Objectives of this Workshop

The objectives of this workshop are to gain a better understanding of:

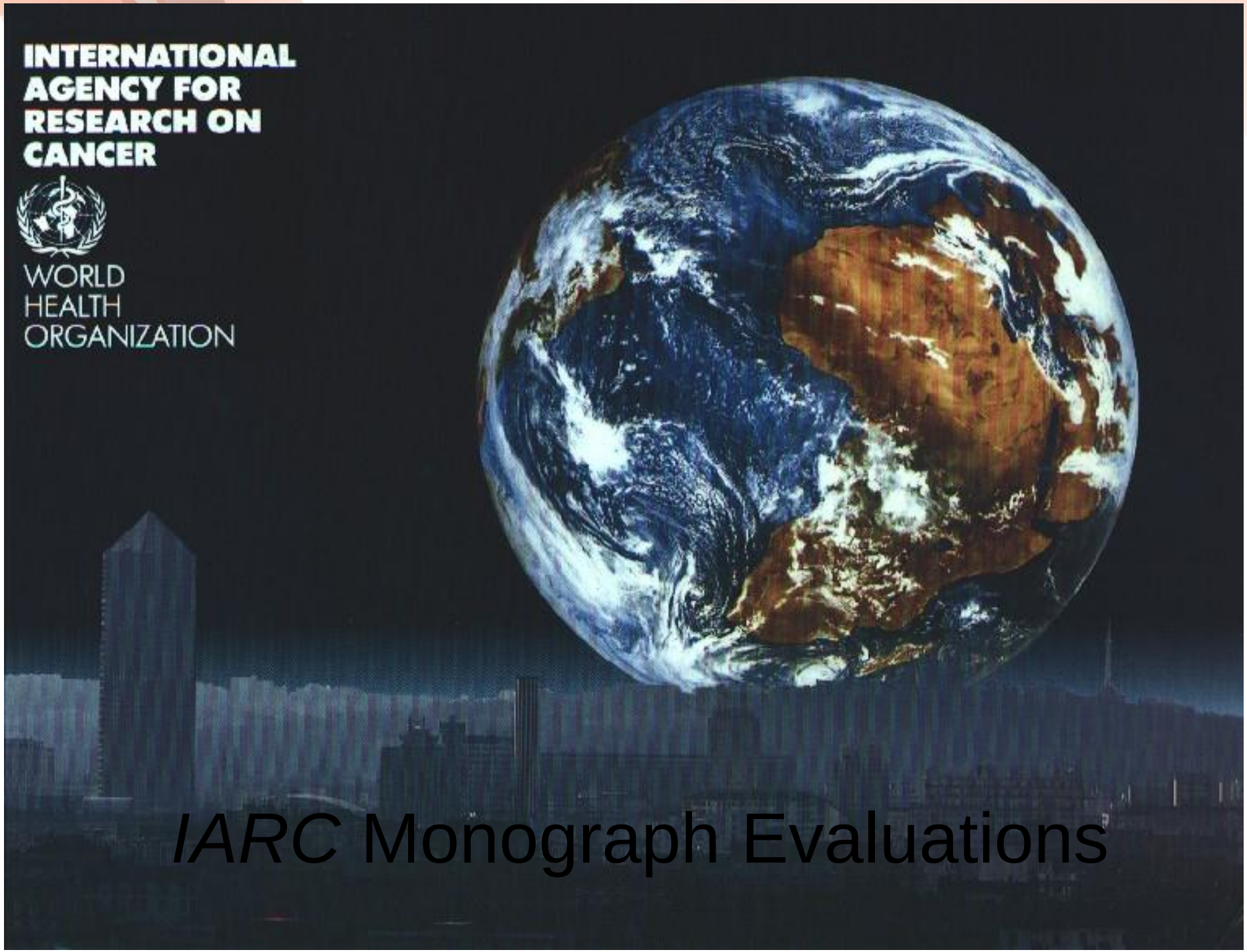
- the process used by IARC to classify carcinogens
- the contribution that data from epidemiologic studies, animal studies, and other experimental studies play in classifying carcinogens
- the role that the classification of carcinogens play in the prevention of cancer

Role of the Classification of Carcinogens in Cancer Prevention

- Helps set priority for other regulatory agencies setting Occupational Exposure Limits or regulating use in Canada (e.g. provincial ministries of labour, PMRA, ...) and internationally (E.U., U.S.,...)
- Triggers Controlled Products Regulations and WHMIS rules regarding labelling and training
- Impacts workers' compensation policy
- Raises awareness
- Encourages voluntary measures to reduce or eliminate exposure

Classification of Carcinogens

- Canada has no independent classification of carcinogens for regulatory or other purposes
- Internationally recognized classifications:
  - International Agency for Research on Cancer (IARC)
  - US National Toxicology Program (NTP)
  - American Conference of Governmental Industrial Hygienists (ACGIH) TLV Committee
  - Other OEL guideline groups (e.g. MAK Committee (Germany) and DECOS (Netherlands))


INTERNATIONAL
AGENCY FOR
RESEARCH ON
CANCER
WORLD
HEALTH
ORGANIZATION
IARC Monograph Evaluations

IARC Monograph Program

- IARC Working Groups evaluate
  - Chemicals
  - Complex mixtures
  - Occupational exposures
  - Physical and biological agents
  - Lifestyle factors
  - Exposure circumstances
- More than 900 agents have been evaluated
- National/international health agencies use *Monographs*
  - As a source of scientific information
  - As scientific support for actions to prevent exposure

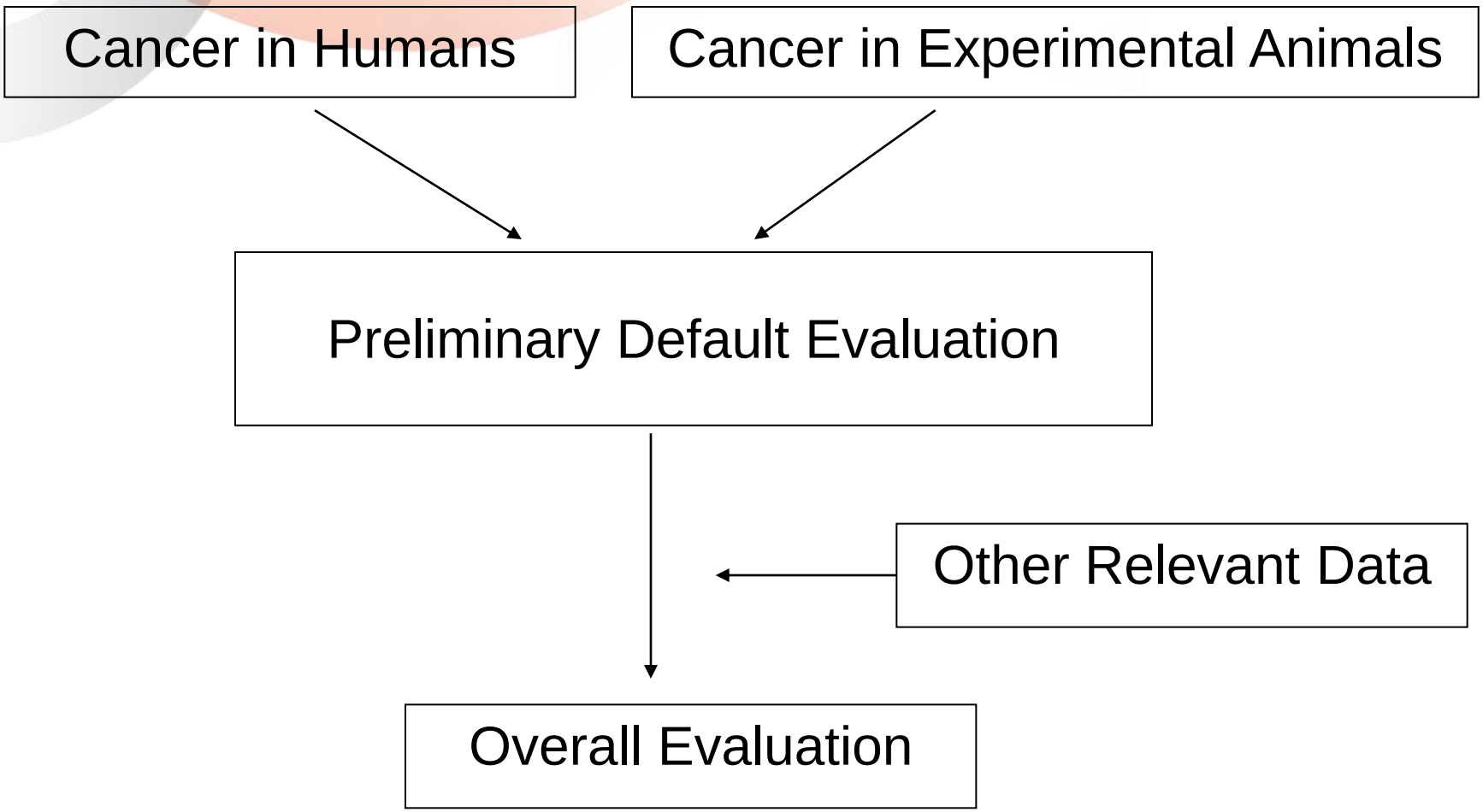
IARC Working Groups

- Generally 20-30 scientists from many countries, invited approximately 1 year in advance
- Public conflict of interest disclosure
- Responsible for complete review of literature
- Four sub-groups
  - Exposure data
  - Studies of cancer in humans (epidemiology)
  - Studies of cancer in experimental animals
  - Mechanisms & other relevant data

Preparing the draft and the meeting

- WG sent results of IARC literature search six months before meeting
- First draft of the first 4 sections of the monograph produced by members prior to meeting
- 8 day meeting at IARC in Lyon, France
  - Attended by WG, invited specialists, representatives, observers, IARC Secretariat
  - First days, meet in sub-group, subgroup evaluations
  - Last days, meet in “plenary” for formal evaluation
- Summary of meeting published in Lancet Oncology
- Full monograph published in paper and PDF

Overview of Process



Evaluating Human Data

☐ *Sufficient Evidence*	Causal relationship established: chance, bias, & confounding ruled out with reasonable confidence
☐ *Limited Evidence*	Causal interpretation credible, but chance, bias, or confounding not ruled out
☐ *Inadequate Evidence*	Studies permit no conclusion about causal association
☐ *Evidence suggesting lack of carcinogenicity*	Several adequate negative studies that cover the full range of human exposure & chance, bias, & confounding ruled out

Quality of the Human Studies

- Studies must be published in the peer-reviewed literature or by a government agency
- Adequate information on the study methods
- Bias: A distortion of the studies results due to how data on disease and exposure was collected or who was included in the study
- Confounding: A distortion of the studies results due to another factor not accounted for
- Chance: The study was too small to detect an effect or provide reliable information

Evaluating Animal Data

☐ *Sufficient Evidence*	Increased incidence of benign & malignant neoplasms in two or more species or independent studies; exceptionally, a single study with unusual incidence, site, type of tumour, or age at onset
☐ *Limited Evidence*	Carcinogenic effect is suggested, but in a single study; or there are questions about adequacy; or neoplasms are benign or may occur spontaneously
☐ *Inadequate Evidence*	Studies permit no conclusion about carcingenic effect
☐ *Evidence suggesting lack of carcinogencity*	

Quality of the Animal Studies

Experimental Conditions

- How clearly was the agent defined
- Was dose monitored adequately
- Were doses, duration of treatment & route of exposure appropriate
- Were there an adequate number of animals, males & females used, & random allocation to groups
- Was duration of observation adequate
- Were the data reported & analyzed adequately

IARC Evaluation of Carcinogens

- Group 1: Carcinogenic in humans
- Group 2A: Probably carcinogenic in humans
- Group 2B: Possibly carcinogenic in humans
- Group 3: Not classifiable, generally inadequate evidence in humans and limited or inadequate in animals.
- Group 4: Evidence of a lack of carcinogenicity in both humans & animals

IARC Evaluation of Carcinogens

- Group 1 (carcinogenic): 107 agents
- Group 2A (probable): 59 Agents
- Group 2B (possible): 267 Agents
- Group 3 (not classifiable): 508 Agents
- Group 4 (probably not): 1 Agent

Preliminary Default Evaluation

Cancer in Humans	Cancer in Experimental animals: *Sufficient*	*Limited*	*Inadequate*
Sufficient	*Group* **1**	*Group* **1**	*Group* **1**
Limited	*Group* **2A**	*Group* **2B** **Exceptionally: Group 2A**	*Group* **2B** **Exceptionally: Group 2A**
Inadequate	*Group* **2B**	*Group* **3**	*Group* **3**

Group 1 *Carcinogenic to Humans*
Group 2A *Probably Carcinogenic to Humans*
Group 2B *Possibly Carcinogenic to Humans*
Group 3 *Not classifiable as to its Carcinogenicity to Humans*
Group 4 *Probably Not Carcinogenic to Humans*

Evaluating Mechanistic/Other Data

How strong is the mechanistic data?

- Has the mechanism been well established?
- Can the steps of the mechanism be described?
- Are results consistent in different experimental systems?
- Has each step been challenged experimentally?

Is the mechanism likely to operate in humans?

- Is there human evidence for each step?
- Could different mechanisms operate in different dose ranges, in humans and experimental animals, or in a susceptible group?

Using Mechanistic Data to Adjust the Overall Evaluation

In some cases

UPGRADE TO GROUP 2A

Strong Evidence* that the carcinogenesis is mediated by a mechanism that also *operates in humans

Cancer in Humans	Cancer in Experimental animals: *Sufficient*	*Limited*	*Inadequate*
Sufficient	*Group* **1**	*Group* **1**	*Group* **1**
Limited	*Group* **2A**	*Group* **2B**/2A	*Group* **2B**/2A
Inadequate	*Group* **2B**	*Group* **3**	***Group* 3**

Carcinogenicity of shift-work, painting, and fire-fighting

Kurt Straif, Robert Baan, Yann Grosse, Béatrice Secretan, Fatiha El Ghissassi, Véronique Bouvard, Andrea Altieri, Lamia Benbrahim-Tallaa, Vincent Cogliano, on behalf of the WHO International Agency for Research on Cancer Monograph Working Group

In October, 2007, 24 scientists from ten countries met at the International Agency for Research on Cancer (IARC), Lyon, France, to assess the carcinogenicity of shift-work, painting, and fire-fighting. These assessments will be published as volume 98 of the IARC Monographs.[1]

About 15–20% of the working population in Europe and the USA is engaged in shift-work that involves nightwork, which is most prevalent (above 30%) in the health-care, industrial manufacturing, mining, transport, communication, leisure, and hospitality sectors. Among the many different patterns of shift-

on tumour development. More than 20 studies investigated the effect of constant light, dim light at night, simulated chronic jet lag, or circadian timing of carcinogens, and most showed a major increase in tumour incidence. No clear effect was seen for light pulses at night or constant darkness. A similar number of studies investigated the effect of reduced nocturnal melatonin concentrations or removal of the pineal gland (where melatonin is produced) in tumour development and most showed increases in the incidence or growth of tumours.[5,6]

Exposure to light at night

disruption is probably carcinogenic to humans" (Group 2A).[15]

Painters are potentially exposed to many chemicals used as pigments, extenders, binders, solvents, and additives. Painters can also be exposed to other workplace hazards, such as asbestos or crystalline silica.

Cohort and linkage studies of painters have shown consistent and significant increases in lung cancer compared with the general population. No information on tobacco smoking was available in the cohort studies; however, the increases are comparable to results from many case–control studies that controlled

Upcoming meetings
February 5–12, 2008
Industrial and cosmetic dyes and related exposures
http://monographs.iarc.fr/

Members of the Working Group Monograph 98: Shiftwork, Firefighting, Painting

Aaron Blair, NCI, USA
David Blask, Bassett Healthcare Research Institute, USA
Thomas Brock, University of Applied Sciences, Germany
Magne Bråtveit, University of Bergen, Norway
Jefferey L. Burgess, University of Arizona, USA
Giovanni Costa, University of Milan, Italy
Scott Davis, University of Washington, USA
Paul A. Demers, UBC, Canada
Johnni Hansen, Danish Cancer Society, Denmark
Erhard Haus, University of Minnesota, USA
Grace K. LeMasters, University of Cincinnati, USA
Francis Lévi, INSERM, France
Franco Merletti, University of Turin, Italy
Chris Portier, NIEHS, USA
Eero Pukkala, Finnish Cancer Registry, Finland
Eva Schernhammer, Harvard Medical School, USA
Kyle Steenland, Emory University, USA
Richard Stevens, University of Connecticut, USA
Roel Vermeulen, University of Utrecht, Netherlands
Tongzhang Zheng, Yale University, USA
Yong Zhu, Yale University, USA

Invited Specialists

Josephine Arendt, University of Surrey, UK
Claire Austin, Université du Québec, Canada
John Cherrie, Institute of Occupational Medicine, UK

Exposure Data in the IARC Monograph

Information generally included in Section 1 (exposure data) of the monograph

- General information on the agent
- Analysis and detection
- Production and use
- Occurrence and exposure
- Regulations and guidelines

What are Shift Work & Night Work?

- Work outside of regular day hours (7:00/8:00 to 17:00/18:00) or work at night?
  - Length and duration: e.g. 3+ hours between 23:00 & 6:00 (Finland) or a 7 hour shift that includes some time between midnight & 5:00 (UK)
  - Frequency: e.g. at least twice a week (France) or 48 days in a year (Germany)

Shiftwork in Canada

Regular daytime schedule	66.4%
Rotating shift	11.9%
Irregular schedule	9.0%
Regular evening schedule	6.0%
Regular night or graveyard shift	2.3%
On call	2.2%
Split shift	0.8%
Other	1.4%

- Survey of Labour and Income Dynamics (SLID), Statistics Canada, 2005.

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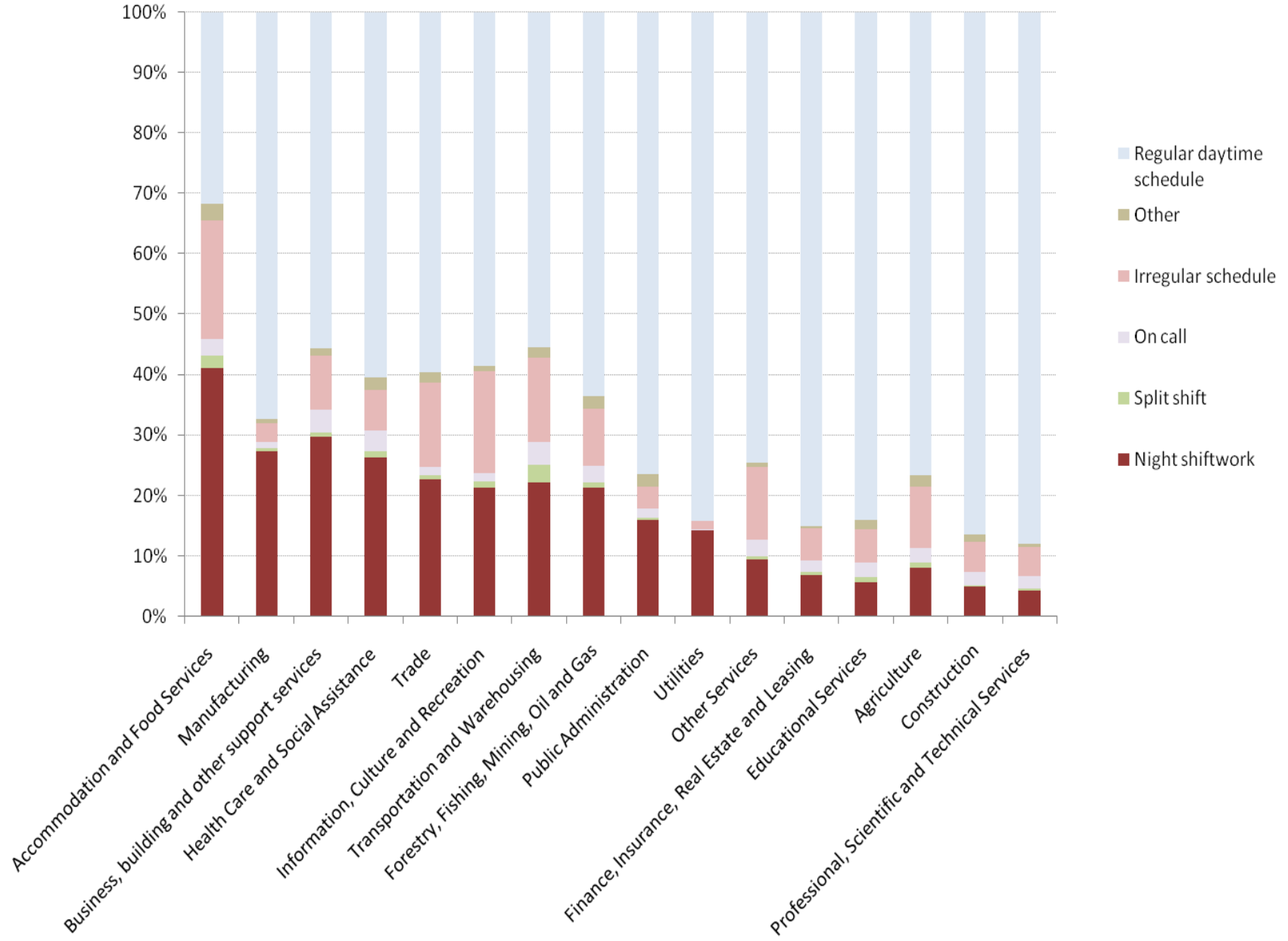
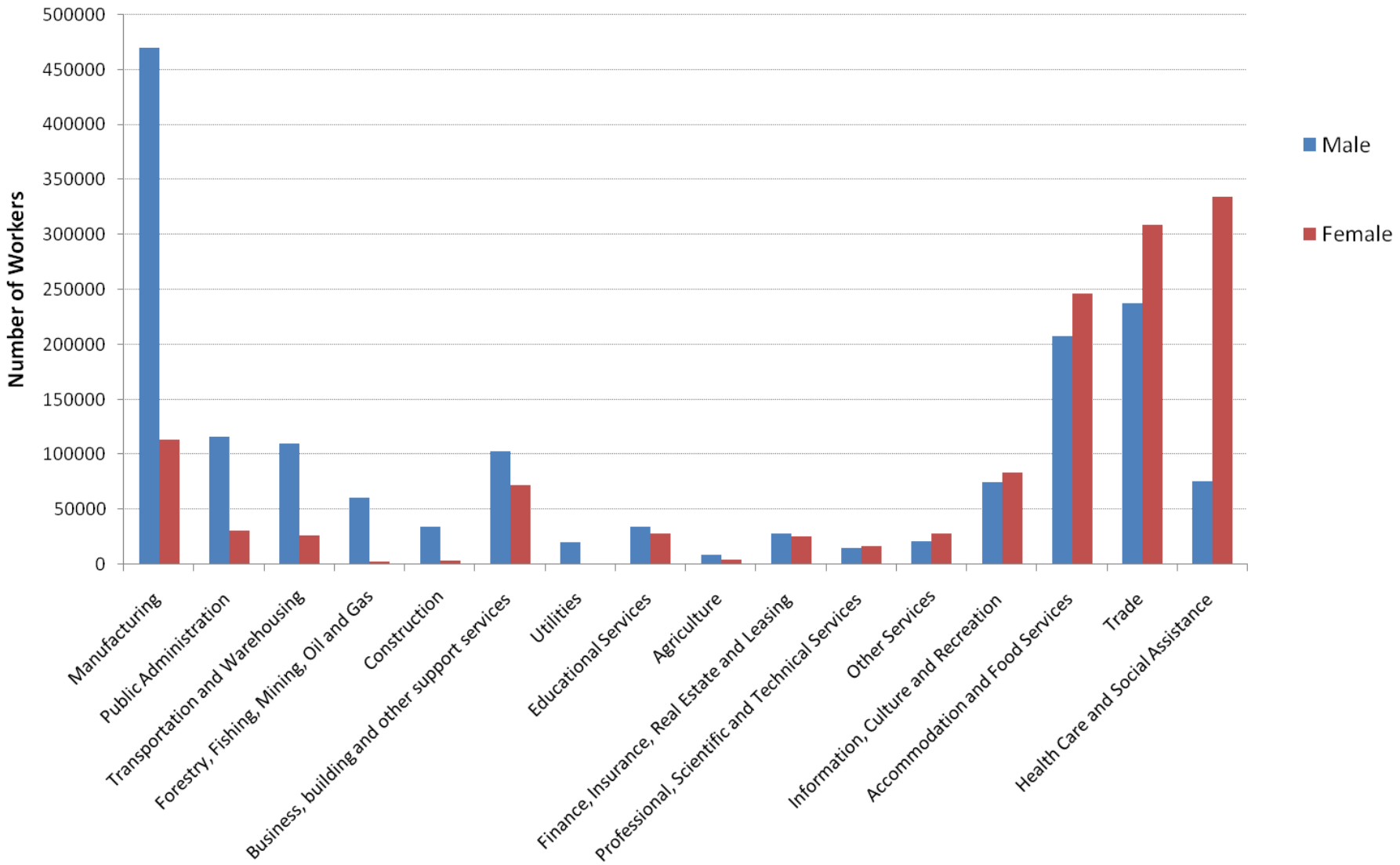
Shift type by Industry



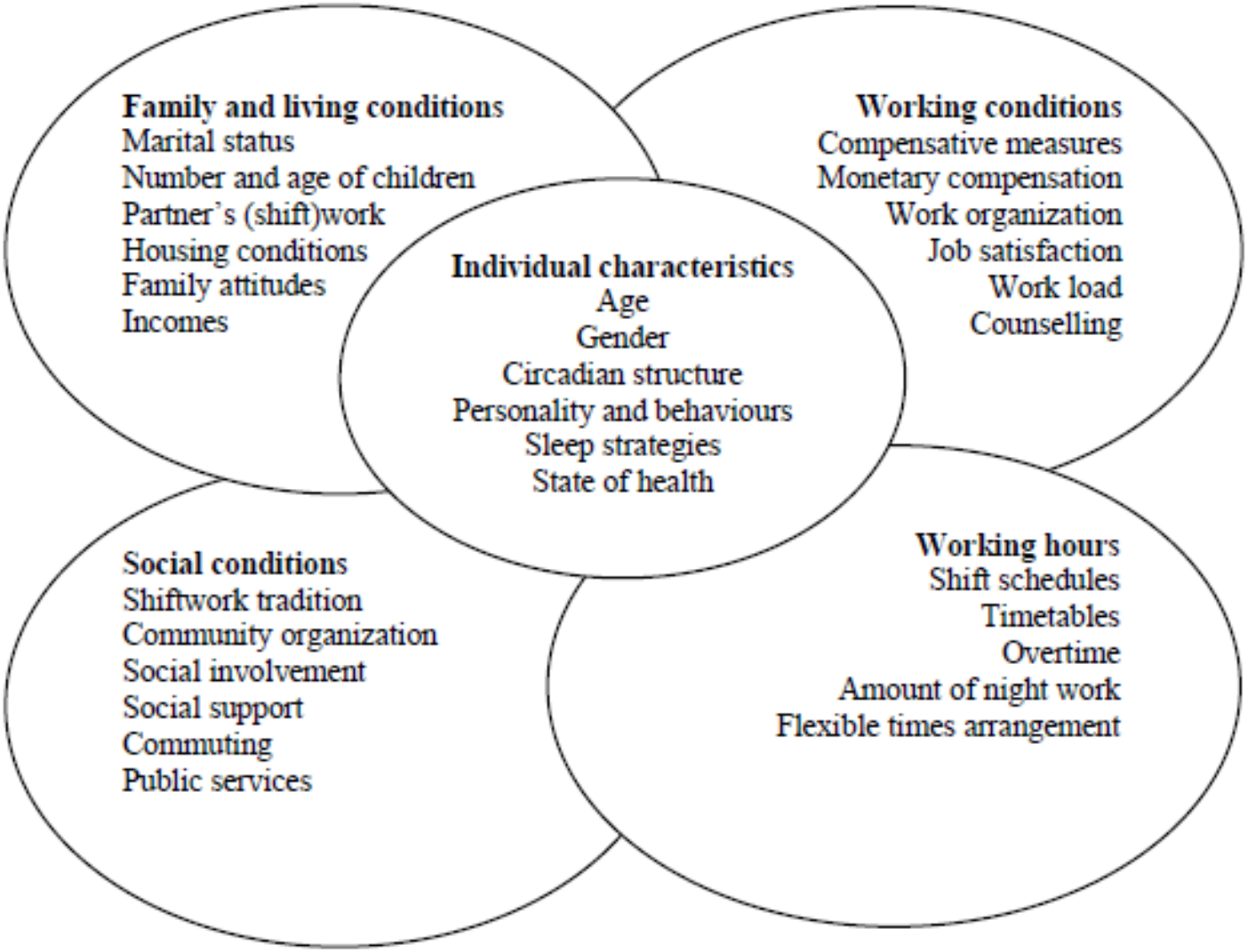
Number of Shiftworkers by Industry



Other Factors to Consider

- Work involving disruption of circadian rhythms?
- How do we match the definition between human and animal studies?
- Shiftwork that involves work at night disrupts both biological systems and social lives, leading to stress, dietary changes, …

Figure 1.1. Factors that can affect tolerance to shiftwork and night work



(Costa, 2003)

Studies of Cancer in Humans Evidence Considered

- 8 studies of breast cancer
- A very limited number of studies for cancers at other sites
- 10 cohort studies of flight crew initiated because of concern over cosmic radiation

Shiftwork and Breast Cancer

Study	Design/population	Shiftwork
Tynes et al, 1996 (Norway)	2,619 female radio & telegraph operators, 50 breast cancers	Night shift work on ships
Davis et al, 2001 (USA)	Population-based case-control, 813 breast cancer cases	Begin after 19:00 & end before 09:00
Schernhammer et al, 2001 (USA)	Prospective 1976 cohort of 121,701 registered nurses	Rotating, evening or night shift
Hansen, 2001 (Denmark)	Registry-based case-control study, 7,565 breast cancers	4 industries w/ 60+% night shift
Lei et al, 2005 (Norway)	Registry-based case-control study, 537 breast cancers	Hospital nurses
Schernhammer et al, 2006 (USA)	Prospective 1989 cohort of 116,087 registered nurses	Rotating, evening or night shift
O'Leary et al, 2006 (USA)	Population-based case-control, 576 breast cancer cases	Begin after 19:00
Schwartzbaum et al, 2007 (Sweden)	Registry-based cohort study, 3057 women, 98 breast cancers	Industries w/ 40+% night shift

Shiftwork and Breast Cancer
Prospective Studies of Nurses

- 2 large prospective cohort studies, same investigators, same design
- All Rotating, evening or night shift
- Schernhammer et al, 2001 (USA)
  - 78,562 registered nurses, 2,441 breast cancers
  - RR=1.4 for 30+ yrs
- Schernhammer et al, 2006 (USA)
  - 116,087 registered nurses, 1,352 breast cancers
  - RR=1.8 for 20+ yrs

Shiftwork and Breast Cancer
Population-based Case-Control Studies

- Very good information on other causes of breast cancer
- Davis et al, 2001 (USA)
  - OR=1.6 for ever Begin after 19:00 & end before 09:00
- O'Leary et al, 2006 (USA)
  - OR=0.6 for ever Begin after 19:00 and work over night
  - Very high prevalence of shiftwork (~35%)

Shiftwork and Breast Cancer
Nordic Tumour Registry-based Studies

- 3 Nordic tumour registry-based studies
- Hansen, 2001 (Denmark)
  - OR=1.7 for 6+ yrs in 60% shiftwork industries
- Lei et al, 2005 (Norway)
  - OR=2.2 for 30+ yrs as hospital nurse
- Schwartzbaum et al, 2007 (Sweden)
  - SMR=1.0 for 10+ yrs in 60% shiftwork industries

Shiftwork and Breast Cancer

Study	Design/population	Results
Tynes et al, 1996 (Norway)	Ship radio & telegraph operators cohort	OR=5.9 for 3.2+ yrs night shift, 50+ age
Schernhammer et al, 2001 (USA)	Prospective nurses cohort	RR=1.4 for 30+ yrs
Schernhammer et al, 2006 (USA)	Prospective nurses cohort	RR=1.8 for 20+ yrs
Davis et al, 2001 (USA)	Population-based case-control study	OR=1.6 for ever
O'Leary et al, 2006 (USA)	Population-based case-control study	OR=0.6 for ever
Hansen, 2001 (Denmark)	Registry-based study	OR=1.7 for 6+ yrs
Lei et al, 2005 (Norway)	Registry-based study of nurses	OR=2.2 for 30+ yrs
Schwartzbaum et al, 2007 (Sweden)	Registry-based study	SMR=1.0 for 10+ yrs

Breast Cancer in Flight Attendants

Study	Design/Population	Results
Pukkala et al, 1995 (Finland)	1577 Finnair flight crew, 20 breast cancers	SIR=1.9, 95% CI=1.2-2.2
Lynge, 1996 (Denmark)	915 flight attendants, Danish Census, 14 breast cancers	SIR=1.6, 95% CI=0.9-2.7
Wartenberg et al, 1998 (USA)	Retired flight attendants, 7 breast cancers	SIR=2.0, 95% CI=1.0-4.3
Haldorson et al, 2001 (Norway)	3105 Norwegian female cabin crew, 38 breast cancers	SIR=1.1, 95% CI=0.8-1.5
Rafnsson et al, 2001 (Iceland)	1532, Icelandic cabin crew, 26 breast cancer cases	SIR=1.5, 95% CI=1.0-2.1
Blettner et al, 2002 (Germany)	16,014 cabin crew from two companies, 19 breast cancers	SMR=1.3, 95% CI=0.7-2.2
Reynolds et al, 2002 (USA)	California flight attendants cohort	SIR=1.4, 95% CI=1.1-1.8
Linnersjo, 2003 (Sweden)	Swedish SAS cohort	SIR=1.3, 95% CI=0.9-1.7
Zeeb et al, 2003 (8 European countries)	33063 female cabin crew	SMR=1.1, 95% CI=0.8-1.5

Epidemiologic Evidence for Breast Cancer and Shiftwork

- 5/8 studies observed a clearly increased risk
  - 3 were of nurses (2 prospective cohorts)
- 1 study had mixed results (only increased among women over 50)
- 2 studies were negative
- Supportive evidence from flight crew studies
- Studies from other cancer sites did not contribute to the evaluation

Limitations of the Epidemiologic Evidence for Breast Cancer

- Inconsistent definition of shift-work
- Limited number of studies
- Some studies focused on single profession
  - i.e. could it be something else about night nurses?
- Potential uncontrolled confounding by reproductive factors & cosmic radiation

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Preliminary Default Evaluation

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In some cases

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Limited	*Group* **2A**	*Group* **2B**/2A	*Group* **2B**/2A
Inadequate	*Group* **2B**	*Group* **3**	***Group* 3**

2007 Working Group Evaluation

- Cancer in Humans
  - There is limited evidence in humans for shiftwork that involves night work
- Cancer in Experimental Animals
  - There is sufficient evidence for light during the daily dark period (biological night)
- Overall Evaluation
  - Shiftwork that involves circadian disruption is probably carcinogenic to humans (2A)