Occupational Carcinogen Exposure: The challenges of uncertainty and management

Professor Lin Fritschi
The dilemmas and challenges that arise when there is uncertainty with occupational cancer causes and when even recognized causes are tricky to avoid.

Shift work as an example

Disclaimer
I’m an epidemiologist not an occupational hygienist
Uncertainty

How do we know what is carcinogenic?
• *IARC Monographs* identify environmental factors that can increase the risk of human cancer
  – Chemicals, complex mixtures, occupational exposures, physical agents, biological agents, and lifestyle factors
  – Panel of expert scientists review the published studies and evaluate the weight of the evidence that an agent can increase the risk of cancer
Classification process

- Carcinogenicity in humans
  - Sufficient evidence of carcinogenicity
  - Limited evidence of carcinogenicity
  - Inadequate evidence of carcinogenicity
  - Evidence suggesting lack of carcinogenicity

- Carcinogenicity in experimental animals
  - Sufficient evidence of carcinogenicity
  - Limited evidence of carcinogenicity
  - Inadequate evidence of carcinogenicity
  - Evidence suggesting lack of carcinogenicity

- Mechanistic and other relevant data
## IARC classifications

### Overall evaluation of carcinogenicity to humans

<table>
<thead>
<tr>
<th>Group</th>
<th>Classification</th>
<th>Count</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Carcinogenic</td>
<td>107</td>
<td>agents</td>
</tr>
<tr>
<td>Group 2A</td>
<td>Probably carcinogenic</td>
<td>63</td>
<td>agents</td>
</tr>
<tr>
<td>Group 2B</td>
<td>Possibly carcinogenic</td>
<td>271</td>
<td>agents</td>
</tr>
<tr>
<td>Group 3</td>
<td>Not classifiable</td>
<td>509</td>
<td>agents</td>
</tr>
</tbody>
</table>
• 509 agents “not classifiable”, Group 3
• 271 agents “possibly carcinogenic”, Group 2B
• Including the following 2B classifications:
  – Mobile phone use
  – Bitumens
  – Gasoline engine exhaust
  – Lead
• Prevention of exposure?
  – Preventive principle
    • ALARA (As Low As Reasonably Achievable)
  – Wait until they are classified as a carcinogen
  – Somewhere in between
    • Reduce as much as possible
    • Manage based on other health effects
    • Undertake high quality studies to help make the situation less uncertain
• In the situation when we are reasonably certain something is carcinogenic
  – 107 agents “carcinogenic”, Group 1
  – 63 agents “probably carcinogenic”, Group 2A

• How do we decide where to act?
• Some carcinogens don’t fit traditional OHS models
– TURA toxics
– REACH Authorisation List
– Canadian Environmental Protection Act Toxic Substances List
– US National Priorities List
– US EPA Extremely Hazardous Substances List
– Danish list of undesirable substances
– Swedish Chemicals Agency Tool for Risk Reduction of Chemicals
• International Agency for Research on Cancer (IARC)
  – Carcinogenic to humans (Group 1)
  – Probably carcinogenic to humans (Group 2A)
• Exclude exposure circumstances

• 165 agents
• 19 exposure circumstances excluded
• Removed Group 1 and 2A agents for which exposure was not primarily occupational:
  – dietary agents
  – hormonal agents
  – pharmaceutical agents
  – infectious agents

• 59 agents excluded
• Wide range of sources consulted to determine if the chemical was used in Australian industry
• Surprising how difficult this was to find out

• 26 agents excluded
# Priority carcinogens list (n = 38)

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combustion Products</td>
<td>Diesel engine exhaust, PAHs, Second-hand tobacco smoke</td>
</tr>
<tr>
<td>Inorganic dusts</td>
<td>Asbestos, Crystalline silica</td>
</tr>
<tr>
<td>Organic dusts</td>
<td>Leather dust, Wood dust</td>
</tr>
<tr>
<td>Metals</td>
<td>Arsenic and inorganic As compounds, Beryllium and Be compounds, Cadmium and Cd compounds, Chromium (VI) compounds, Cobalt metal and tungsten carbide, Inorganic lead compounds, Nickel compounds</td>
</tr>
<tr>
<td>Nitrosamines</td>
<td>N –Nitrosodimethylamine, N - Nitrosodiethylamine</td>
</tr>
</tbody>
</table>
# Priority carcinogens list (n = 38)

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation</td>
<td>Artificial UV radiation, Ionising radiation, Radon-222 and decay products, Solar radiation</td>
</tr>
<tr>
<td>Other industrial chemicals</td>
<td>Acrylamide, Alpha-Chlorinated toluenes, Benzene, 1, 3-Butadiene, Diethyl sulphate, Dimethyl sulphate, Epichlorhydrin, Ethylene oxide, Formaldehyde, Glycidol, 4, 4’-Methylenebis(2-chloroaniline) (MOCA), ortho-Toluidine (2-Aminotoluene), Polychlorinated biphenyls (PCBs), Strong inorganic acid mists, Styrene-7, 8-oxide, Tetrachloroethylene (Perchloroethylene), Trichloroethylene, Vinyl chloride</td>
</tr>
<tr>
<td>Non-chemical agents</td>
<td>Shiftwork</td>
</tr>
</tbody>
</table>

Fernandez et al, 2012
Hierarchy of control

- Elimination
- Substitution
- Separation
- Procedures

Personal protective equipment
Do traditional frameworks always apply?

- Industrial chemicals
- Inorganic dusts
- Organic dusts
- Metals
- Ionizing radiation
- Combustion products
- Solar radiation
- Shift work
Examples

- Pesticides
- Ionizing radiation
- Solar radiation
- Diesel exhaust
- Painting
- Shift work

SafeWork 2008 – National Hazard Exposure Worker Surveillance
### Pesticides

<table>
<thead>
<tr>
<th>Agent</th>
<th>Degree of evidence of carcinogenicity&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Overall evaluation of carcinogenicity to humans&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Humans</td>
<td>Animals</td>
</tr>
<tr>
<td>Aldicarb</td>
<td>ND</td>
<td>I</td>
</tr>
<tr>
<td>Atrazine</td>
<td>I</td>
<td>L</td>
</tr>
<tr>
<td>Captafol</td>
<td>ND</td>
<td>S</td>
</tr>
<tr>
<td>Chlordane</td>
<td>I</td>
<td>S</td>
</tr>
<tr>
<td>DDT</td>
<td>I</td>
<td>S</td>
</tr>
<tr>
<td>Deltamethrin</td>
<td>ND</td>
<td>I</td>
</tr>
<tr>
<td>Dichlorvos</td>
<td>I</td>
<td>S</td>
</tr>
<tr>
<td>Fenvalerate</td>
<td>ND</td>
<td>I</td>
</tr>
<tr>
<td>Heptachlor</td>
<td>I</td>
<td>S</td>
</tr>
<tr>
<td>Monuron</td>
<td>ND</td>
<td>L</td>
</tr>
<tr>
<td>Occupational exposures in spraying and application of nonarsenical insecticides</td>
<td>L</td>
<td></td>
</tr>
<tr>
<td>Pentachlorophenol</td>
<td>I</td>
<td>S</td>
</tr>
<tr>
<td>Permethrin</td>
<td>ND</td>
<td>I</td>
</tr>
<tr>
<td>Picloram</td>
<td>ND</td>
<td>L (tech.-grade)</td>
</tr>
<tr>
<td>Simazine</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Thiram</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Trifluralin</td>
<td>I</td>
<td>L (tech.-grade)</td>
</tr>
<tr>
<td>Ziram</td>
<td>ND</td>
<td>L</td>
</tr>
</tbody>
</table>

<sup>a</sup>I, inadequate evidence; S, sufficient evidence; L, limited evidence; ND, no data

<sup>b</sup>For definitions of degrees of evidence and groupings of evaluations, see Preamble, pp. 26-28.

<sup>c</sup>Other relevant data influenced the making of the overall evaluation.
• Lack of evidence of carcinogenicity
  – IARC Group 2B and 3
• Locations of exposure
  – Agriculture, but mainly SME
  – ~2% of workers
  • Safe Work Australia, 2008
• Control measures well understood
  – Elimination, substitution
Ionizing radiation

- Good evidence of carcinogenicity
  - IARC Group 1
- Limited locations of exposure
  - Medical, security, industry
  - About 50,000 workers in Australia
    - average dose of 0.12 mSv pa (ARPANSA)
- Control measures well understood
  - Procedures and PPE
  - ARPANSA
• Good evidence of carcinogenicity
  – IARC Group 1

• Many locations of exposure
  – Any outdoor work, welding arcs
  – ~30% of Australian workers?

• Control measures well understood
  – Procedures and PPE
  – 17% of exposed take no preventive action
    • Safe Work Australia, 2008
 Diesel exhaust

• Reasonable evidence of carcinogenicity
  – IARC Group 2A

• Many locations of exposure
  – Transport (road, rail, sea), mining, construction
  – ~15% of workers
    • Safe Work Australia, 2008

• Control measures well understood
  – Separation and procedures
• Good evidence of carcinogenicity
  – IARC Group 1
• Many locations of exposure
  – Construction and services
  – ~6% of workers
  • SafeWork Australia, 2008
• Control measures
  – depend on the agent
• Disentangling the mechanism
• IARC lists 91 substances that workers may be exposed to in the painting trades
  – Including 12 Group 1 carcinogens
    • Arsenic, cadmium, chromium, nickel
    • Asbestos, silica, talc
    • Coal tar pitches, dyes and pigments, formaldehyde, hydrocarbon solvents, synthetic rubber,
• Control measures depend on the agent
• IARC: no definition given “involves night work”
• ABS: Work whereby the daily hours of operation are split into at least two set work periods (shifts), for different groups of workers
• In Australia in 2009, 1.4 million employees usually worked shift work
  – 16% of the working population

Working Time Arrangements, ABS, 2009
Table 5  Statistics for meta-analysis of shift work and breast cancer

<table>
<thead>
<tr>
<th></th>
<th>Number of studies</th>
<th>FES(^a) (95% CI)</th>
<th>Homogeneity (\chi^2)-squared</th>
<th>Homogeneity degrees of freedom</th>
<th>Homogeneity p-value(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies combined</td>
<td>(n=7)</td>
<td>1.4 (1.3–1.6)</td>
<td>9.0</td>
<td>6</td>
<td>0.18</td>
</tr>
<tr>
<td>Cohort studies</td>
<td>(n=2)</td>
<td>1.4 (1.1–1.8)</td>
<td>0.8</td>
<td>1</td>
<td>0.36</td>
</tr>
<tr>
<td>Case-control studies</td>
<td>(n=5)</td>
<td>[1.4 (1.2–1.7)](^c)</td>
<td>8.1</td>
<td>4</td>
<td>0.09</td>
</tr>
<tr>
<td>Europe</td>
<td>(n=3)</td>
<td>1.6 (1.3–1.8)</td>
<td>2.4</td>
<td>2</td>
<td>0.31</td>
</tr>
<tr>
<td>North America</td>
<td>(n=4)</td>
<td>1.3 (1.1–1.6)</td>
<td>4.9</td>
<td>3</td>
<td>0.18</td>
</tr>
</tbody>
</table>

\(^{a}\) Fixed-effects summary
\(^{b}\) Random-effects summary
\(^{c}\) Pooled RRs in square brackets indicate substantial heterogeneity (i.e., \(p<.10\)) in the contributing data.
<table>
<thead>
<tr>
<th>Study, country</th>
<th>Main exposure variable</th>
<th>Finding in highest group</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pesch et al, 2010 Germany</td>
<td>&gt;20 yrs night shift</td>
<td>2.48 (0.6-10)</td>
<td>No dose-response Based on 12 cases</td>
</tr>
<tr>
<td>Pronk et al, 2010 China</td>
<td>&gt;17 yrs night shift</td>
<td>0.8 (0.5-1.2)</td>
<td>Cohort study Based on 19 cases</td>
</tr>
<tr>
<td>Lie et al, 2011 Norway</td>
<td>&gt;12 yrs night shift</td>
<td>1.3 (0.9-1.8)</td>
<td>Based on 187 cases</td>
</tr>
<tr>
<td>Hansen et al, 2011 Denmark</td>
<td>&gt;20 yrs night shift</td>
<td>2.1 (1.3-3.2)</td>
<td>Based on 39 cases</td>
</tr>
</tbody>
</table>
• Jury is still out on the carcinogenicity of shiftwork
• So what do we do?
  – Preventive principle?
• Traditional controls
  – not applicable
• Analogy with painters
  – Control measures depend on the agent
### Shiftwork in Australia

<table>
<thead>
<tr>
<th>Industry</th>
<th>% usually Worked shiftwork</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mining</td>
<td>48.9</td>
</tr>
<tr>
<td>Accommodation and food services</td>
<td>37.0</td>
</tr>
<tr>
<td>Health care and social assistance</td>
<td>31.5</td>
</tr>
<tr>
<td>Transport, postal and warehousing</td>
<td>30.7</td>
</tr>
<tr>
<td>Arts and recreation services</td>
<td>23.0</td>
</tr>
<tr>
<td>Manufacturing</td>
<td>17.2</td>
</tr>
<tr>
<td>Public administration and safety</td>
<td>16.1</td>
</tr>
</tbody>
</table>
Characteristics of shiftwork

• Permanent night shift
• Rotating rosters
  – Fast or slow rotating
  – Backward or forward rotating
• Blocks of shiftwork (e.g. Fly-In Fly-Out)
• Irregular shifts
• Normal work hours + on-call
### Type of shiftwork, Australia, 2009

<table>
<thead>
<tr>
<th>Type of shift usually worked</th>
<th>% of shiftworkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotating shift which periodically changes</td>
<td>42.9</td>
</tr>
<tr>
<td>Regular evening shift</td>
<td>15.1</td>
</tr>
<tr>
<td>Regular morning shift</td>
<td>6.7</td>
</tr>
<tr>
<td>Regular afternoon shift</td>
<td>7.9</td>
</tr>
<tr>
<td>Irregular shift</td>
<td>19.0</td>
</tr>
<tr>
<td>Split shift</td>
<td>3.5</td>
</tr>
<tr>
<td>On call</td>
<td>2.4</td>
</tr>
<tr>
<td>Other</td>
<td>2.6</td>
</tr>
</tbody>
</table>
Characteristics of job

- Control of work and sleep at work
- Naps
- Level of concentration required
Characteristics of work

- Outside/inside
- Lighting
- Temperature
- Sedentary/active
- Hazards in the workplace
  - Driving, heavy machinery
  - Production lines
  - Drunk people, violent situations
Characteristics of the environment at work

- Availability of healthy food which is easily digested in the middle of the night
- Use of caffeine and high-sugar drinks to stay awake
- Smoking
- Lack of exercise
• Sleep hygiene
• Alcohol
• Sleeping pills
• Diet and weight
• Physical activity – time and inclination
• Lack of vitamin D
Biological effects of shift work

- Reduced melatonin
- Phase shift
- Sleep disruption
Melatonin

The pineal gland begins producing melatonin in the evening.

Melatonin levels peak in the middle of the night.

Melatonin levels decline to low daytime amounts.

Time of Day

2:00 P.M.  8:00 P.M.  3:00 A.M.  7:00 A.M.
Circadian rhythms of PER2::LUCIFERASE in SCN explants in response to medium change.

Vitaterna M H et al. PNAS 2006;103:9327-9332
Sleep disruption

Charles et al, 1997
Effects of Sleep deprivation

- Irritability
- Cognitive impairment
- Memory lapses or loss
- Impaired moral judgement
- Severe yawning
- Hallucinations
- Symptoms similar to ADHD

- Increased heart rate variability
- Risk of heart disease

- Decreased reaction time and accuracy
- Tremors
- Aches

Other:
- Growth suppression
- Risk of obesity
- Decreased temperature

- Impaired immune system
- Risk of diabetes Type 2
Possible biological mechanisms

Shiftwork

- Phase shift
- Light at night
- Sleep disruption
- Lifestyle disturbance
- Less sunshine

Physiological disruptions

- Suppression melatonin
- Stress axis activation
- Disrupted diet, alcohol, physical activity
- Decreased Vitamin D

Intra-cellular disruptions

- ↓ anti-cancer effects
- Immune suppression
- Metabolic changes
- ↓ anti-cancer effects

Breast cancer

Fritschi et al, 2011
Mechanism:
- Phase shift
- Light at night
- Sleep disruption
- Lifestyle disturbance
- Less sunshine

Solution:
- Shorter shift rotations
- Dimmer workplaces
- Better sleep strategies
- Improved food availability, lifestyle advice
- Sun exposure at appropriate times
• Some evidence of carcinogenicity
  – IARC Group 2A
• Many locations of exposure
  – mining, manufacture, health care, services
  – ~16% of workers
  • ABS, 2009
• Control measures not understood as mechanism not clear
<table>
<thead>
<tr>
<th>Agent</th>
<th>Carcinogen understood?</th>
<th>Most practical level of control</th>
<th>Scope of exposure</th>
<th>Certainty</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pesticides</td>
<td>No (chemical), 2B and 3</td>
<td>Elimination and substitution</td>
<td>Limited, but SME</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Ionizing radiation</td>
<td>Yes, 1</td>
<td>Procedures and PPE</td>
<td>Very limited</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Solar radiation</td>
<td>Yes, 1</td>
<td>Procedures and PPE</td>
<td>Widespread</td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>Diesel exhaust</td>
<td>Yes, 2A</td>
<td>Procedures and PPE</td>
<td>Widespread</td>
<td>?</td>
<td>✗</td>
</tr>
<tr>
<td>Painting</td>
<td>No (chemical), 1</td>
<td>Substitution</td>
<td>Widespread</td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>Shift work</td>
<td>No, 2A</td>
<td>???</td>
<td>Widespread</td>
<td>?</td>
<td>✗</td>
</tr>
</tbody>
</table>
Conclusions

• Dilemmas and challenges of
  – Uncertain risks
  – Widespread and scattered exposure
  – Inability to eliminate the agent
• Clarify the components of the exposure which may be the causative factors
• Aim to minimize these
Thanks:
My team
NHMRC
Cancer Council WA