Die IARC Monographien: Die Idenitifaktion krebs-erzeugender Arbeitsstoffe unter besonderer Berücksichtigung des Beitrags der Epidemiologie

International Agency for Research on Cancer
Lyon, France

ÖSTERREICHISCHE GESELLSCHAFT FÜR ARBEITSMEDIZIN

Kurt Straif, MD MPH PhD

Villach, 21 Sept, 2018

International Agency for Research on Cancer
World Health Organization

Identifying occupational causes of cancer

- Bernadino Ramazzini *De morbis artificium*,1700

  Increased risk of breast cancer among nuns
- Percival Pott, 1775
  Scrotal cancer in chimney sweeps
- Haerting & Hesse, 1879
  Schneeberg lung cancer
- Rehn, 1895

  Blasengeschwülste bei Fuchsin-Arbeitern

  Von

  Dr. L. Rehn,

  Three bladder tumours in 45 workers involved in the manufacture of fuchsin

PAHs, the Histories of Occupational Cancer and Carcinogenesis

1775 Percival Pott	Scrotal cancer in chimney sweeps
1912 Yamagiwa & Itchikawa	Skin Cancer induced by application of coal tar
1925 1. Ordinance of Occupational Diseases, Germany	Skin cancer related to soot paraffin, tar, anthracene & pitch
1933 Cook	Identification of benzo[a]pyrene in coal tar
1947 Kennaway & Kennaway	Lung cancer in coal gas & tar workers
1964 Berenblum	2-Stage theory of carcinogenesis (benzo[a]pyrene & croton oil)
2005 IARC Monographs	Benzo[a]pyrene Group 1 carcinogen (mechanistic upgrade)

International Agency for Research on Cancer

World Health Organization

Schneeberg Lung Disease

1168 Discovery of silver in the Erz Mountains

1470 Silver mining from mines 60 – 70 m underground

1533/34 Paracelsus „ Von der Bergsucht oder Bergkranckheiten drey Bücher“

1879 Härting & Hesse: Schneeberg Lung disease is Lung cancer

1925 1. BKVO: „Schneeberg Lung Cancer “

ca 1940 Radon causes lung cancer in underground miners

1949 Archer, prospective cohort in uranium miners (1962)

1989 SDAG Wismut, 1945-1955 up to 200.000 workers exposed to 160 WLM/a

Dose-response analyses of occupational and residential radon exposure and lung cancer

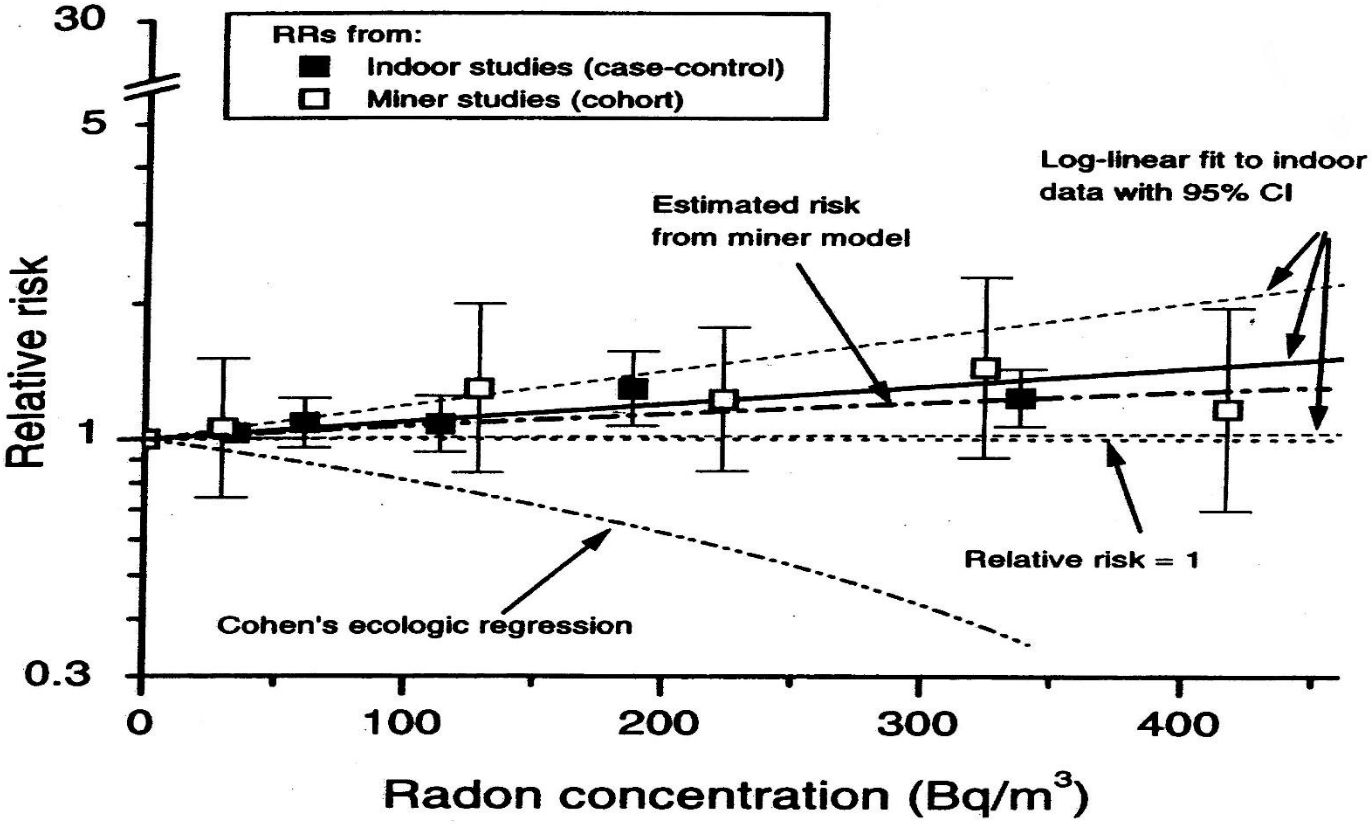

FIGURE 3-2 Summary relative risks (RR) from meta-analysis of indoor-radon studies and RRs from pooled analysis of underground-miner studies, restricted to exposures under 0.175 Jhm^{-3} (50 WLM). Included are RR of 1, fitted exposure-response and its 95% confidence interval from indoor-radon studies, and estimated linear RR based on ecologic analysis by Cohen (1995).

BEIR VI, 1999

IARC Monographs, Group 1 Agents Identified from Occupational Studies

Important burden of cancer

- Asbestos (v7)
- Silica (v68)
- Diesel engine exhaust (v105)

New

- Trichloroethylene (v106)
- PCBs (v107)
- 1,2-Dichloropropane (v110)
- Pentachlorophenol (v117)
- Welding fumes (v118)

Asbestos, Vol 100C: Carcinogenic to humans

- There is *sufficient* evidence in humans for the carcinogenicity of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite and anthophyllite). All forms of asbestos cause mesothelioma and cancers of the lung, larynx and ovary.
- The Working Group classified the evidence for colorectal cancer as *limited* although the Members were evenly divided as to whether the evidence was strong enough to warrant classification as *sufficient*.
- There is *limited* evidence in humans for cancers of the pharynx and of the stomach.

International Agency for Research on Cancer

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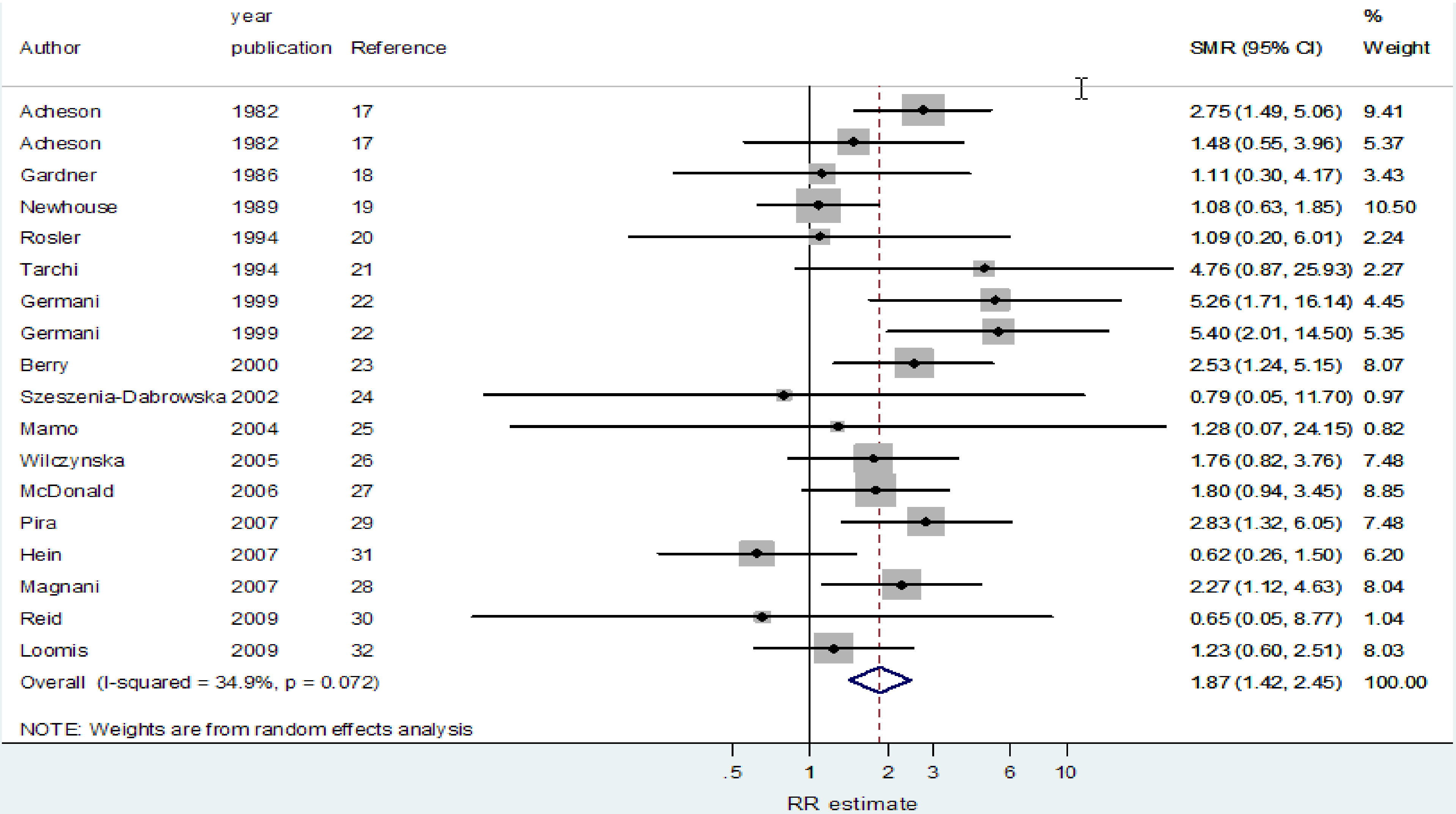
Asbestos and Ovarian cancer, Vol.100C

- Five strongly positive cohort mortality studies of women with heavy occupational exposure to asbestos.
- Supported by studies showing that women with environmental exposure to asbestos had non-significant increases in both ovarian cancer incidence and mortality.
- Modest support from the findings of non-significant associations between asbestos exposure and ovarian cancer in two case-control studies.
- Finding is consistent with laboratory studies documenting that asbestos can accumulate in the ovaries of women with occupational and household exposure to asbestos.

Asbestos and Ovarian Cancer



Camargo et al. Env Health Perspectives (2011)

World Health Organization

Exposure to asbestos & cholangiocarcinoma (NOCCA)

- Case-control study nested in the Nordic Occupational Cancer (NOCCA) cohort.
- 1,458 intrahepatic CC (ICC) and 3,972 extrahepatic (ECC) cases
- Each case individually matched by birth year, gender, and country to 5 population controls.
- Cumulative exposure to asbestos by applying NOCCA job exposure matrix to censuses data on occupation (conducted in 1960, 1970, 1980/81, and 1990).
- Exposure-response trend for ICC
  No association between asbestos exposure and ECC

Occupational exposure to asbestos and risk of cholangiocarcinoma: a population-based case–control study in four Nordic countries

Andrea Farioli,[1] Kurt Straif,[2] Giovanni Brandi,[3,4] Stefania Curti,[1] Kristina Kjaerheim,[5] Jan Ivar Martinsen,[5] Pär Sparen,[6] Laufey Tryggvadottir,[7,8] Elisabete Weiderpass,[5,6,9,10] Guido Biasco,[3,4] Francesco Saverio Violante,[1] Stefano Mattioli,[1] Eero Pukkala[11,12]

Cumulative exposure to asbestos and risk of intrahepatic cholangiocarcinoma. Logistic regression (matching variables: year of birth, gender, country) adjusted by printing industry work

Lag period	Cases N=1,458	Controls N=6,773	OR	(95%CI)[a]	P trend	BIC
No lag					0.004	5036.3
0 f/ml * years	1,171	5,548	1.0	(Ref.)		
0.1–1.1 f/ml * years	144	641	1.2	(1.0–1.4)		
1.2–14.9 f/ml * years	109	480	1.2	(1.0–1.5)		
≥15.0 f/ml * years	34	104	1.7	(1.1–2.6)		
20-year lag					0.003	5035.4
0 f/ml * years	1,196	5,663	1.0	(Ref.)		
0.1–1.1 f/ml * years	133	586	1.2	(1.0–1.5)		
1.2–14.9 f/ml * years	110	477	1.2	(1.0–1.5)		
≥15.0 f/ml * years	19	47	2.1	(1.2–3.7)		

IARC Monographs V111, Fluoro-edinite

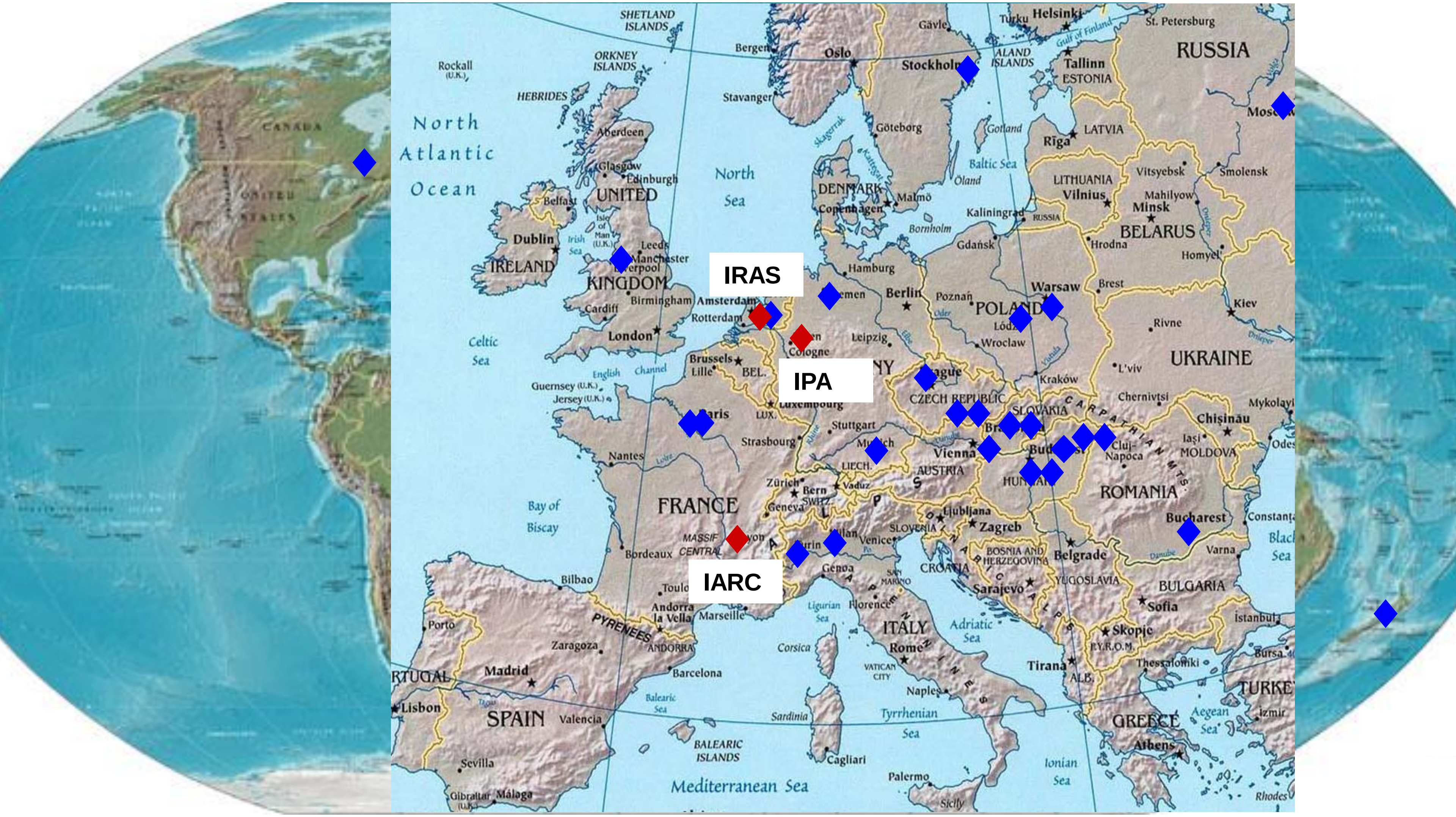
- Fluoro-edenite fibrous amphibole first identified around Etna volcano, Biancavilla, Italy; similar mineral reported from the Kimpo volcano in Japan.
- Unpaved roads made from local quarry products from Biancavilla, since the 1950s,
- Several surveillance studies reported excess of mesothelioma in region of Biancavilla (Bruno et al., 2014).
- Rate ratios for mesothelioma large & stable,
- Excess similar in men and women, most prominent in young adults, suggesting environmental cause.
- Increased incidences of mesotheliomas observed in male and female rats given fibrous fluoro-edenite by i.p. & i. pl. injection (Belpoggi et al., 2011).
- Fluoro-edenite classified as *carcinogenic to humans* (Group 1)

Silica Group 1 Human Carcinogen, V68, 1997

- Among silicotics, consistent excess lung cancer risk across countries, industries and time periods
- Sufficient evidence of carcinogenicity in animals for quartz
- Mechanistic data: most genotoxicity studies negative; oxidative stress , inflammatory response, carcinogenicity may depend on inherent characteristics of the crystalline silica, or external factors affecting its biological activity
- Vol. 100C IARC WG reaffirmed carcinogenicity of crystalline silica dust. Increased risk of lung cancer observed across various industries.

SYNERGY

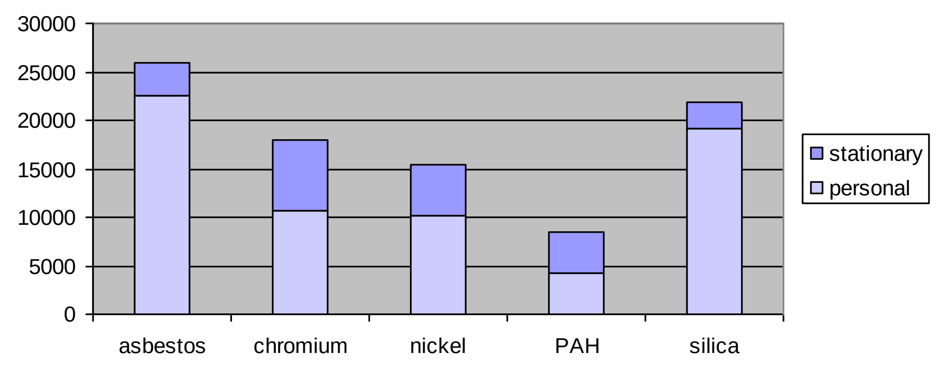
Joint effects of occupational lung carcinogens and smoking



SYNERGY

- 11 case-control studies, Europe, North America, NZ
- 17,021 cases and 20,885 controls.
- 20% women, 80% population controls
- Detailed smoking information
- ~1000 never smoking lung cancer cases
- Complete occupational history (ISCO-68, ISIC-71)
- Quantitative exposure assessment based on various national and industry-specific exposure databases, currently asbestos, PAHs, Cr, Ni, silica;

ExpoSYN includes
>300,000 data points



SYNERGY: Diesel engine exhaust

Cumulative DME exposure and lung cancer risk

Cumulative DME exposure ∑(level^2 * duration)	**Cases**	**Controls**	**OR1**	**95% CI**	**OR2**	**95% CI**
Never	7676	10320	1.00	Reference cat.	1.00	Reference cat.
<6	1270	1514	0.92	0.78 – 1.08	0.88	0.74 – 1.03
6-17.33	1325	1499	1.00	0.88 – 1.12	0.92	0.82 – 1.04
17.34-34.5	1441	1502	0.99	0.85 – 1.15	0.91	0.79 – 1.05
>34.5	1594	1450	1.27	1.14 – 1.41	1.14	1.03 – 1.26
Test for trend, p-value			*0.001*		*0.070*	
Trend among exposed, p-value			*0.000*		*0.002*	
>34.5, never smokers	*47*	*314*	*1,27*	*0.90 - 1.79*	*1.14*	*0.81 - 1.62*
>34.5, never List A job	*1449*	*1337*	*1.35*	*1.23 - 1.48*	*1.21*	*1.10 - 1.33*
>34.5, women	*35*	*45*	*1.61*	*0.98 - 2.65*	*1.41*	*0.86 - 2.32*

Random effect model based on study specific results
OR1 adjusted for age, sex, smoking pack years, time since quitting smoking, ever employed in "List A" job
OR2 in addition adjusted for education

Diesel engine exhaust & lung cancer, Vol 105

- In a large US miners study diesel engine exhaust was quantified via estimated elemental carbon as a proxy of exposure
- Cohort and nested case–control analyses adjusted for tobacco smoking showed positive trends in lung cancer risk with increasing exposure to diesel exhaust, with 2–3-fold increased risk in the highest categories of cumulative or average exposure. (Attfield et al 2012, Silverman et al 2012).
- In US railroad workers exposed to diesel exhaust a 40% increased risk for lung cancer was observed.
- A large cohort study in the US trucking industry reported a 15–40% increased lung cancer risk
- Findings of above cohort studies were supported by those in other occupational groups and by case–control studies including various occupations involving exposure to diesel-engine exhaust.

Diesel engine exhaust, IARC Vol 105 Overall Evaluation

- There is sufficient evidence for the carcinogenicity in humans of diesel engine exhaust. Diesel engine exhaust causes lung cancer. Also, a positive association between diesel engine exhaust and bladder cancer has been observed.
- There is sufficient evidence for the carcinogenicity in experimental animals of whole diesel engine exhaust.

Overall evaluation

- Diesel engine exhaust is carcinogenic to humans (Group 1).

Cholangiocarcinoma among workers in the printing industry

- 16 cases of intrahepatic or extrahepatic cholangiocarcinoma among male (former) employees in a printing plant (around 70 workers) in Osaka, Japan
- Claim for compensation as occupational cancer, 3/2012 - 2/2013.
- Age range of 16 cases: 20 to 49 years
  - no chronic biliary inflammation such as primary cirrhotic cholangitis, intrahepatic cholelithiasis and liver fluke infection,
  - no chronic hepatitis B nor C
  - no malfusion of pancreaticobiliary ducts.
- SIR for biliary tract cancer ~1200 (95%CI 714-1963)
- Kumagai et al, Short report published in OEM-online 3/2013
- Suspected chemicals: 1,2-dichloropropane & dichloromethane

The NOCCA study

Including:

- all subjects aged 30–64 years
- occupational information from 1960, 1970, 1980/1981, and/or 1990 censuses
- in Finland, Iceland, Norway, and Sweden, (Denmark not included in present study)
- still alive and living in the respective countries on 1st January in the year following the census
- divided into 53 broad occupational groups

Follow-up:

- from 1st January of the year after the first available census
- through emigration, death, or to 31st December of the following years: in Finland 2005, in Iceland 2004, in Norway 2003, and in Sweden 2005

NOCCA Results, men & women

	Liver		ICC		ECC	
	Obs	**SIR**	**Obs**	**SIR**	**Obs**	**SIR**
Men						
Typographers	90	1.18 (0.95-1.46)	11	2.01 (1.00-3.60)	34	1.09 (0.75-1.52)
Printers	25	2.22 (1.44-3.28)	6	3.54 (1.30-7.70)	9	1.37 (0.63-2.59)
Lithographers	8	2.38 (1.03-4.70)	2	3.91 (0.47-14.1)	[2.02][a]	0 (0.00-1.83)
Bookbinders	15	1.37 (0.77-2.27)	1	1.17 (0.03-6.54)	7	1.41 (0.57-2.90)
Other occupations	4	1.19 (0.33-3.06)	1	2.15 (0.05-12.0)	3	1.48 (0.30-4.32)
All printers & related	142	1.35 (1.14-1.60)	21	2.34 (1.45-3.57)	53	1.13 (0.85-1.48)
Women						
Typographers	6	1.22 (0.45-2.65)	3	3.14 (0.65-9.17)	9	1.12 (0.51-2.14)
Printers	2	0.55 (0.07-1.98)	1	1.38 (0.03-7.68)	5	0.78 (0.25-1.83)
Lithographers	2	5.03 (0.61-18.2)	1	10.34 (0.26-57.6)	[0.68][a]	0 (0.00-5.36)
Bookbinders	18	1.35 (0.80-2.14)	1	0.50 (0.01-2.81)	19	0.82 (0.49-1.27)
Other occupations	4	2.67 (0.73-6.84)	2	5.93 (0.72-21.4)	2	0.75 (0.09-2.70)
All printers & related	32	1.35 (0.92-1.90)	8	1.95 (0.84-3.85)	35	0.85 (0.59-1.19)

a= expected number

1,2-Dichloropropane, Vol 110

- Sufficient evidence for carcinogenicity in experimental animals, with malignant lung and hepatocellular tumours observed in exposed mice.
- Most of the WG concluded that 1,2-DCP was the causative agent responsible for the large excess of cholangiocarcinoma in the exposed workers.
- A minority concluded that the association between 1,2-DCP and cholangiocarcinoma was credible, but the role of other agents, mainly DCM, could not be separated with complete confidence.
- 1,2-DCP was classified as carcinogenic to humans (Group 1), on the basis of sufficient evidence in humans that exposure to 1,2- DCP causes cholangiocarcinoma.

Welding, IARC Monographs Vol 118

- Increased lung cancer risk was associated with welding in the majority of studies
    - >20 case-control, >20 cohorts, some overlapping, several of high-quality
    - Increased risks were observed regardless of welding technique, study design, occupational setting, geographic region, time period, adjustment for tobacco smoking and asbestos exposure
- Exposure-response associations were observed in several studies using various metrics (e.g cumulative exposure, duration of employment)

Lung Cancer Risk Among Workers in Welding-Related Occupations, Synergy Project

Occupation	No. of Controls	No. of Cases	OR[a] (Model 1)	OR[b] (Model 2)	95% CI (Model 2)
All subjects					
Reference group[d]	16,031	12,921	1.00	1.00	Referent
Welders					
Ever	427	568	1.69	1.45	1.25, 1.68
Longest-held occupation	172	246	1.78	1.48	1.19, 1.86
Occasional welding occupations					
Ever	1,930	1,994	1.27	1.18	1.10, 1.28
Longest-held occupation	697	746	1.37	1.31	1.16, 1.48
Never employed in a List A job[e]					
Never worked in welding-related occupations	14,765	11,323	1.00	1.00	Referent
Welders					
Ever	314	394	1.70	1.46	1.23, 1.74
Longest-held occupation	129	186	1.92	1.63	1.26, 2.11

Kendzia et al, AJE,2013

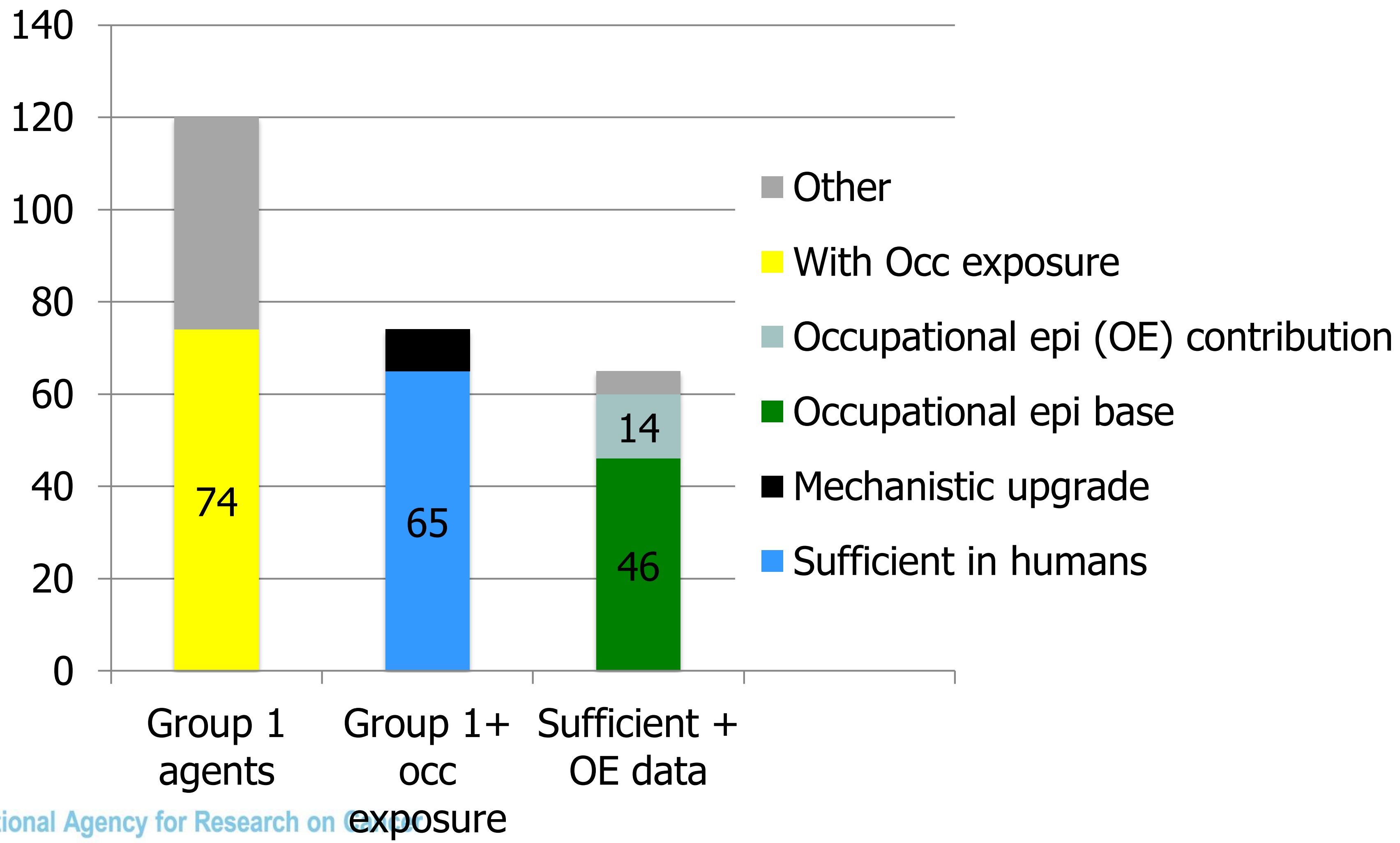
Meta-analysis of lung cancer in welders

Analyses	N	I^2	RR (95% CI)
Overall	**37**	**54.6%**	**1.43 (1.31-1.55)**
Cohort	**22**	**26.4%**	**1.29 (1.20-1.39)**
Population-based	6	59.7%	1.27 (1.12-1.44)
Industrial	16	6.7%	1.32 (1.20-1.45)
Case-control	**15**	**44.1%**	**1.87 (1.53-2.29)**
Hospital-based	8	0.0%	1.84 (1.36-2.49)
Population-based	5	13.9%	2.03 (1.61-2.57)
Mixed	2	70.8%	1.92 (0.91-4.08)
Major Confounders			
Smoking and asbestos	8	41.2%	1.17 (1.04-1.38)
Asbestos exposure	11	52.7%	1.22 (1.09-1.32)
Smoking	20	61%	1.34 (1.15-1.55)
Pack/year	8	65.9. %	1.46 (1.05-2.02)

Counting occupational carcinogens

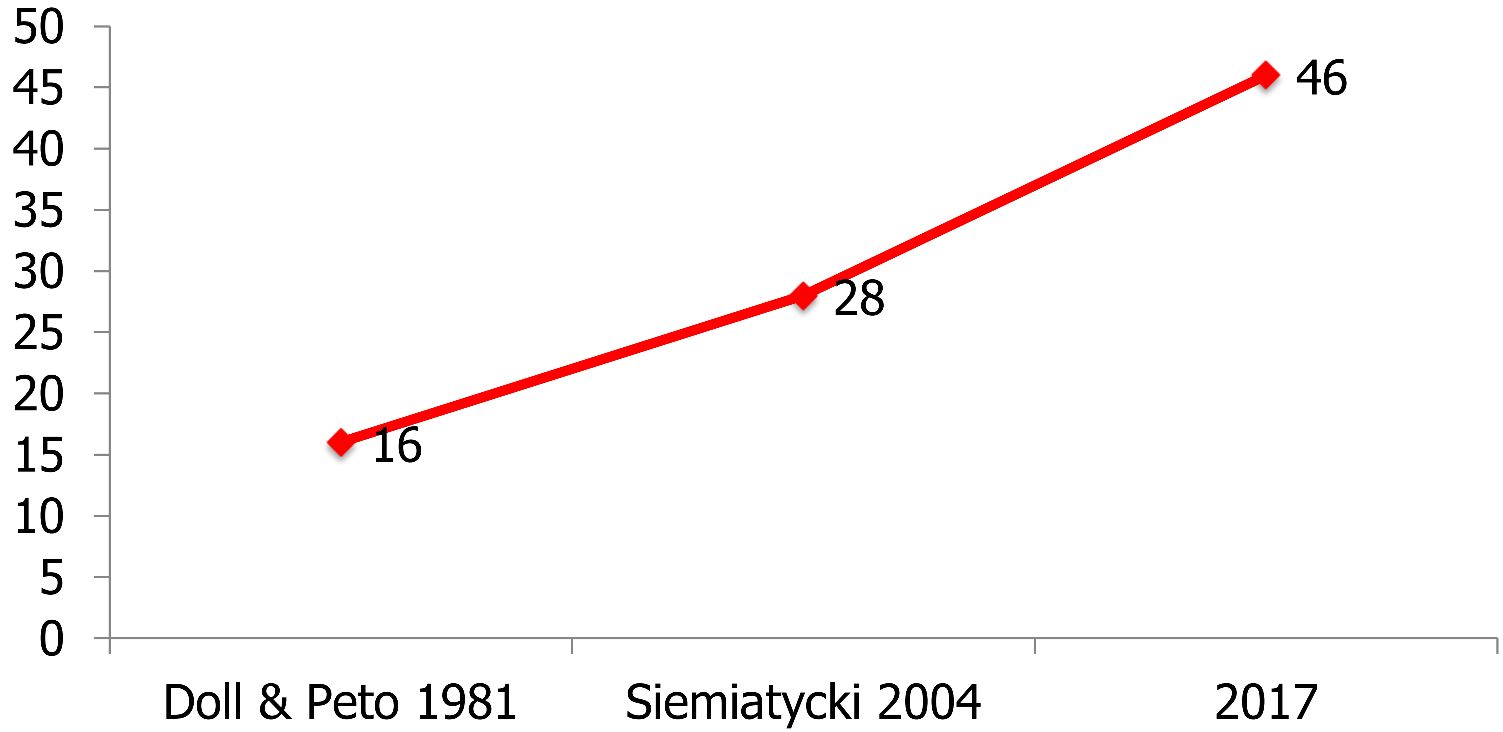
- An occupational carcinogen can be defined as:
  - An IARC Group 1 agent with sufficient evidence in humans
  - and occupational exposure documented in the pertinent Monograph
  - and evaluation based on data from occupational studies

Counting occupational carcinogens



Significant progress

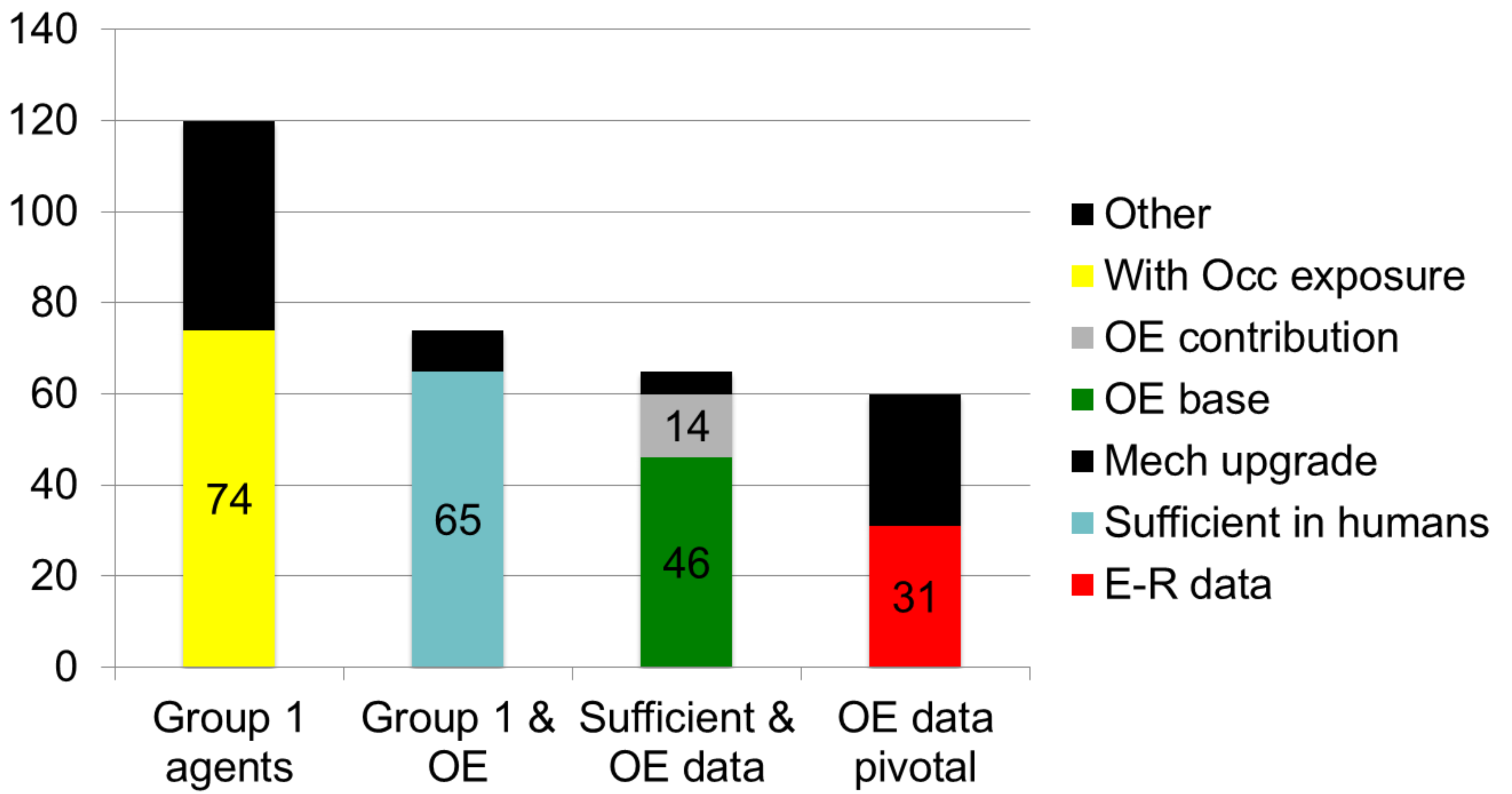
The number of recognized occupational carcinogens is one measure of how much progress has been made:



Yet more work to be done

- Important progress, but…
- More than 80,000 chemicals used in industry
- And there are other kinds of exposures, e.g.
  - Metals
  - Fibres
  - Work organization (shift work, sedentary work)
- Most agents have never been evaluated…
- And human evidence is inadequate for most that have been evaluated

Epidemiologic data for occupational carcinogen risk assessment



Features of studies that are likely to contribute

- Cohort & case-control studies
- Focused on the exposure of interest
- Clear presentation of methods & results
- High-quality exposure assessment
  - Quantitative exposure data
- High-quality analysis
  - Control of important confounders
  - Consideration of latency
  - Internal comparisons
  - Exposure-response assessment

IARC Workshop: Defining ‘Shift Work’ for epidemiological Studies of Cancer

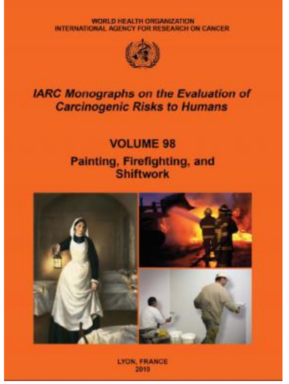
Working time	Workhours/week
Night work	At least 3 hrs of work between midnight and 5 am
Duration	Years employed in non-day shift work
Intensity	Number of non-day shifts per month/year
Cumulative exp.	Duration times intensity over the work history
Permanent shift	# consecutive days of night work, followed by # days off
Rotating type	Continuous (365 days/year) or dis-continuous
Direction of rotation	Forward (morning → afternoon/evening → night) backward (afternoon/evening → morning → night)
Rate of rotation	Daily change, 2-3-4 day change, weekly, etc.
Morning shift	# consecutive days of early morning shift (before 6 am)
Start/end time	Displacement from solar day, duration of the working hours
Rest after shift	Number of rest-days after night shifts
Jetlag	No of time zones crossed; eastward vs. westward
Sleep	Sleep duration &
Light at night	During sleep peri
Characteristics of the individual	Diurnal type (mor

Considerations of circadian impact for defining ‘shift work’ in cancer studies: IARC Working Group Report

Richard G Stevens,[1] Johnni Hansen,[2] Giovanni Costa,[3] Erhard Haus,[4] Timo Kauppinen,[5] Kristan J Aronson,[6] Gemma Castaño-Vinyals,[7] Scott Davis,[8] Monique H W Frings-Dresen,[9] Lin Fritschi,[10] Manolis Kogevinas,[11] Kazutaka Kogi,[12] Jenny-Anne Lie,[13] Arne Lowden,[14] Beata Peplonska,[15] Beate Pesch,[16] Eero Pukkala,[17] Eva Schernhammer,[18] Ruth C Travis,[19] Roel Vermeulen,[20] Tongzhang Zheng,[21] Vincent Cogliano,[22] Kurt Straif[22]

World Health Organization

Shiftwork and circadian disruption (Vol 98)



Cancer in Humans

6 of 8 studies from various geographical regions noted an increased risk of **breast cancer** among shift-workers

Cohort studies of *nurses* (3) and radio and telegraph operators (1) engaged in shift-work at night
Case-control study (1) and national linkage study (1) of occupations with high prevalence of shift-work.

Limitations of the studies
Inconsistent definition of shift-work
Limited number of studies
Studies often focused on single profession

Shiftwork and circadian disruption (Vol 98)

Cancer in humans

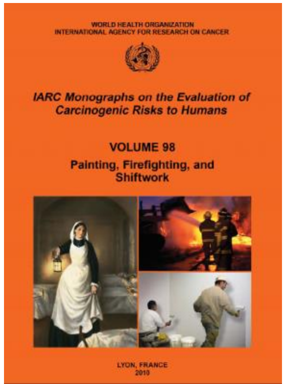
- There is *limited evidence* in humans for the carcinogenicity of shiftwork that involves night work.

Cancer in experimental animals

- There is *sufficient evidence* in experimental animals for the carcinogenicity of light during the daily dark period (biological night).

Overall evaluation

- Shiftwork that involves circadian disruption is *probably carcinogenic to humans (Group 2A)*.



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11 years later…

PubMed: Almost 100 analytical studies on shiftwork and cancer, more than half on breast cancer

Many more positive studies, but increased complexity

- Exposure, type of shiftwork, duration, age at exposure
- Potential confounders and/or effect modifiers, chronotype, reproductive history, obesity, alcohol consumptions, vitamin D, societal context of shiftwork
- Outcome, pre-/post-menopausal breast cancer, hormone-receptor status
- Other cancers, prostate, colon, …

AG on Future Priorities: Shiftwork recommended as "high priority"

Coming up soon

Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (25–27 March 2019)

Call for Experts (closing date 12 August 2018)
Call for Nominations of Agents (closing date 23 December 2018)
Request for Observer Status (closing date 24 October 2018)
WHO Declaration of Interests for this meeting
Code of Conduct
Confidentiality Undertaking

Meeting 124: Shift Work That Involves Circadian Disruption (4–11 June 2019)

Preliminary List of Agents
Call for Data (closing date 6 May 2019)
Call for Experts (closing date 16 October 2018)
Request for Observer Status (closing date 15 January 2019)
WHO Declaration of Interests for this volume
Code of Conduct
Confidentiality Undertaking
Instructions for Authors

Joint IARC, NIOSH-NORA, ACS, US NIEHS and NCI Workshop

Review

Research Recommendations for Selected IARC-Classified Agents

Elizabeth M. Ward,[1] Paul A. Schulte,[2] Kurt Straif,[3] Nancy B. Hopf,[4] Jane C. Caldwell,[5] Tania Carreón,[2] David M. DeMarini,[5] Bruce A. Fowler,[6] Bernard D. Goldstein,[7] Kari Hemminki,[8] Cynthia J. Hines,[2] Kirsti Husgafvel Pursiainen,[9] Eileen Kuempel,[2] Joellen Lewtas,[10] Ruth M. Lunn,[11] Elsebeth Lynge,[12] Damien M. McElvenny,[13] Hartwig Muhle,[14] Tamie Nakajima,[15] Larry W. Robertson,[16] Nathaniel Rothman,[17] Avima M. Ruder,[2] Mary K. Schubauer-Berigan,[2] Jack Siemiatycki,[18] Debra Silverman,[17] Martyn T. Smith,[19] Tom Sorahan,[20] Kyle Steenland,[21] Richard G. Stevens,[22] Paolo Vineis,[23] Shelia Hoar Zahm,[17] Lauren Zeise,[24] and Vincent J. Cogliano[3]

- Acetaldehyde*
- Atrazine
- Carbon black
- Chloroform
- Cobalt metal with tungsten carbide
- Dichloromethane*
- Diesel engine exhaust
- Di-2-ethylhexyl phthalate*
- Formaldehyde
- Indium phosphide
- Lead and lead compounds
- Polychlorinated biphenyls (PCB)
- Propylene oxide
- Refractory ceramic fibers
- Shiftwork that involves nightwork
- Styrene (Vol 121, 3/2018)
- Tetrachloroethylene*
- Titanium dioxide
- Trichloroethylene*
- Welding fumes

International Agency for Research on Cancer

World Health Organization

Future priorities for the IARC Monographs

News

An Advisory Group of 21 scientists from 13 countries met in April, 2014, to recommend topics for assessment in 2015–19 and to discuss strategic matters for the International Agency for Research on Cancer (IARC) Monographs programme. IARC periodically convenes such advisory groups to ensure that the Monographs reflect the current state of priorities for public health.

The Advisory Group assessed the responses to a call for nominations on the IARC website and recommended a broad range of agents and exposures for assessment with high or medium

Lancet Oncol 2014

Published Online
May 6, 2014

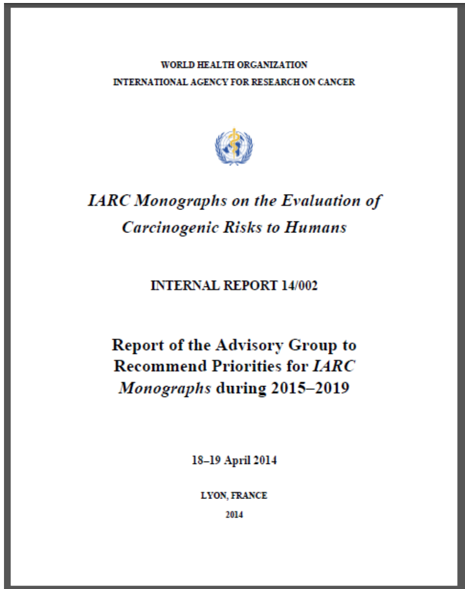
Panel: Agents recommended by the IARC Advisory Group for assessment

High priority

Acrylamide, furan, and 5-(hydroxymethyl) furfural—commonly found in cooked foods; cancer bioassay data are available

Aspartame and sucralose—widespread use and concern about their potential carcinogenicity

- Carbon nanotubes
- Sedentary work
- Tin compounds
- Pesticides
- Shift work
- Metal-working fluids
- Hydrazine
- Job stress
- Lead
- Coal dust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INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

INTERNAL REPORT 14/002

Report of the Advisory Group to Recommend Priorities for *IARC Monographs* during 2015–2019

18–19 April 2014

LYON, FRANCE
2014

International Agency for Research on Cancer

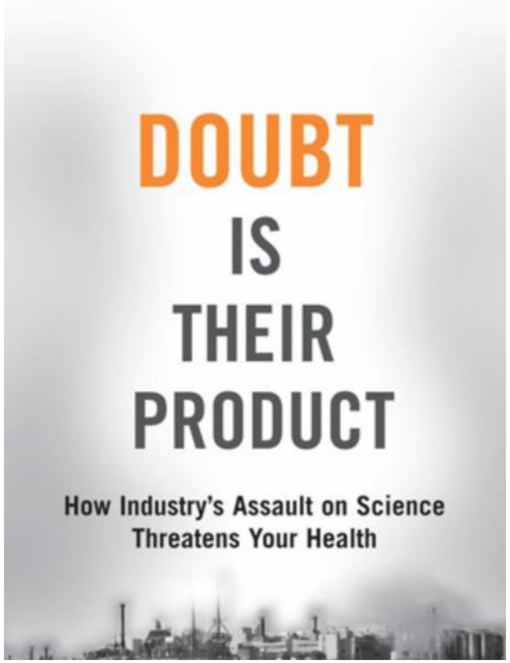
World Health Organization

Interference from Vested Interests

- There is a long history of interference with science of occupational carcinogens
- Asbestos is the best-known example
- Following strategies developed by big tobacco
  - Creating doubt
  - Attacking science
  - Intimidating scientists
  - Lobbying policy-makers
  - Delaying action

News

Industry group "threatens" journals to delay publications



Assessment of exposure to occupational carcinogens

National registries of exposed workers (e.g. the Finnish Register of Workers Exposed to Carcinogens (ASA Register) or the German ODIN Register)

Exposure measurement databases: (with description of workplace determinants), MEGA database (Germany), or COLCHIC database (France)

Exposure information systems: FINJEM, CAREX, and refinements, such as WOODEX, Canadian CAREX; NOCCA
ExpoSYN developed for the SYNERGY project
Problem: not harmonised

The **HazChem@Work database** (EC) aims to collect harmonised data on the workers exposure

OccIDEAS Online app for assessing exposure in workplaces,
Questionnaires for over 50 jobs/industries
Questions on the tasks which are the determinants of exposure
Questions on use of control measures

Australian Workplace Exposure Studies (AWES), Cross-sectional telephone survey of 5000 Australian workers

Prevention of occupational cancer

- Since 1971, the IARC Monographs identified 120 human carcinogens, in 40 – 50% occupational studies played pivotal role
- Still identifying new occupational carcinogens, incl. diesel engine exhaust, welding fumes,
  16 biliary tract cancers in ca. 70 young workers in a printing plant in Japan
- > 80.000 chemicals in workplace, most never tested –
  Need increased funding for prevention research,
- Strong vested interests –
  Need transparent and independent evaluation of the evidence
- Need stronger focus on preventive actions, including primary and secondary prevention
- Need better data to show the economic impact of cost of inaction
- Need better data on global exposure to occupational carcinogens,
  - for burden estimates - joint WHO/ILO Burden of occupational diseases
  - for benchmarking countries and to document our success –

"No Time to Lose"

- From High-level event at WCOSH, Singapore 2017 to **ICOH 2018 Dublin**

XXI WORLD CONGRESS ON SAFETY & HEALTH AT WORK 2017

DUBLIN - IRELAND ICOH 2018 29 APRIL - 4 MAY 2018 gràcies

Acknowledgements

The *IARC Monographs* are supported by grants from

- **U.S. National Cancer Institute (since 1982)**
- **EC, DG Employment, Social Affairs and Inclusion (since 1986)**
- **U.S. National Institute of Environmental Health Sciences (since 1992)**

International Agency for Research on Cancer

World Health Organization

Dankeschön

Joint IARC, NIOSH-NORA, ACS, US NIEHS and NCI Workshop

Review

Research Recommendations for Selected IARC-Classified Agents

Elizabeth M. Ward,[1] Paul A. Schulte,[2] Kurt Straif,[3] Nancy B. Hopf,[4] Jane C. Caldwell,[5] Tania Carreón,[2] David M. DeMarini,[5] Bruce A. Fowler,[6] Bernard D. Goldstein,[7] Kari Hemminki,[8] Cynthia J. Hines,[2] Kirsti Husgafvel Pursiainen,[9] Eileen Kuempel,[2] Joellen Lewtas,[10] Ruth M. Lunn,[11] Elsebeth Lynge,[12] Damien M. McElvenny,[13] Hartwig Muhle,[14] Tamie Nakajima,[15] Larry W. Robertson,[16] Nathaniel Rothman,[17] Avima M. Ruder,[2] Mary K. Schubauer-Berigan,[2] Jack Siemiatycki,[18] Debra Silverman,[17] Martyn T. Smith,[19] Tom Sorahan,[20] Kyle Steenland,[21] Richard G. Stevens,[22] Paolo Vineis,[23] Shelia Hoar Zahm,[17] Lauren Zeise,[24] and Vincent J. Cogliano[3]

- Acetaldehyde*
- Atrazine
- Carbon black
- Chloroform
- Cobalt metal with tungsten carbide
- Dichloromethane*
- Diesel engine exhaust
- Di-2-ethylhexyl phthalate*
- Formaldehyde
- Indium phosphide
- Lead and lead compounds
- Polychlorinated biphenyls (PCB)
- Propylene oxide
- Refractory ceramic fibers
- Shiftwork that involves nightwork
- Styrene (Vol 121, 3/2018)
- Tetrachloroethylene*
- Titanium dioxide
- Trichloroethylene*
- Welding fumes

International Agency for Research on Cancer

World Health Organization

A cohort mortality study of lead-exposed workers in the USA, Finland and the UK

Kyle Steenland,[1] Vaughn Barry,[1] Ahti Anttila,[2] Markku Sallmén,[3] Damien McElvenny,[4] AC Todd,[5] Kurt Straif[6]

- Mortality among 88 000 workers with data on blood lead levels in three countries, with 14 000 deaths, and a median maximum blood lead of 26 μg/dL.
- Significant($p<0.05$) positive trends were found between blood lead levels and lung cancer, chronic obstructive pulmonary disease (COPD), stroke and heart disease.

Table 4 Categorical and continuous results of mortality by blood lead category for selected cancers*

Cause	Number of deaths by lead category	Lead category, μg/dL	HR†	95% CI	Coefficient for ln max blood lead; p value for test for trend
Lung cancer n=1333	271	20 to <30	1.39	1.19 to 1.64	1.36; p=<0.0001‡
	214	30 to <40	1.54	1.29 to 1.84	
	500	40+	1.78	1.51 to 2.08	

International Agency for Research on Cancer

World Health Organization

Occup Environ Med. 2017 Nov;74(11):785-791

Occupational cancer: AF

"Occupational cancer, moreover, tends to be concentrated among relatively small groups of people among whom the risk of developing the disease may be quite large, and

such risks can usually be reduced or even eliminated, once they have been identified.

The detection of occupational hazards should therefore have a higher priority in any program of cancer prevention than their proportional importance might suggest."

Doll & Peto, 1981

Occupational cancer: AF

- Very divergent estimates <1% to 40%
  - Prevalence of risk factor & exposure level
  - Strength of evidence for causal association
- Doll & Peto 1981 4% of US cancers
- Simonato et al, 1988: 0.6 – 40% of lung cancers
- Leigh et al, 1997 „WHO Global Burden of Disease“ direct & indirect methods: 6-10%
- Nurminen & Karjalainen, 2001: 8% of cancers in Finns
- Steenland et al 2003: 2.4 – 4.8% of US cancers
- Rushton et al 2008, UK....

UK HSE Burden of occupational cancer

Occupational AF for cancers of lung, bladder, non-melan. skin, sinonasal cancers, leukaemia, mesothelioma:

All cancer deaths
- Group 1,   3.6% of (6% in men)
- Group 1 & 2A,   4.9% in total (8.0% in men)

Lung cancer
- Group 1,   16.5%
- Group 1 & 2A   21.6%

Lung cancer almost 70% of occupational cancers,

UK Burden of Occupational Cancer

All IARC Group 1 and 2A carcinogens with "sufficient" or "limited" evidence for specific site in humans

Cancer Site	AF (%)			Deaths (2005)			Registrations (2004)		
	M	F	Total	M	F	Total	M	F	Total
Mesothelioma	97.0	82.5	95.0	1699	238	1937	1699	238	1937
Sinonasal	46.0	20.1	34.4	29	10	40	102	32	134
Lung	22.2	5.5	15.2	4236	757	4993	4877	850	5727
Nasopharynx	11.1	2.5	8.3	7	1	8	16	1	17
Bladder	7.2	1.9	5.4	218	31	248	503	55	558
Breast		4.6	4.6		555	555		1971	1971
NMSC	7.0	1.2	4.6	20	2	23	2542	367	2909
Larynx	2.9	1.6	2.6	18	3	20	51	6	56
Oesophagus	3.3	1.1	2.5	157	28	185	160	29	189
STS	3.4	1.1	2.3	12	4	16	25	6	30
Stomach	3.0	0.3	2.0	102	6	108	150	9	159
NHL	2.1	1.1	1.7	49	23	71	110	51	161
Melanoma (eye)	2.9	0.4	1.6	1	0	1	6	1	7
Total	8.45	2.35	5.51	6588	1702	8290	10406	3703	14109

World Health Organization

Rushton et al, Occ Env Med; 2008. Straif, Occ Env Med, 2008

Counting occupational carcinogens

- An occupational carcinogen can be defined as:
  - An IARC Group 1 agent with sufficient evidence in humans
  - and occupational exposure documented in the pertinent Monograph
  - and evaluation based on data from occupational studies
- As of 2017, 46 agents meet this definition
- Occupational data contributed to the evaluation for another 14 agents
- So 46-60 recognized occupational carcinogens

Identifying Occupational Carcinogens

- Studies of workers have had a major role in identifying human carcinogens
- About 40% of the 120 *IARC Group 1* carcinogens were identified in occupational studies with sufficient evidence in humans
- Over 60% of *Group 1* agents have documented occupational exposures

1,2-Dichloropropane, Vol 110

- Most important human evidence comes from studies of workers in a small offset printing plant in Osaka, Japan, where a very high risk of cholangiocarcinoma was reported.
- Additional cases were later identified from several other printing plants in Japan.
- Workers were exposed to more than 20 different chemicals, but exposure to 1,2-DCP was common to all except one of the 24 patients with cholangiocarcinoma, and six of the patients had no known exposure to dichloromethane.
- The WG considered the rarity of cholangiocarcinoma, the very high relative risk, the young ages of the patients, the absence of non-occupational risk factors, and the intensity of the exposure as indications that the excess of cholangio-carcinoma was unlikely to be the result of chance, bias, or nonoccupational confounding.

Why so much more to do?

- Lack of epidemiologic data
- Insufficient support for occupational health research
- Inadequate study quality
- Interference from vested interests

Lack of Epidemiologic Data

- Many agents with occupational exposures have never been studied
- Epidemiologic studies are expensive and time consuming!
- Access to workers and workplaces is important
- There are not enough researchers, especially in low- and middle-income countries

Insufficient Support for Research

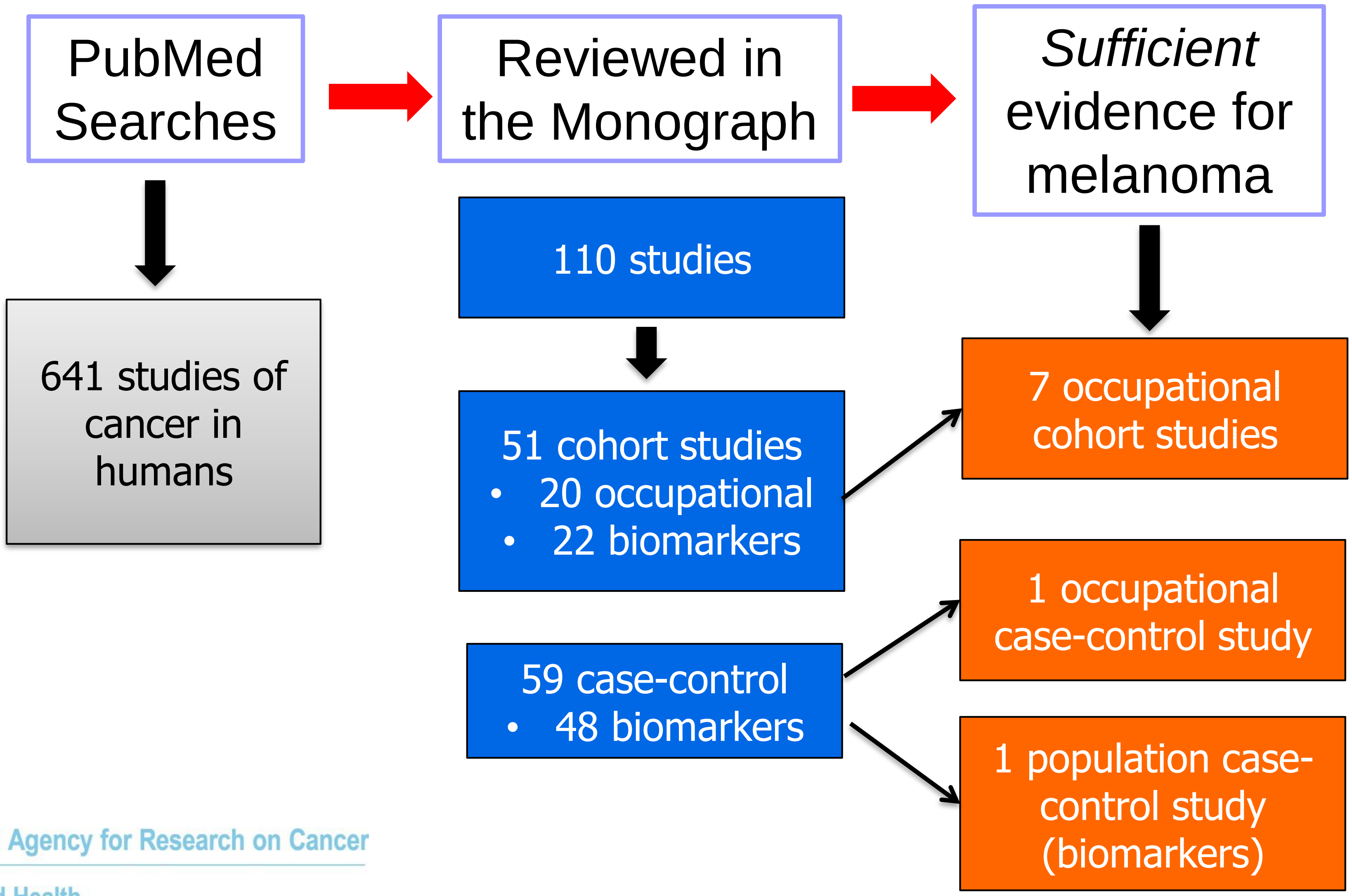
- Declining exposures in high-income countries
  - "We solved that problem…"
- Changing priorities
  - Environment, infectious diseases, genetics
- Reduced power of labour
- Changing attitudes about science

“More research is needed…”

- We have made important progress…
- but there is more work to do!
- More, better epidemiologic studies
- A new generation of researchers to train
- Especially in middle-income countries
- Innovative research approaches
- Courage and perseverance

Study quality: how many studies contribute?

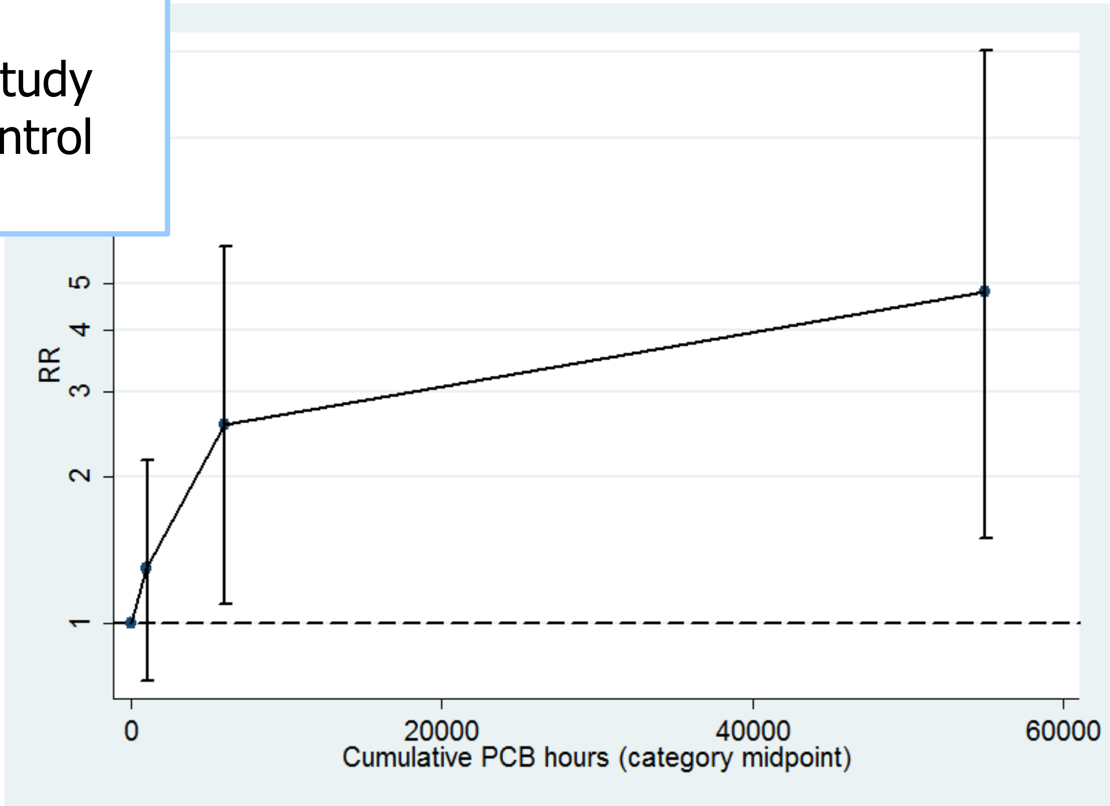
PCBs, IARC Monographs v. 107



PCBs & Malignant Melanoma
Sufficient Evidence

<u>Influential Studies</u>

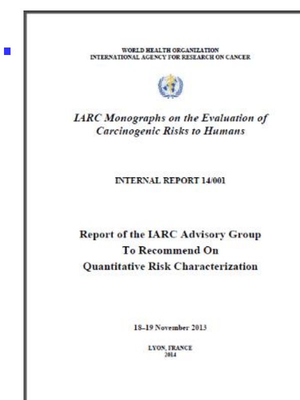
- 4 transformer mfg & repair cohorts
- 3 electric power cohorts
- 1 occupational case-control study
- 1 general population case-control study



Loomis et al., OEM 1999

IARC Monographs Vol.120, Benzene

- **Preamble**, 2006 and **AG Quantitative Risk Characterisation**, 2013
  A Monograph may undertake to estimate dose–response relationships within the range of the available epidemiological data.
- **Benzene** *causes* ANLL, including AML; *limited evidence* for CLL, MM, NHL, chronic myeloid leukaemia, AML in children and lung cancer.
- *Strong evidence*, including in exposed humans, that benzene is metabolically activated, induces oxidative stress, is genotoxic, is immunosuppressive, and causes haematotoxicity.
- Meta-regression analyses of 6 published occupational cohort studies with suitable data on benzene exposure and AML.
- Exposure–response gradient in human studies for endpoints relevant to key characteristics of carcinogens (e.g. MN, CA).


WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

INTERNAL REPORT 14/001

Report of the IARC Advisory Group To Recommend On Quantitative Risk Characterization

18–19 November 2013

LYON, FRANCE
2014

International Agency for Research on Cancer

World Health Organization

Mendelian Randomisation informing evidence synthesis process

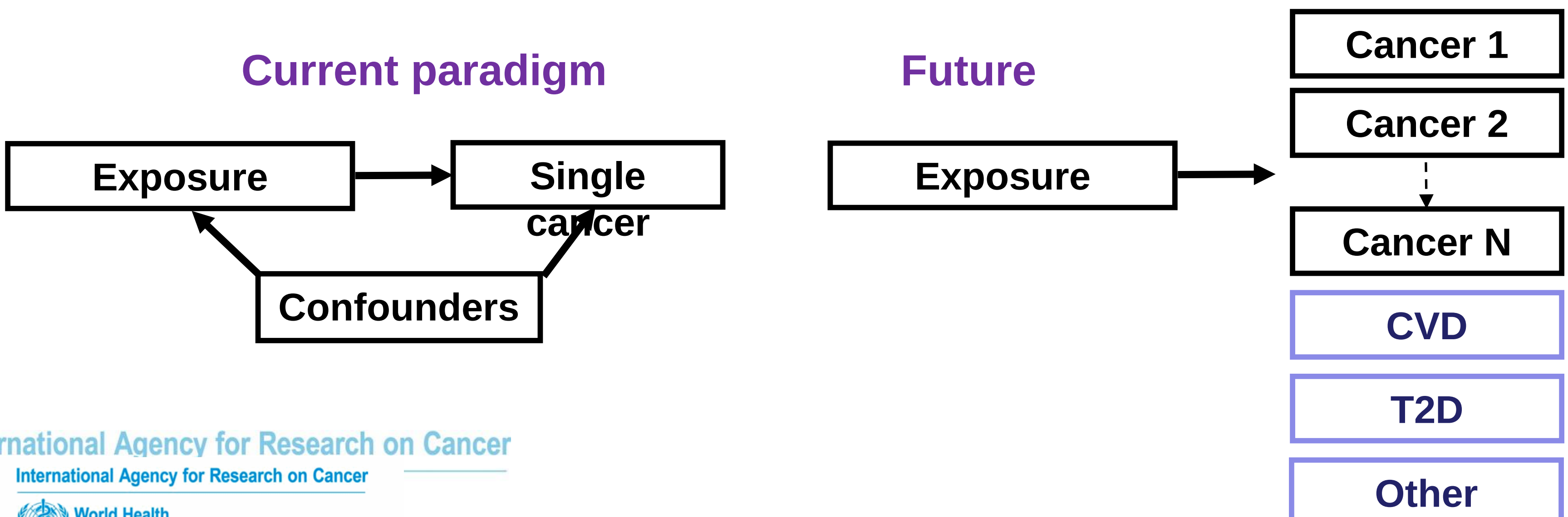
N ENGL J MED 375;8 NEJM.ORG AUGUST 25, 2016

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

Body Fatness and Cancer — Viewpoint of the IARC Working Group

Béatrice Lauby-Secretan, Ph.D., Chiara Scoccianti, Ph.D., Dana Loomis, Ph.D., Yann Grosse, Ph.D., Franca Bianchini, Ph.D., and Kurt Straif, M.P.H., M.D., Ph.D., for the International Agency for Research on Cancer Handbook Working Group



Glyphosate: a case study
IARC evaluation

Cancer in humans (NHL)

Limited evidence

- Studies of real-world exposures (occupational)
- ***Glyphosate formulations*** in different regions at different times

Cancer in animals

Sufficient evidence

- Studies of pure ***glyphosate***
- Rare cancers in valid studies

DNA damage & oxidative stress

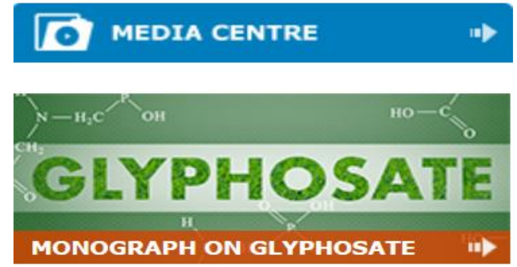
Strong evidence

- Few studies of real-world exposures (communities)
- Experimental studies of pure ***glyphosate***
- Experimental studies of ***glyphosate formulations***

IARC Evaluation, March 2015

Group 2A *Probably carcinogenic to humans*

Glyphosate: a case study
the reaction



- Unprecedented, “Orchestated outcry” from industry
- Demands to Directors of IARC and WHO to withdraw the evaluation
- Lobbying politicians, agencies, WHO & member states
- Paid consultants criticize methods and findings
- Re-evaluation by an industry-funded committee
- Ghost-written scientific papers & press articles
- Legal demands aimed to harrass US scientists
- Intimidating letters to international scientists
- Inquiries by the the US Congress
- Briefing Note for IARC Scientific and Governing Council

http://governance.iarc.fr/ENG/infocouncils.php

WHO's IARC cancer hazard agency: Can it be reformed or should it be abolished?

Alan Boobis & Angelo Moretto & Samuel Cohen | April 18, 2017 | Genetic Literacy Project

PRINTER FRIENDLY

75 2 2

Editor's note: Over four decades, the World Health Organization's International Agency for Research on Cancer (IARC) has assessed 989 substances and activities, ranging from arsenic to red meat to working as a painter to sunlight, and found all but one of them were likely to cause cancer in humans. Ranked among the "Group 1 Carcinogens" are wood dust and Chinese salted fish.

IARC

SECTIONS THE CORNER NATIONAL REVIEW

Who's Getting Money from NIH?

by JULIE KELLY & JEFF STIER April 3, 2017 4:00 AM

@JULIE_KELLY2

A pair of foreign research organizations have gotten numerous grants for work of unclear value.

REUTERS

#SPECIAL REPORTS

JUNE 14, 2017 / 3:27 PM / 2 MONTHS AGO

Special Report: Cancer agency left in the dark over glyphosate evidence

Kate Kelland

Monsanto Spin Doctors '

Scientist In Flawed Reuters Story

06/16/2017 06:09 pm ET | Updated Jun 18, 2017

Le Monde

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LA GUERRE CONTRE LA SCIENCE DU GÉANT DES PESTICIDES

Monsanto Was Its Own Ghostwriter for Some Safety Reviews

n on

The New York Times

Business Day

Monsanto Emails Raise Issue of Influencing Research on Roundup Weed Killer

http://www.lemonde.fr/planete/visuel/2017/06/01/operation-intoxication-les-reseaux-de-monsanto_5136945_3244.html