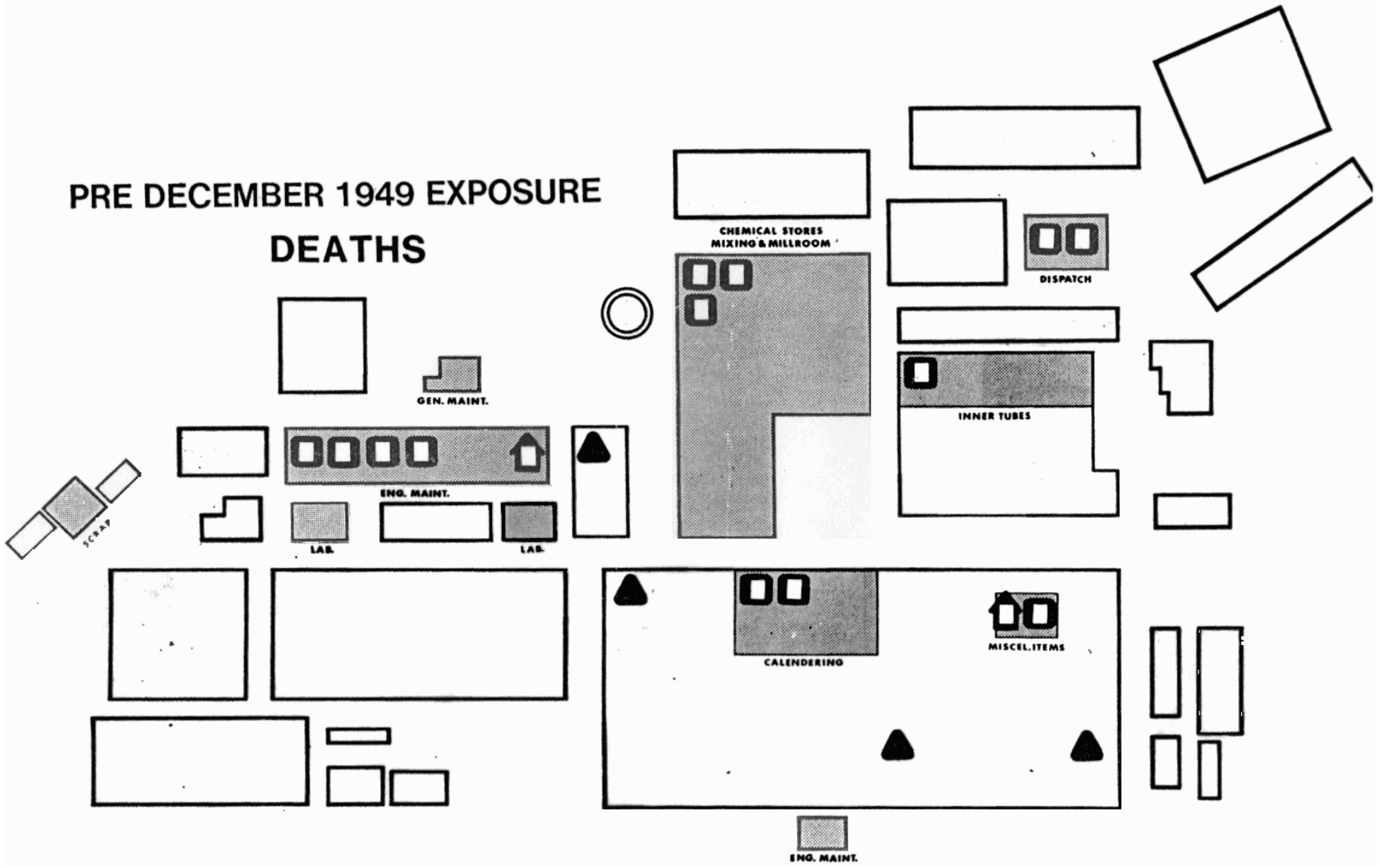

Rubber-Tire Industry "Michelin", England

Historical paper by R Case in 1951 on exposure to aromatic amines and bladder cancer

TUMOURS OF THE URINARY BLADDER IN WORKMEN ENGAGED IN THE MANUFACTURE AN USE OF CERTAIN DYESTUFF INTERMEDIATES IN THE BRITISH CHEMICAL INDUSTRY

PART I. THE ROLE OF ANILINE, BENZIDINE, ALPHA-NAPHTHYLAMI AND BETA-NAPHTHYLAMINE

BY

R. A. M. CASE, MARJORIE E. HOSKER,* DREVER B. McDONALD, and JOAN T. PEARSON

From the Chester Beatty Research Institute, the Institute of Cancer Research, University of London

(RECEIVED FOR PUBLICATION NOVEMBER 3, 1951)

The Scope of the Report

The genesis, history, and achievements of the Association of British Chemical Manufacturers' research scheme for the investigation of tumour of the urinary bladder in a section of the chemical industry have recently been described in some detail

2-naphthylamine or 3-naphthylamine shown to produce tumours of the urinary men so engaged. Accordingly, the scop report has been limited to this topic, with digressio substanc

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Phases in occupational epidemiology
(overlapping)

- ***The case-series phase***
- ***SMR study phase*** (high risks, fairly simple designs)

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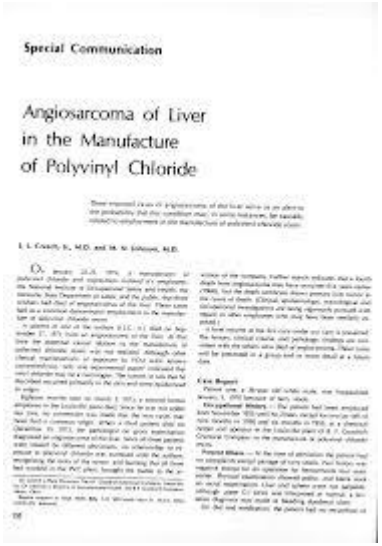
Creech JL Jr, Johnson MN. Angiosarcoma of liver in the manufacture of polyvinyl chloride *(J Occup Med. 1974; 16: 150-1)*



Special Communication

Angiosarcoma of Liver in the Manufacture of Polyvinyl Chloride

Between September 1967 and December 1973, 4 cases of angiosarcoma of the liver were diagnosed among men employed in the polyvinyl chloride polymerization section of a B.F. Goodrich plant near Louisville, Kentucky. Angiosarcoma of the liver is an exceedingly rare tumor. It is estimated that only about 25 such cases occur each year in the United States

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Principal evidence leading to the identification of occupational carcinogens (Group 1 IARC)

Carcinogen	Case Reports	Case-Control	Cohort Retrospective	Cohort Prospective	Mechanistic Data
Aminobiphenyl			x		
Aromatic amines	x		x		
Arsenic	x		x		
Asbestos			x		
Benzene	x	x	x		
Benzidine		x	x		
Beryllium			x		
Cadmium			x		
Chloromethyl ethers				x	
Chromium			x		
Dioxin			x		x
Erionite	x				
Ethylene oxide			x		x
Mustard gas			x		
Nickel					x
Pitch, Tar, Sorts	x				
Radon		x			
Silica					x
Talc	x			x	
Vinyl chloride	x				
Wood dust		x	x		x

Slide from Paolo Vineis

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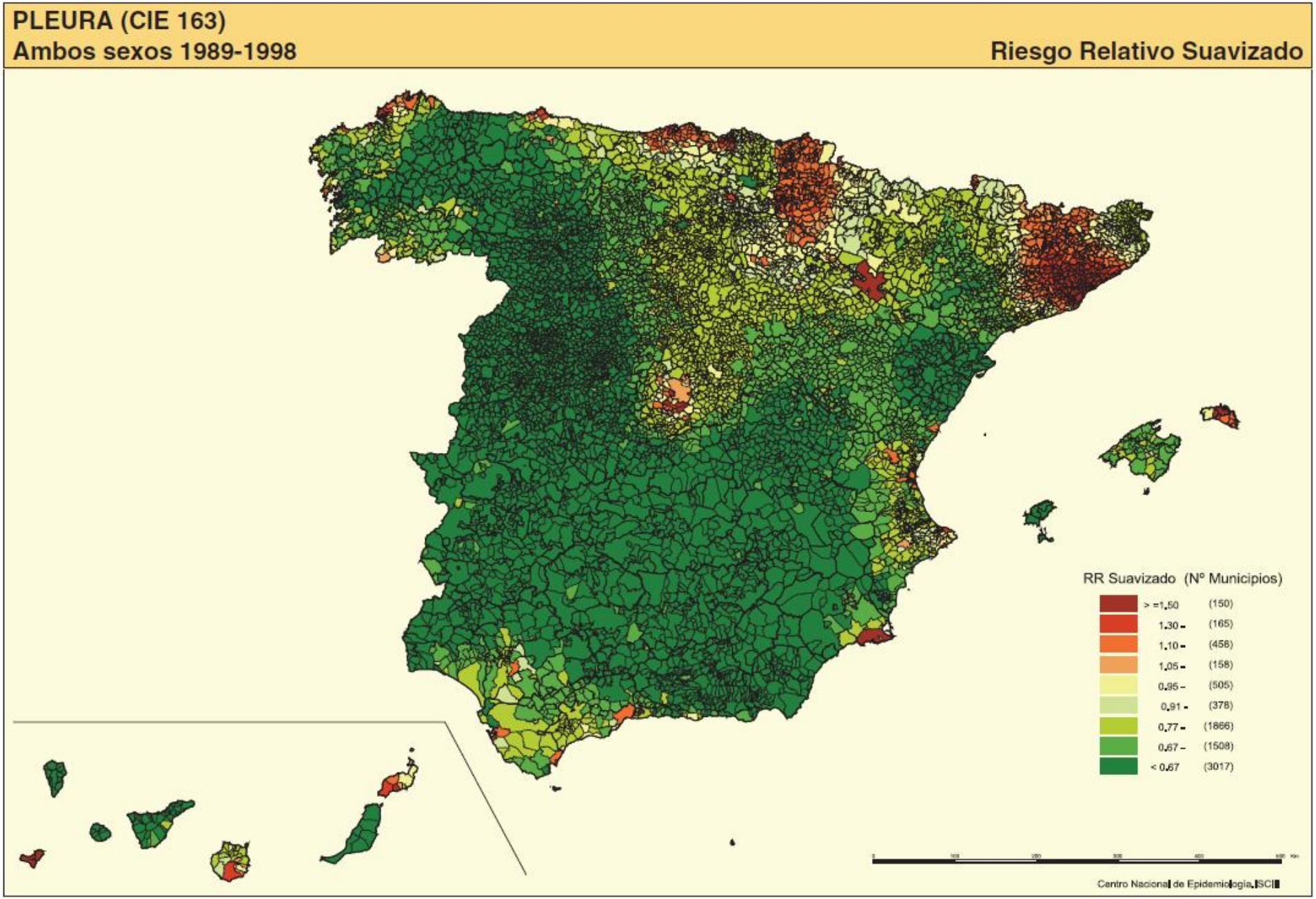

Atlas Municipal de Mortalidad por Cáncer en España 1989-1998. ISCIII, Madrid 2006

Phases in occupational epidemiology
(overlapping)

- ***The case-series phase***
- ***SMR study phase*** (high risks, fairly simple designs)
- ***Advanced exposure assessment phase*** (development of advanced methods for exposure assessment in cohort and case-control studies)

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Siemiatycki J, Richardson L, Gérin M, Goldberg M, Dewar R, Désy M, Campbell S, Wacholder S. *Associations between several sites of cancer and nine organic dusts: results from an hypothesis-generating case-control study in Montreal, 1979-1983*. Am J Epidemiol. 1986; 123: 235-49.

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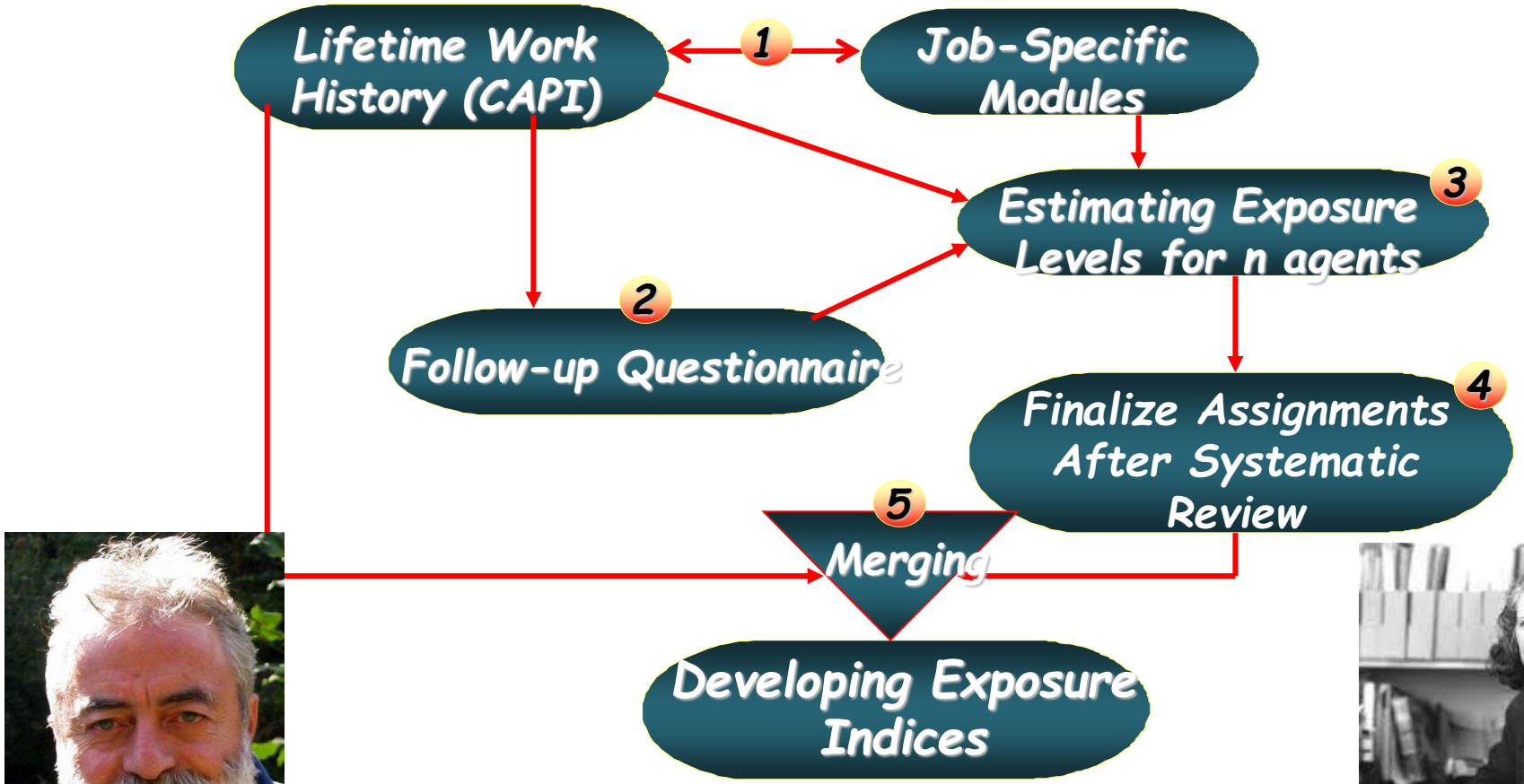
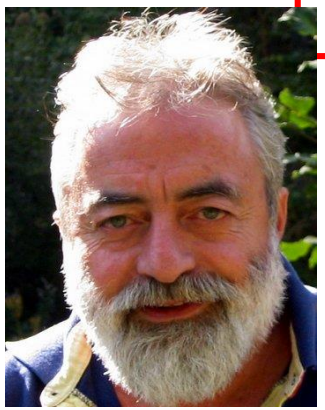
Siemiatycki J, Richardson L, Gérin M, Goldberg M, Dewar R, Désy M, Campbell S, Wacholder S. *Associations between several sites of cancer and nine organic dusts: results from an hypothesis-generating case-control study in Montreal, 1979-1983*. Am J Epidemiol. 1986; 123: 235-49.





Mustafa Dosemeci, Trish Stewart and many more

Ana, carrying the 63 occupational modular questionnaires. EPICURO study (Spanish bladder Cancer Study)

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Occupational Asthma Job Exposure Matrix (JEM): examples of occupations

ISCO88	title	Unlikely	Check	HMW latex	HMW Bioaerosols	LMW Isocyanates	MIXED Agriculture
5132	Care aides in institutions	0	0	1	0	0	0
5139	Other personal care aides	0	1	1	0	0	0
5152	Fortunetellers	1	0	0	0	0	0
6122	Poultry farming workers	0	0	0	1	0	1
7213	Sheet metal worker	0	1	0	0	0	0

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(Susan Kennedy, OEM 2003)

Phases in occupational epidemiology
(overlapping)

- ***The case-series phase***
- ***SMR study phase*** (high risks, fairly simple designs)
- ***Advanced exposure assessment phase*** (development of advanced methods for exposure assessment in cohort and case-control studies)
- ***Molecular epidemiology phase*** (incorporation of molecular and omic techniques)

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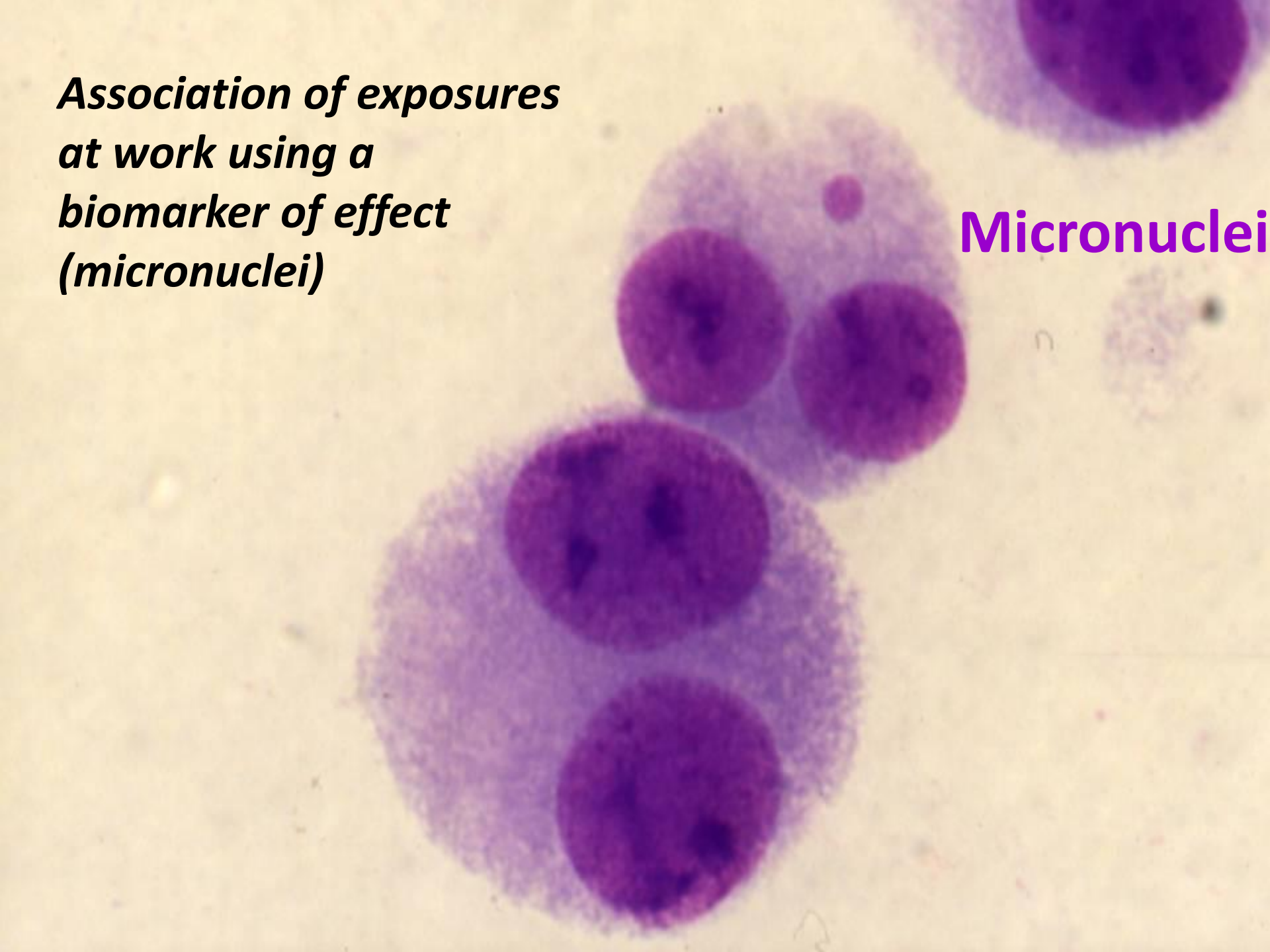
Association of exposures at work using a biomarker of effect (micronuclei)



Use of mechanistic data – the case of ethylene oxide (IARC 1994)

5.5 Evaluation[1]

There is *limited evidence* in humans for the carcinogenicity of ethylene oxide.

There is *sufficient evidence* in experimental animals for the carcinogenicity of ethylene oxide.

In making the overall evaluation, the Working Group took into consideration the following supporting evidence. Ethylene oxide is a directly acting alkylating agent that:

(i) induces a sensitive, persistent dose-related increase in the frequency of chromosomal aberrations and sister chromatid exchange in peripheral lymphocytes and micronuclei in bone-marrow cells of exposed workers;

(ii) has been associated with malignancies of the lymphatic and haematopoietic system in both humans and experimental animals;

(iii) induces a dose-related increase in the frequency of haemoglobin adducts in exposed humans and dose-related increases in the numbers of adducts in both DNA and haemoglobin in exposed rodents;

(iv) induces gene mutations and heritable translocations in germ cells of exposed rodents; and

(v) is a powerful mutagen and clastogen at all phylogenetic levels.

Overall evaluation

Ethylene oxide *is carcinogenic to humans (Group 1).*

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Phases in occupational Epidemiology: more "recent" trends

- **exposome research;**
- **advanced exposure assessment** (sensors etc)
- **pooled analyses** (sharing of data)**;**
- **record linkage;**
- **emphasis on cohort studies**;
- **new approaches to causal inference** *(Neil Pearce later this week)*

and

- **new (and old) problems!** (societies are not static)

The Exposome

Recognizing the disparity in current knowledge between genes and environmental exposures, Chris Wild (2005) defined the "exposome" representing *all environmental exposures (including those from diet, lifestyle, and endogenous sources) from conception onwards,* as a quantity of critical interest to disease etiology.

Features of the Exposome

1. Holistic – many exposures
2. Life-course – dynamic
3. New tools / technology
4. Integrate biological responses (“internal exposome”)
5. Untargeted discovery

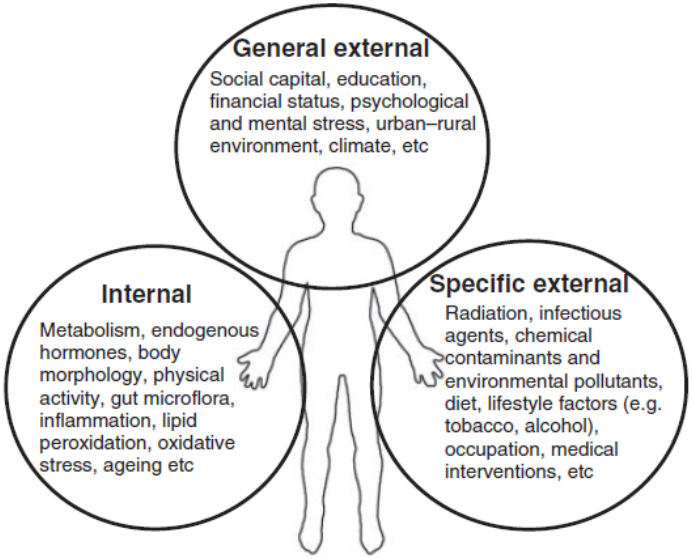
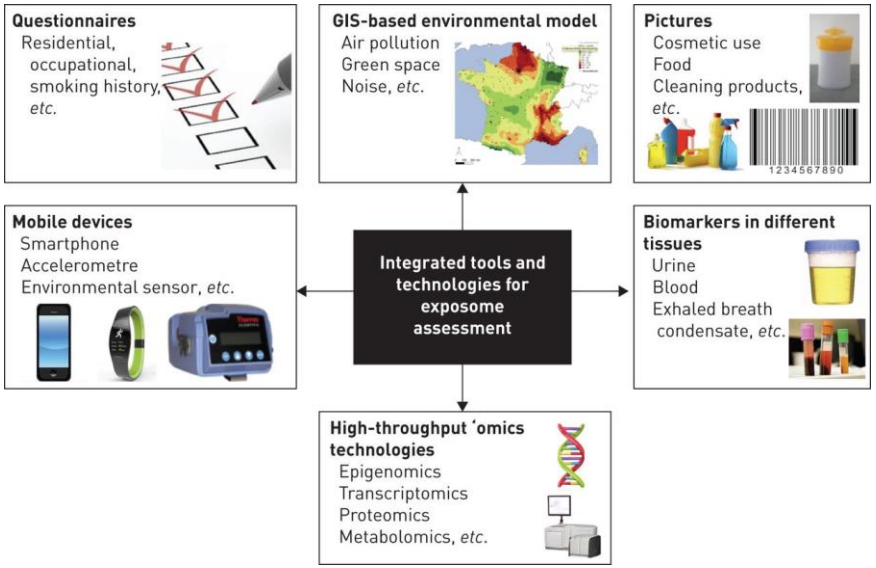
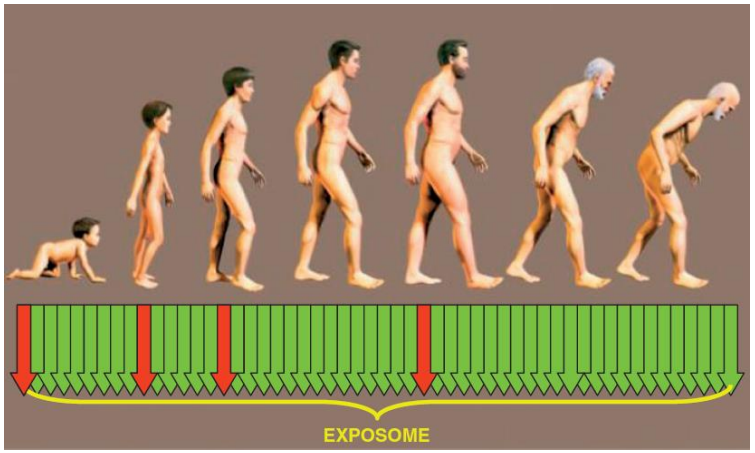


Figure 1 Three different domains of the exposome are presented diagrammatically with non-exhaustive examples for each of these domains

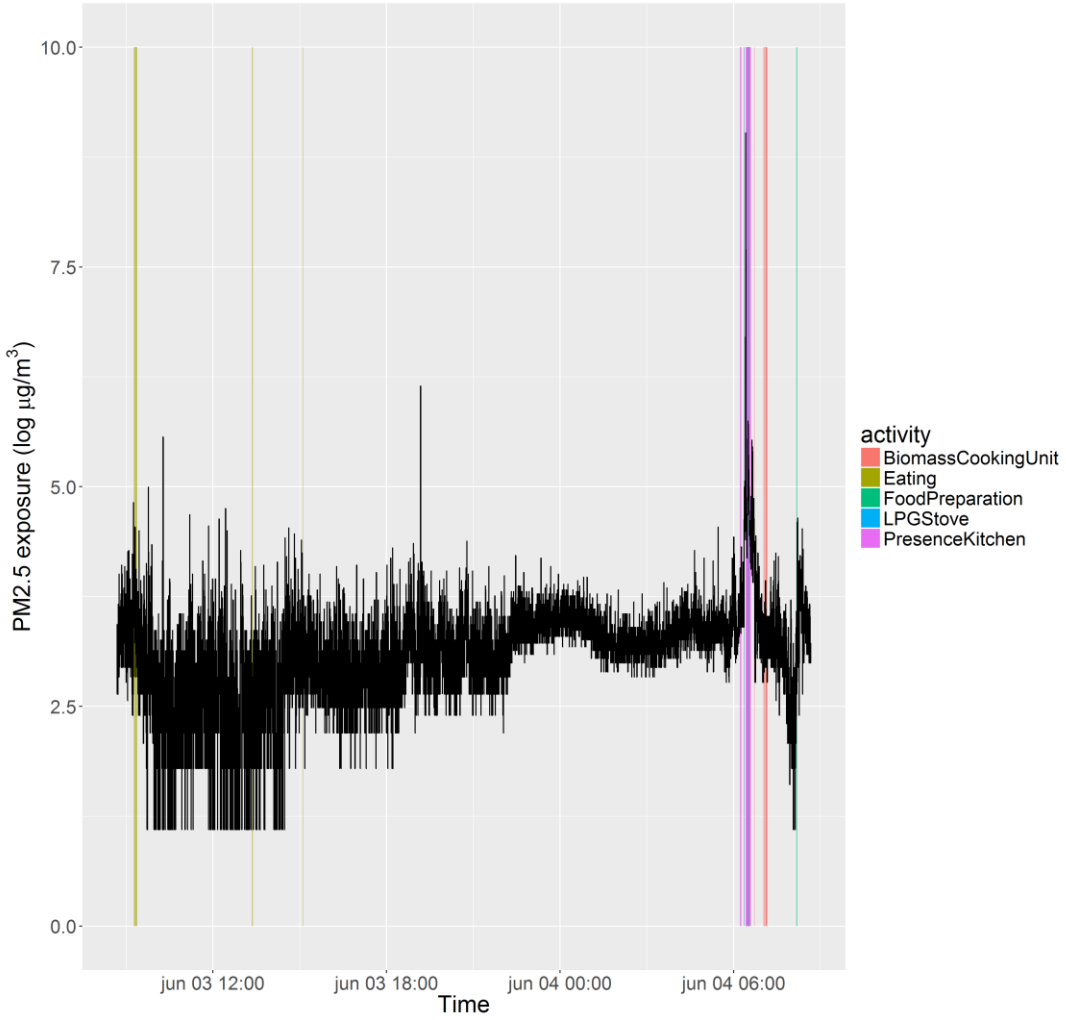




Wild, Int J Epidemiol, 2012

CHAI
Cardiovascular Health effects of Air pollution in Telangana, India

CHAI Project, India, Cathryn Tonne, ISGlobal



Long working hours and risk of coronary heart disease and stroke: a systematic review and meta-analysis of published and unpublished data for 603 838 individuals

Mika Kivimäki, Markus Jokela, Solja T Nyberg, Archana Sir
Hermann Burr, Annalisa Casini, Els Clays, Dirk De Bacquer,
Irene L Houtman, Karl-Heinz Jöckel, France Kittel, Anders K
Maria Nordin, Tuula Oksanen, Jan H Pejtersen, Jaana Pent
Sakari B Suominen, Töres Theorell, Jussi Vahtera, Peter J M
Jane E Ferrie, Marianna Virtanen, for the IPD-Work Consor
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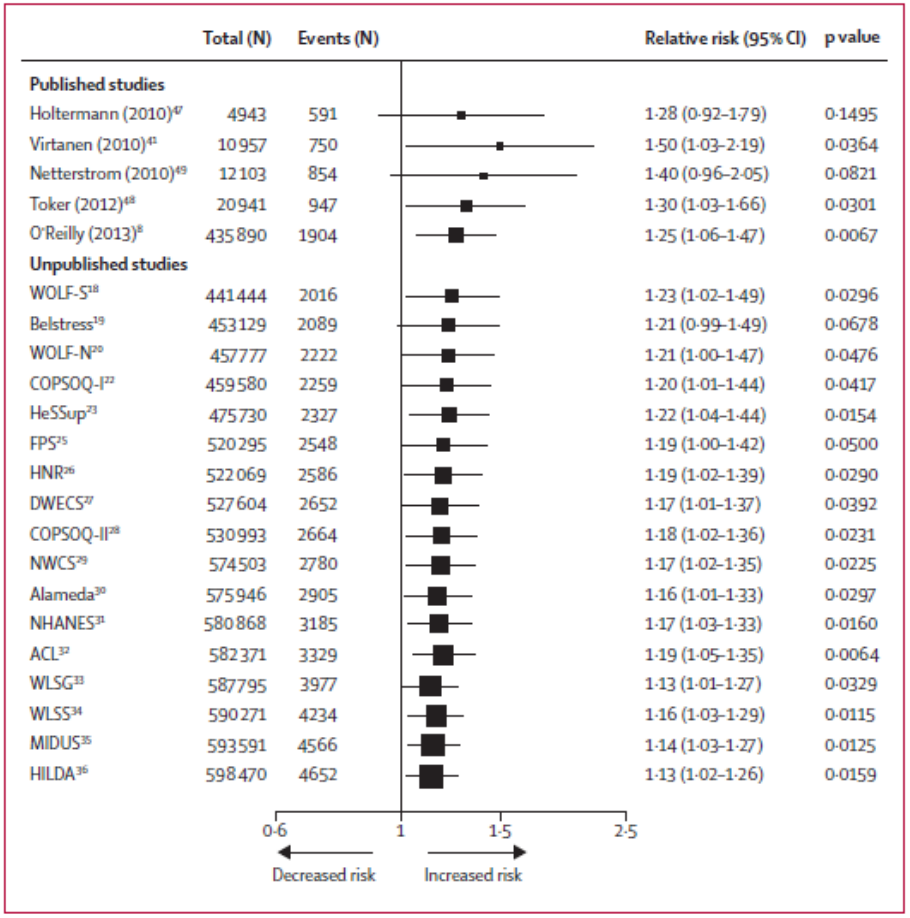


	Total (N)	Events (N)	Relative risk (95% CI)	p value
Published studies				
Holtermann (2010)[47]	4943	591	1·28 (0·92–1·79)	0·1495
Virtanen (2010)[41]	10 957	750	1·50 (1·03–2·19)	0·0364
Netterstrom (2010)[49]	12 103	854	1·40 (0·96–2·05)	0·0821
Toker (2012)[48]	20 941	947	1·30 (1·03–1·66)	0·0301
O'Reilly (2013)[8]	435 890	1904	1·25 (1·06–1·47)	0·0067
Unpublished studies				
WOLF-S[18]	441 444	2016	1·23 (1·02–1·49)	0·0296
Belstress[19]	453 129	2089	1·21 (0·99–1·49)	0·0678
WOLF-N[20]	457 777	2222	1·21 (1·00–1·47)	0·0476
COPSOQ-I[22]	459 580	2259	1·20 (1·01–1·44)	0·0417
HeSSup[23]	475 730	2327	1·22 (1·04–1·44)	0·0154
FPS[25]	520 295	2548	1·19 (1·00–1·42)	0·0500
HNR[26]	522 069	2586	1·19 (1·02–1·39)	0·0290
DWECS[27]	527 604	2652	1·17 (1·01–1·37)	0·0392
COPSOQ-II[28]	530 993	2664	1·18 (1·02–1·36)	0·0231
NWCS[29]	574 503	2780	1·17 (1·02–1·35)	0·0225
Alameda[30]	575 946	2905	1·16 (1·01–1·33)	0·0297
NHANES[31]	580 868	3185	1·17 (1·03–1·33)	0·0160
ACL[32]	582 371	3329	1·19 (1·05–1·35)	0·0064
WLSG[33]	587 795	3977	1·13 (1·01–1·27)	0·0329
WLSS[34]	590 271	4234	1·16 (1·03–1·29)	0·0115
MIDUS[35]	593 591	4566	1·14 (1·03–1·27)	0·0125
HILDA[36]	598 470	4652	1·13 (1·02–1·26)	0·0159

Figure 2: **Cumulative meta-analysis of published and unpublished data of the association between long working hours and incident coronary heart disease**
Estimates adjusted for age, sex, and socioeconomic status.

Kivimaki, Lancet 2015

Occupation and cancer – follow-up of 15 million people in five Nordic countries

EERO PUKKALA[1,2], JAN IVAR MARTINSEN[3], ELSEBETH LYNGE[4], HOLMFRIDUR KOLBRUN GUNNARSDOTTIR[5], PÄR SPARÉN[6], LAUFEY TRYGGVADOTTIR[7], ELISABETE WEIDERPASS[3,6,8,9] & KRISTINA KJAERHEIM[3]

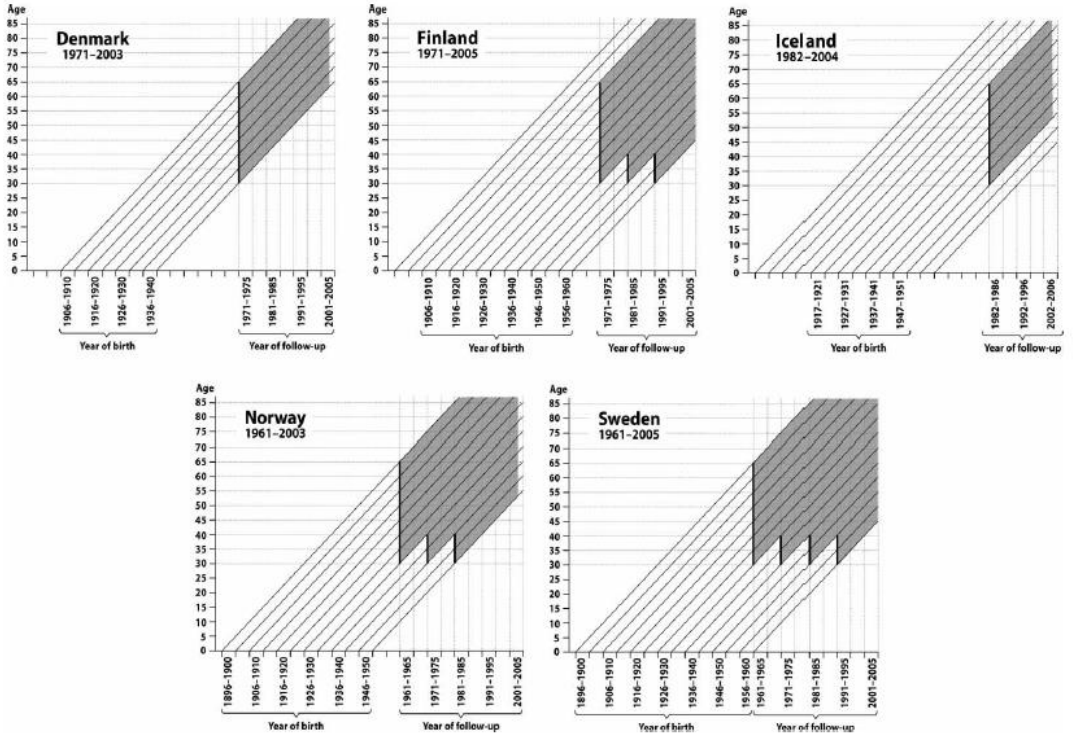
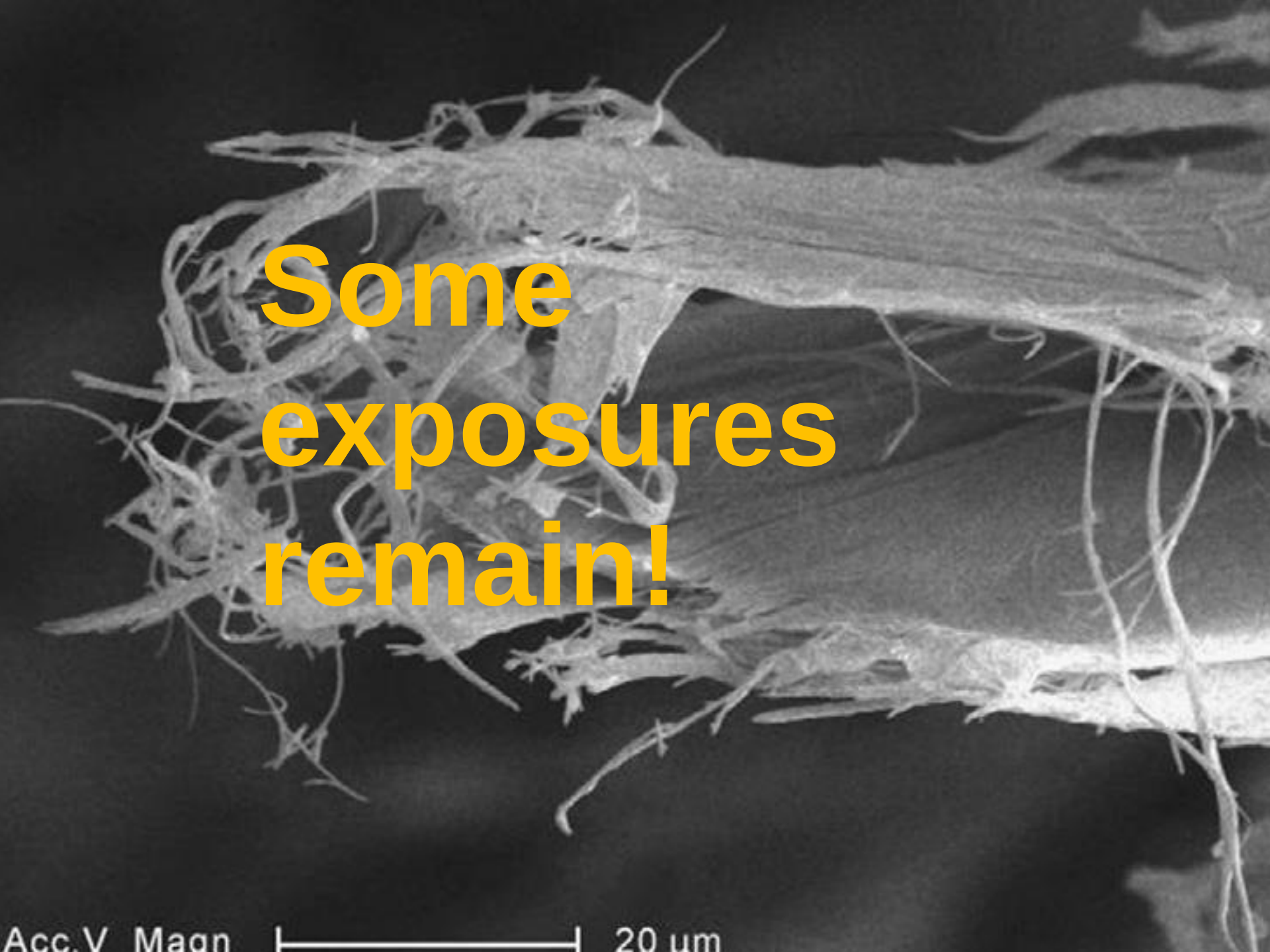
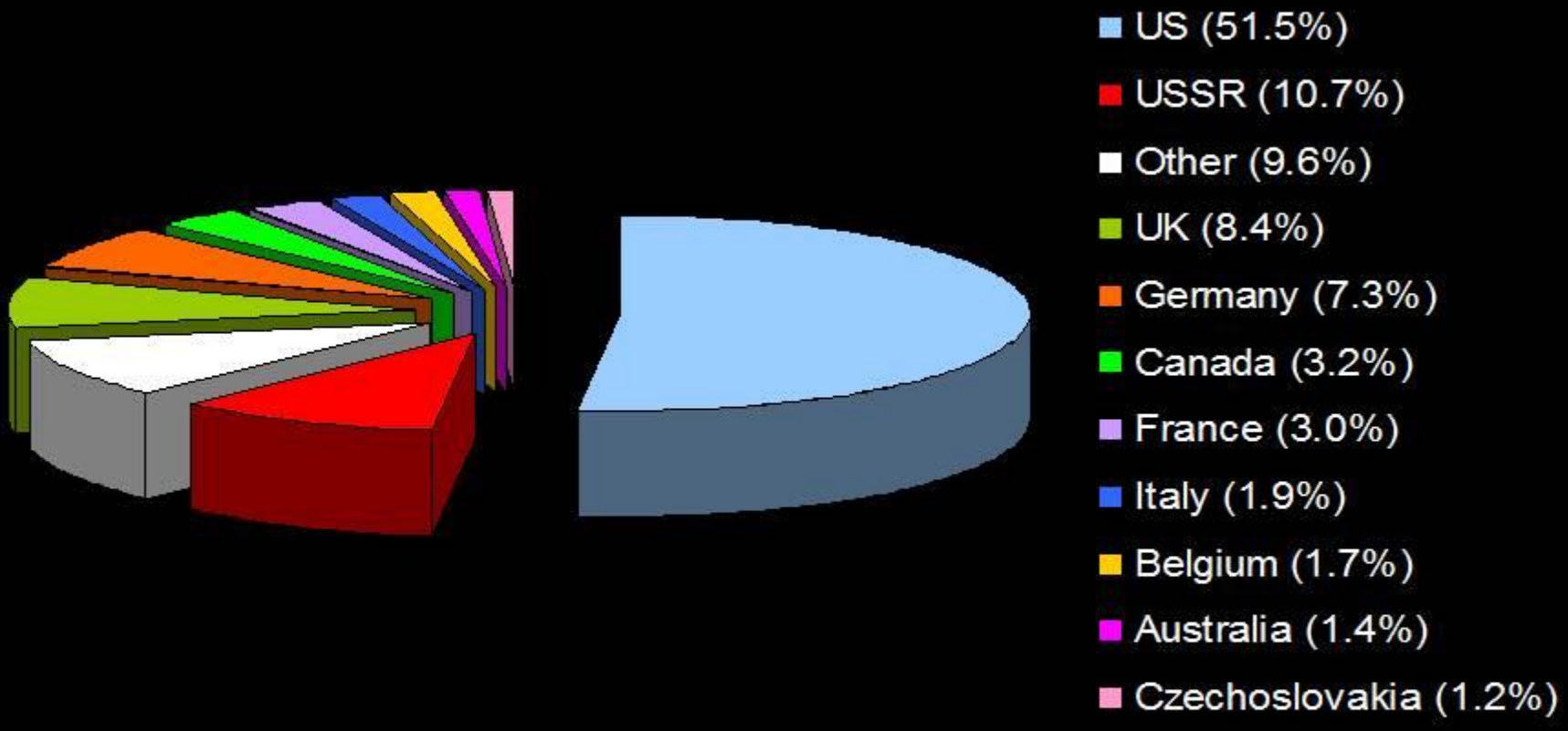


Figure 11. Time windows of follow-up of the study cohort defined by year of birth and age, by country. Bold vertical lines indicate time of baseline census used for allocation of the occupational category.

Acta Oncol 2009


Some exposures remain!
Acc.V Magn
20 µm

Global Asbestos Fiber Consumption, 1950

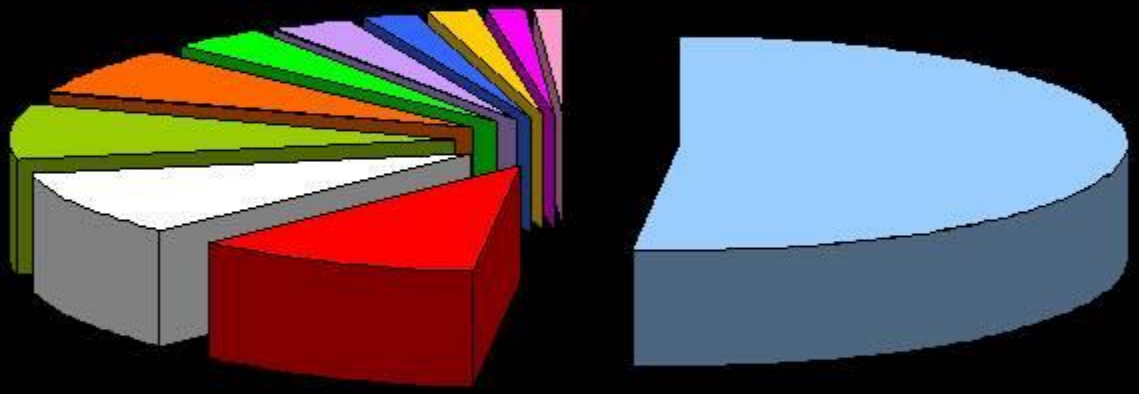


Notes:

- Based on USGS data on apparent asbestos consumption.
- Figure for Germany is the combined percentage for East and West Germany.
- Belgium, above refers to Belgium and Luxembourg.
- Other: around 40 smaller consumers listed by the USGS.

Compiled by: International Ban Asbestos Secretariat

Global Asbestos Fiber Consumption, 1950



- US (51.5%)
- USSR (10.7%)
- Other (9.6%)
- UK (8.4%)
- Germany (7.3%)
- Canada (3.2%)
- France (3.0%)
- Italy (1.9%)
- Belgium (1.7%)
- Australia (1.4%)
- Czechoslovakia (1.2%)

A question for you:

How many countries shown in this slide keep being major users of asbestos nowadays?

d West Germany.

Compiled by: International Ban Asbestos Secretariat

Societies change
New Issues in Occupational Health

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HERA Research Goals

RG2.4 Changing work and employment conditions

Research Needs

1. Climate change, key enabling technologies, the Green Deal
2. Changing and ageing workforce
3. Working time
4. Changing employment patterns
5. Neglected occupational diseases
6. Monitoring, electronic health records, and surveillance in occupational health

Carcinogenicity of shift work

IARC (WHO), 2007

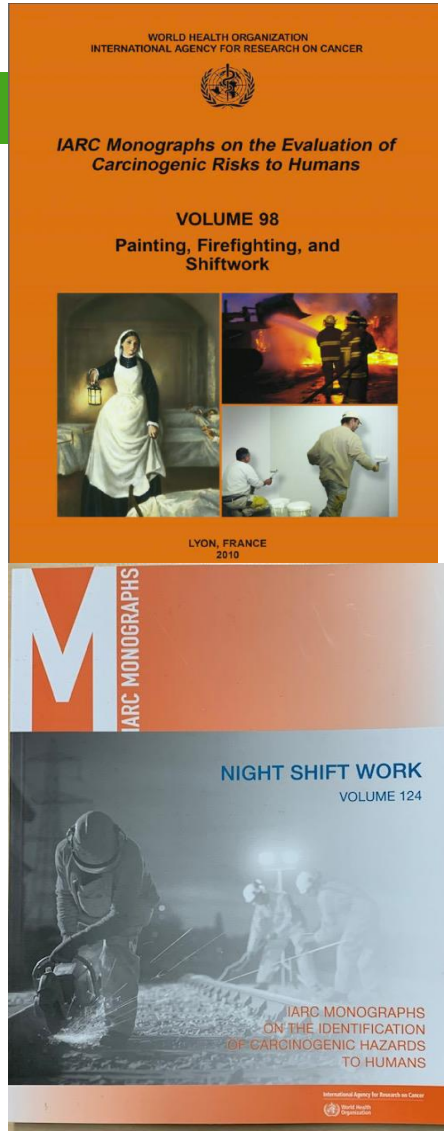
"Shift work involving circadian disruption is probably carcinogenic to humans" (Group 2A)

IARC 2019

"Night shift work is probably carcinogenic to humans" (Group 2A)

based on…

- **Sufficient** evidence from animal studies, alteration of light-night schedule
- **Limited** evidence from epidemiological studies showing higher risks for **breast, prostate and colorectal** cancer



Straif K et al, 2007; IARC Monographs Vol 98, 2010; IARC Mono Vol 124, 2021

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Occupational asthma

It has been estimated that approximately 15% of adult asthma can be attributed to occupational exposures (ATS statement, AJRCCM, 2003).

Approximately 250 workplace exposures have been associated with the occurrence of asthma

Few of these exposures have been evaluated in epidemiological studies and even fewer in general population studies

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New-onset occupational asthma, ECRHS-II. Job exposure matrix (Kogevinas, Lancet 2007)

	Exposed cases	RR	95%CI	Attributable risk (%)
Current asthma	40	1.6	(1.1 -2.3)	10%
Current asthma and BHR	16	2.4	(1.3 -4.6)	23%

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CUPID study Crete. Physical activities in an average working day – prevalence (%) by occupational group.

	Use keyboard >4 hours	Other repeated wrist/hand movement >4 hours
Nurses	3%	71%
Office workers	87%	59%
Post office workers	1%	84%

	Use keyboard >4 hours	Other repeated wrist/hand movement >4 hours	Repeated elbow bending >1 hour	Hands above shoulder height >1 hr	Lifting =25 kg by hand	Kneeling/ squatting >1 hour
Nurses	3%	71%	89%	29%	70%	30%
Office workers	87%	59%	75%	6%	7%	7%
Post office workers	1%	84%	96%	66%	47%	22%

Occupational cohorts: why we need coordination

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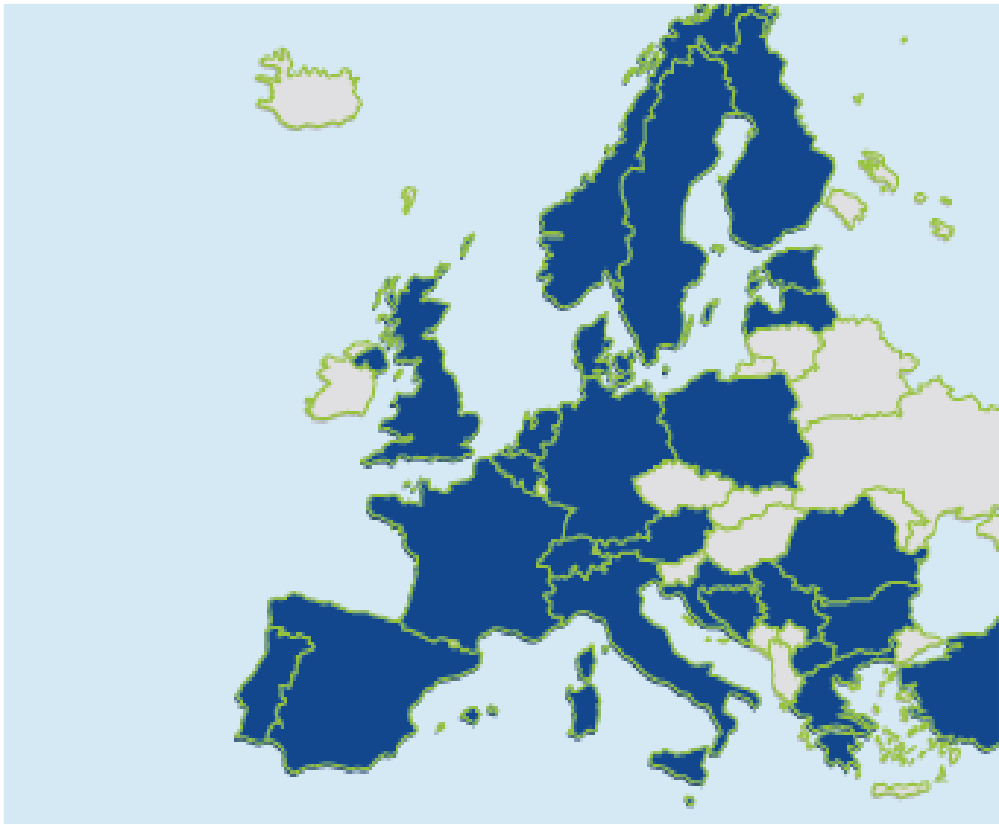
Network on the Coordination and Harmonisation of European Occupational Cohorts



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Occupational cohorts in the EU: fait accompli (i.e. we have it!)

- Long experience in EU countries in occupational epidemiology and collaborative research
- Huge cohorts mostly in Nordic countries
- Numerous smaller cohorts all around Europe

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Occupational cohorts

- we have the know how
- we have the numbers
- we have dispersion (that is good and bad)
- we have wide poorly studied populations

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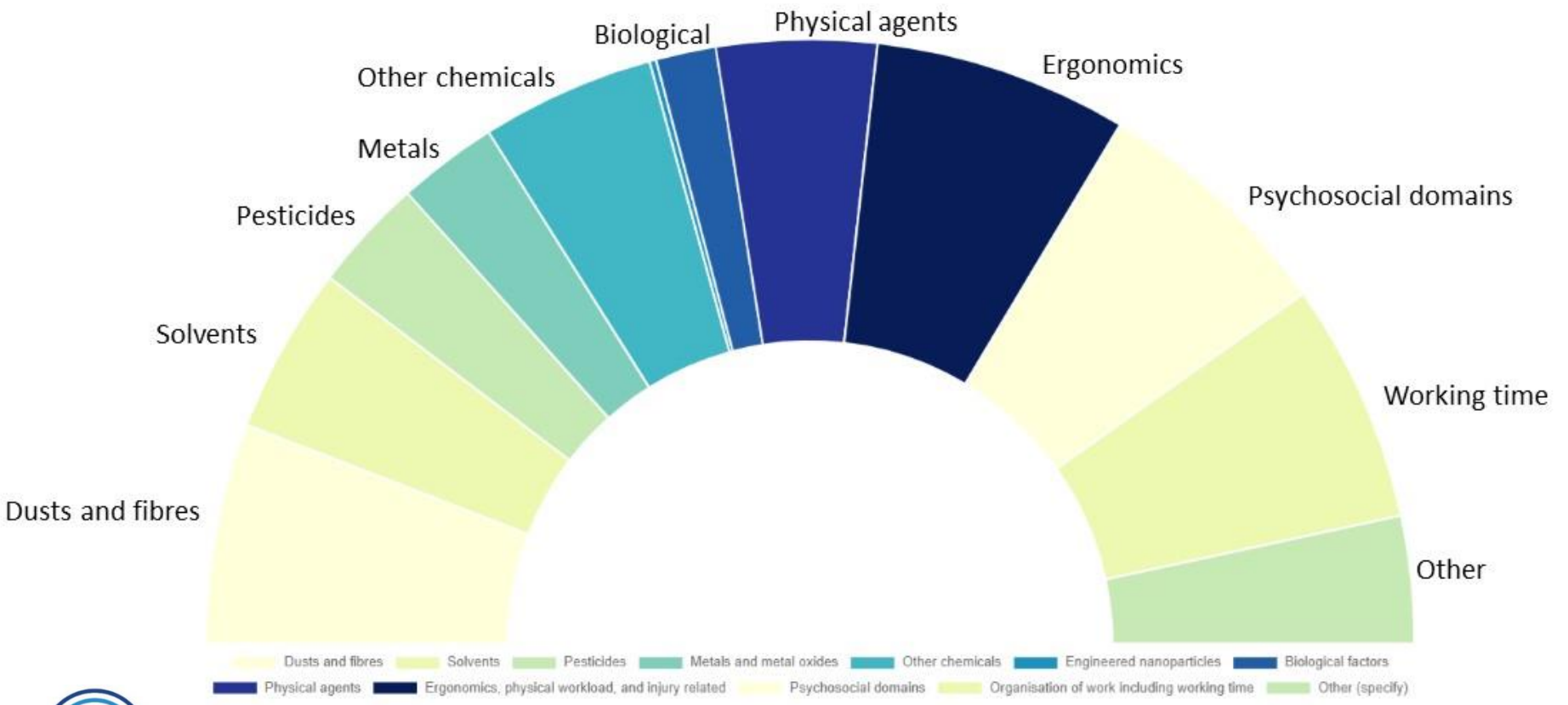
Exposures evaluated by existing occupational cohorts (from OMEGA-NET inventory)



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Why should we collaborate?

- Statistical power
- Efficient design
- Replication
- Promotion of research

A prerequisite is the standardisation of methods

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Why should we collaborate?

Statistical Power

- Rare outcomes (e.g. some cancers) or rare exposures
- Stratified analyses (e.g. sub- populations) and interactions
- Dose-response analysis and risk assessment

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Why should we collaborate:
Efficient design: sampling from the EU population

- Handle the Occupational, environmental, cultural and genetic differences within the EU populations as an asset rather than a problem
- Sample for outcomes, exposures and genetic traits using cohort or nested case-control designs, so as to maximise efficiency

→ use the OMEGA-NET inventory to find out what is available

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Why should we collaborate?

Replication

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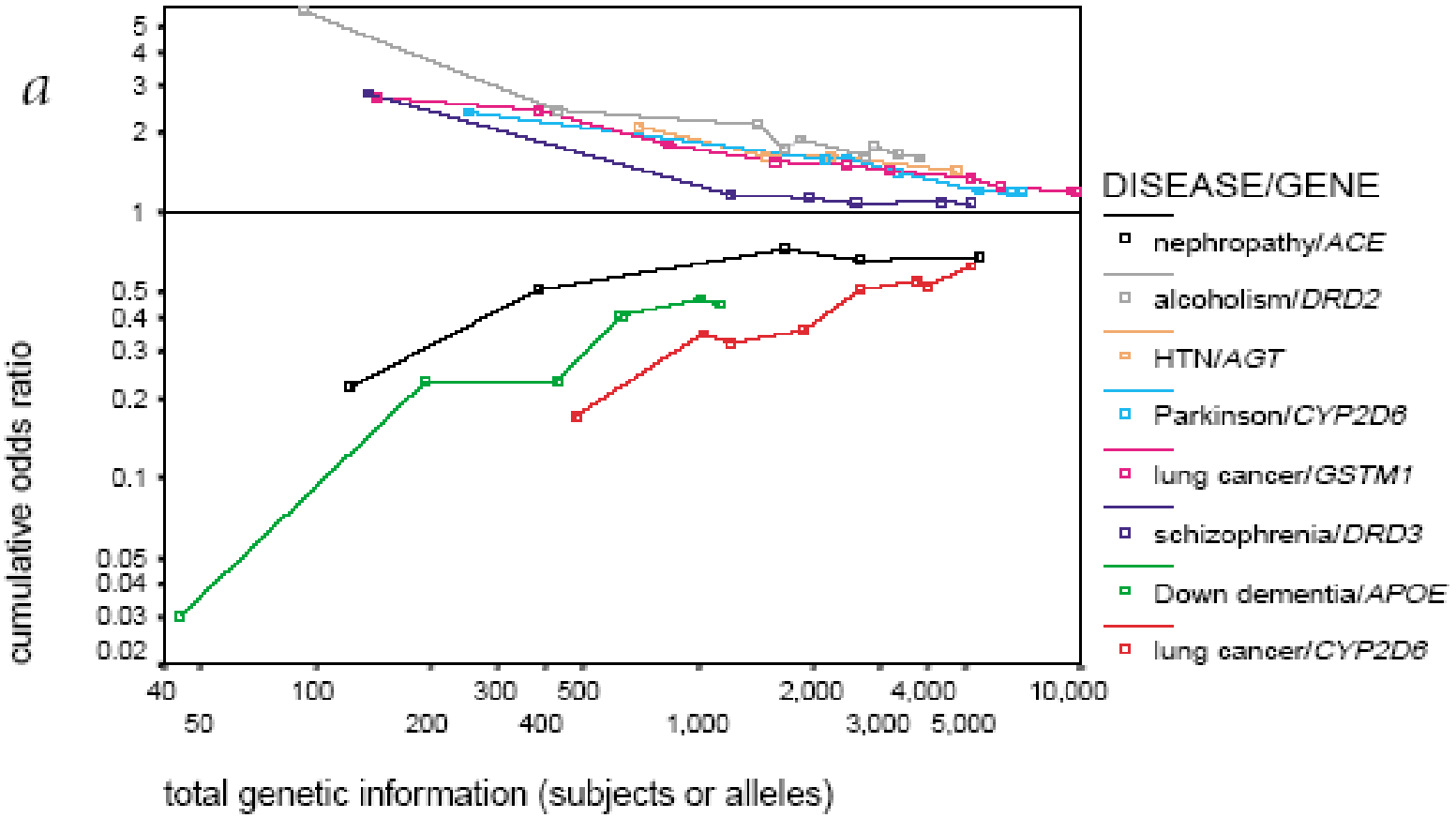
Evolution of the strength of an association (Odds Ratios) as more information is accumulated (Ioannidis et al Nat Gen 2001)



Failure to replicate has been attributed to several factors

- Population specific
  - Different distributions of exposures and other risk factors (potential confounding factors or effect modifiers)
  - Genetic heterogeneity between populations
- Study specific
  - Sample size (related to chance & multiple testing)
  - Different study designs and biases
  - Differences in definitions of outcomes
  - Differences in the evaluation of occupational exposures
- Publication bias (related also to multiple testing)

Occupational cohorts: types of collaboration

- *Ad-hoc* coordination on specific projects
- Close coordination, something like a virtual mega occupational cohort
- Initiation of large cohorts de novo

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The future

- Several studies on occupational health are conducted in Europe [illegible] dinated
- Indivic [illegible] oblem is in integrat [illegible]
- Progr [illegible] esearch of extraor [illegible] nly come:
  - ➢fr [illegible] an level that com [illegible] cohorts
  - ➢wi [illegible] ses
  - ➢su [illegible] spectrum of exp [illegible]
  - ➢a [illegible] e to do more efficient and conclusive studies

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