Dealing with uncertainty in the evidence

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Outline

- How do IARC make decisions?
- What happens when there isn't enough evidence?
  - Shiftwork
  - Pesticides
- How do we deal with this?

Working group

- Experts
  - Exposure assessment
  - Epidemiology
  - Animal studies
  - Mechanisms
- Invited specialists
- Representatives of national and international health agencies
- Observers
- Secretariat

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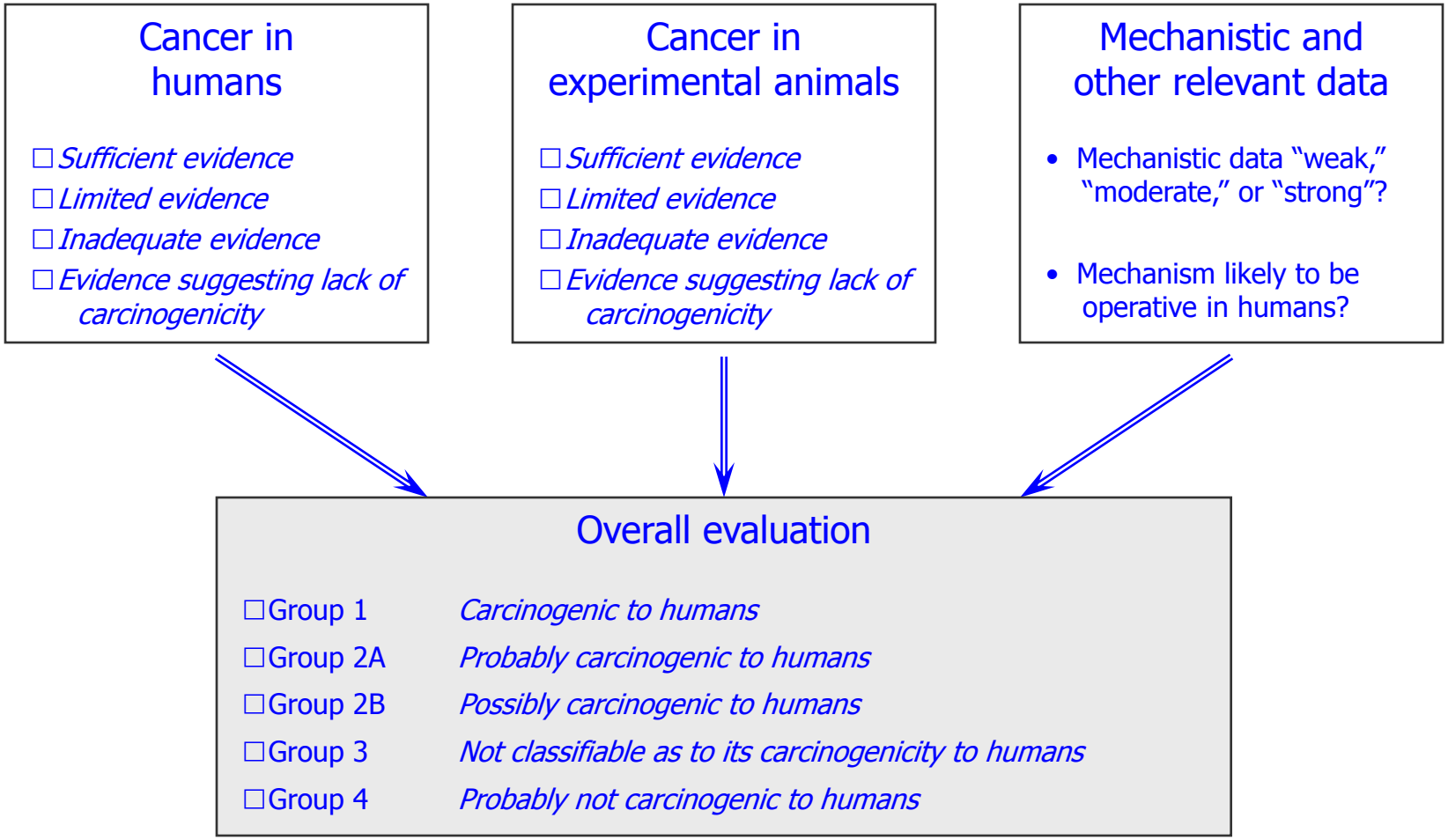
Subgroup work



Combining the human and experimental evaluations

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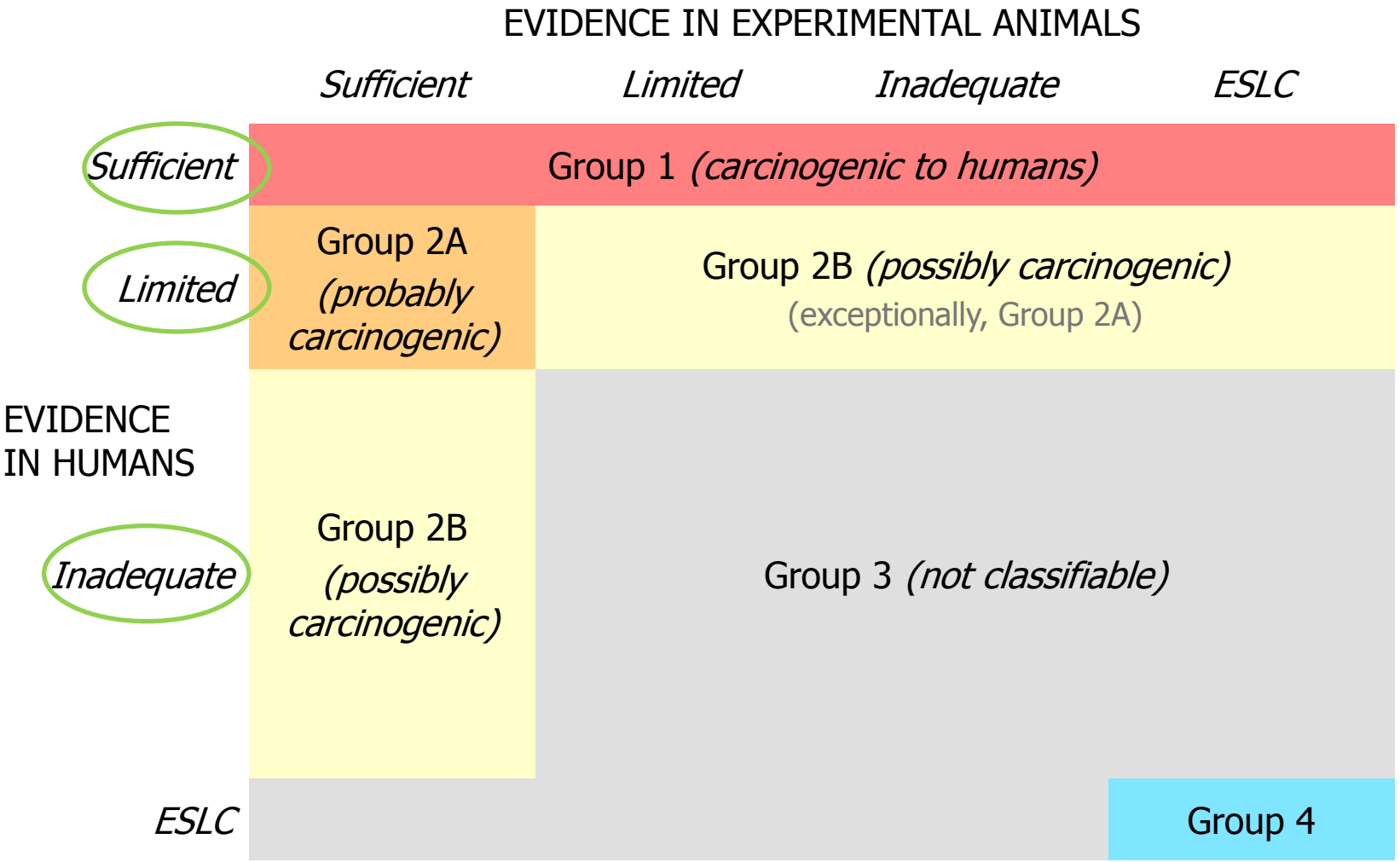

Mechanistic data can be pivotal

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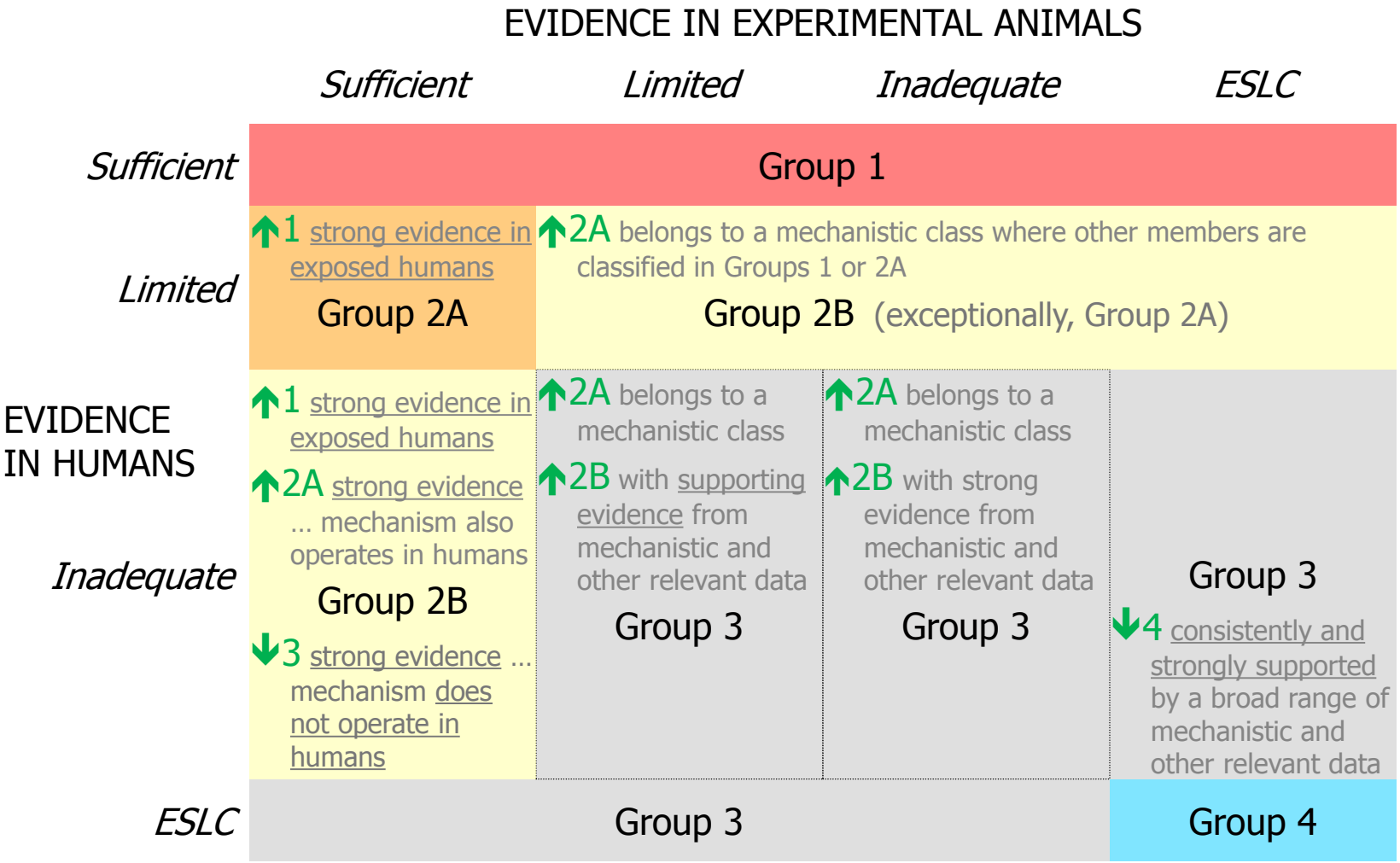

Shiftwork and breast cancer

- “Shiftwork that involves circadian disruption”
- Probable human carcinogen (2A)

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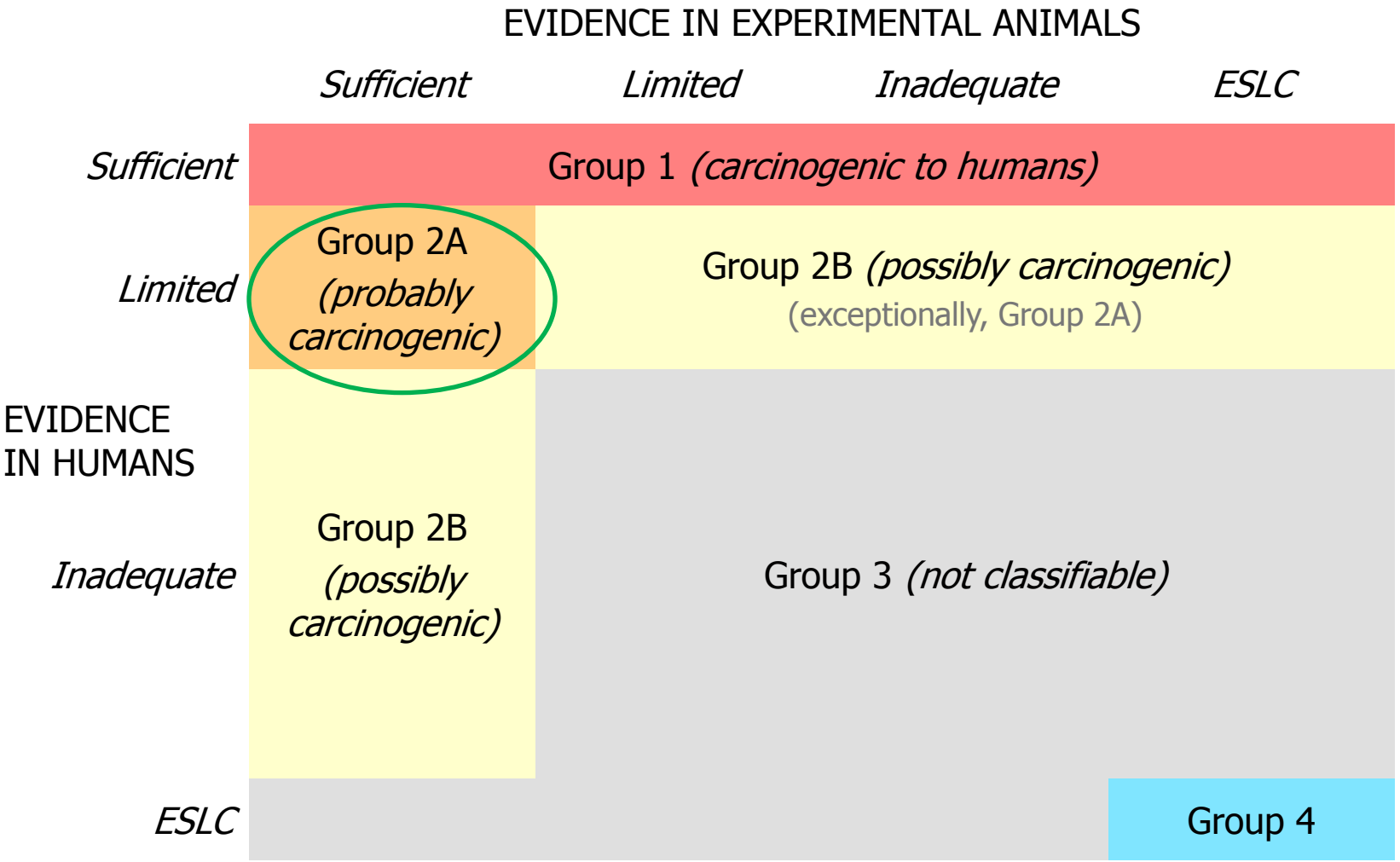
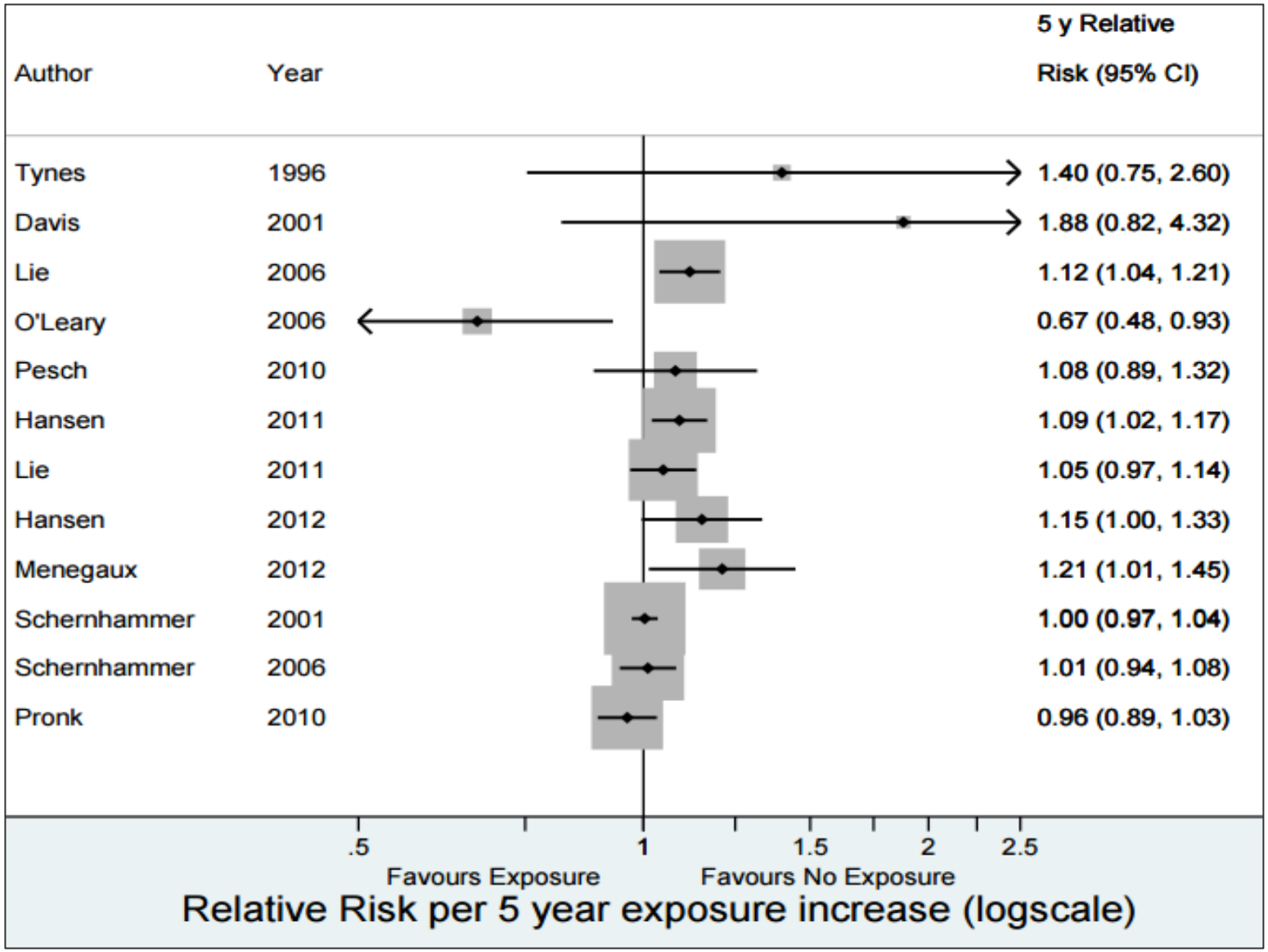


Human data (2010)

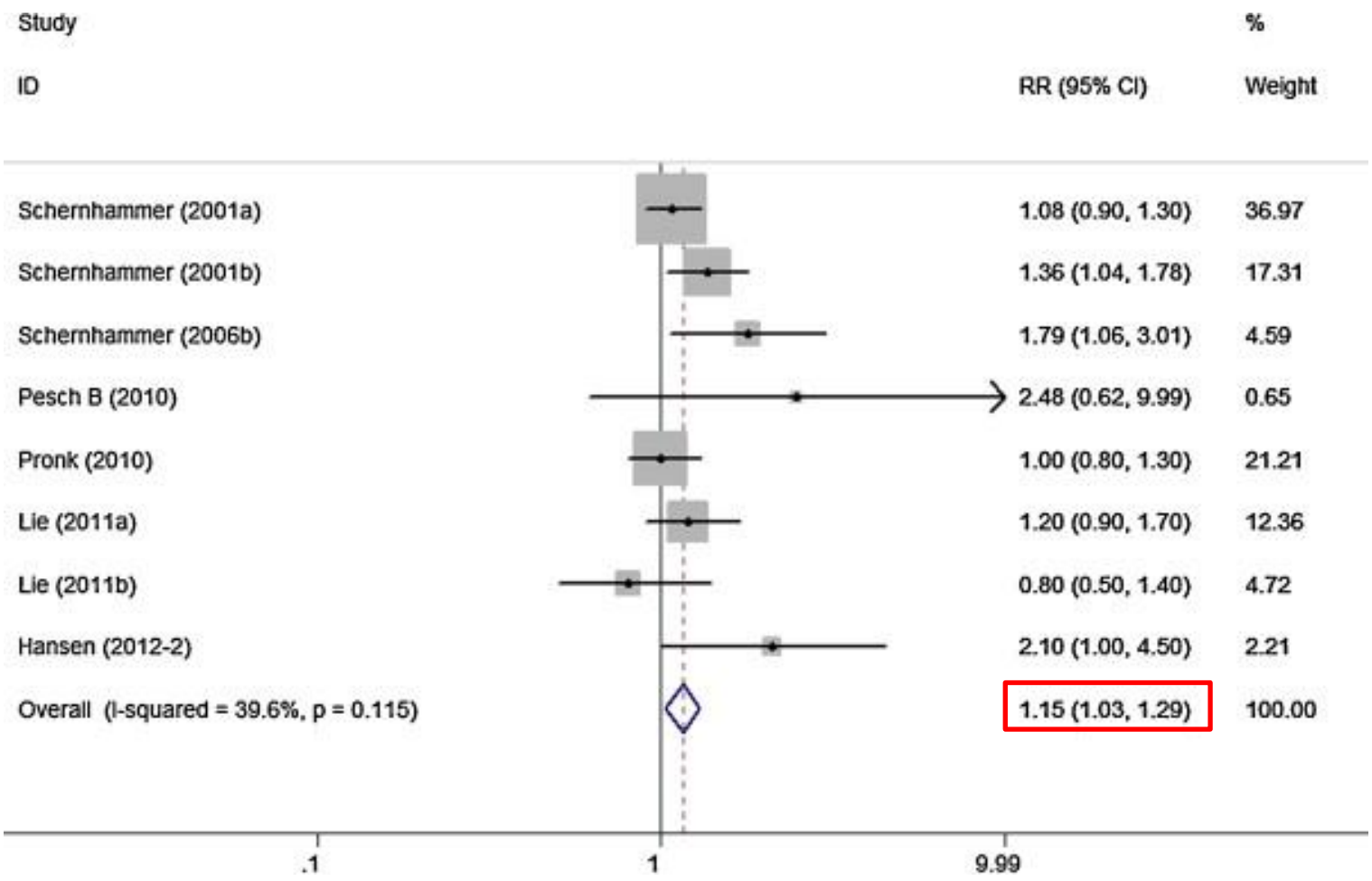
- 6 of 8 studies showed “modestly increased risk of breast cancer” for long term night shiftworkers
  - Studies limited by
    - Mainly studies of nurses
    - Poor assessment of shiftwork
    - Potential for confounding
- 7 of 8 cohorts of flight attendants showed increase risk of breast cancer with longer employment
  - Studies limited by
    - Poor assessment of circadian disruption
    - Potential for confounding and detection bias



Overall 1.09 (1.02-1.20) in case-control studies, but 1.01 (0.97-1.05) in cohort studies

Ijaz et al, 2013

Forest plot of studies examining the association between ≥15 years of night work and breast cancer risk.



Yijun et al.2013

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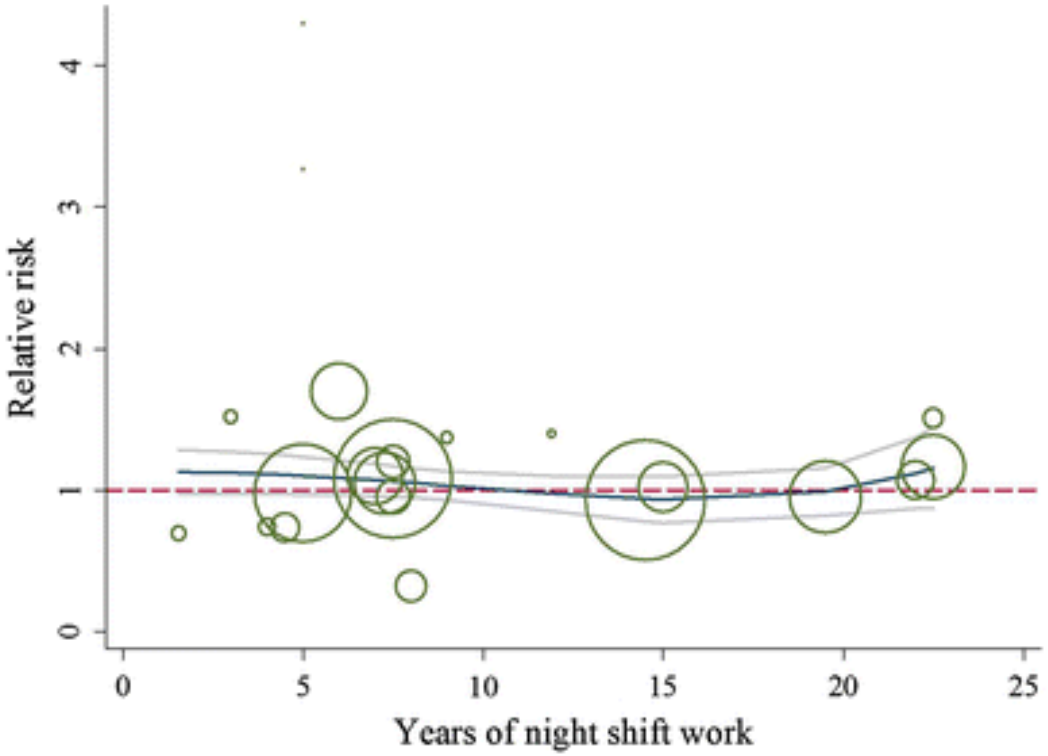
Dose response pattern



Kamdar et al, 2013

Some more confusion

- Latest results from the Nurses Health Study:

  "Long-term rotating night shift work, particularly early in career, may be associated with an increased risk of breast cancer, which appears to diminish after nightshift work ceases." Schernhammer, 2014

- Erren's hypothesis that night work is only carcinogenic if you are a lark rather than an owl. (Erren and Morfeld, 2014)

  However our Australian study didn't support this. Fritschi et al, 2014

- One study suggests survival is worse in those who have done shiftwork. (Hansen 2014)

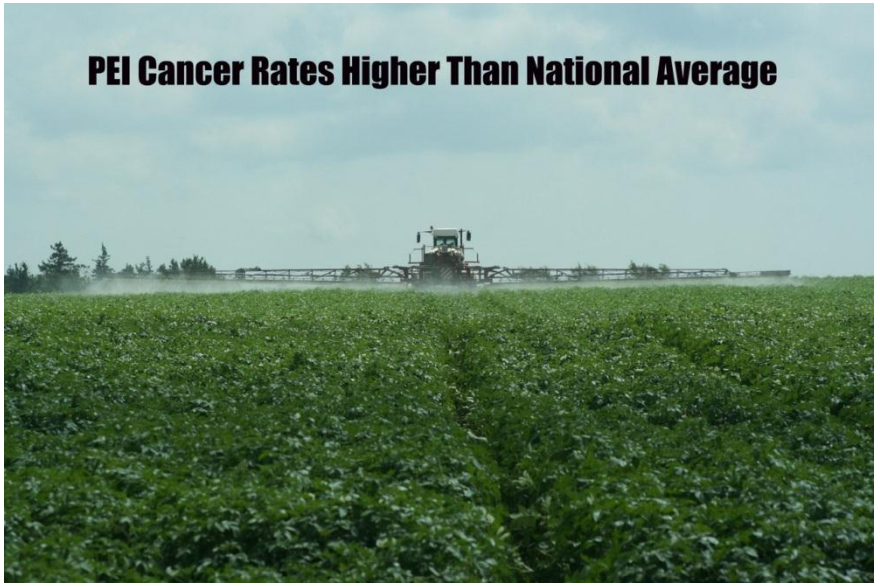
So, what to do?

- No compensation so far in the Australian system for shiftwork and breast cancer
- Small effect, no dose-response
- Probably safe to wait until there is more evidence

Pesticides and cancer

- As of 2014 Group 1 (definite) carcinogens were
  - arsenic
  - ethylene oxide
  - 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), which may occur as a contaminant in certain pesticides.

http://www.beyondpesticides.org



http://www.preventcancernow.ca

PROOF THAT EATING ORGANIC CAN REDUCE CANCER

AND HOW TO REDUCE PESTICIDES IN YOUR SYSTEM BY 90% IN ONE WEEK

http://www.ancestral-nutrition.com

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Why is it so hard to determine carcinogenicity? (1)

- Small numbers of subjects
  - The highest exposure (agricultural) is relatively rare
  - So researchers tend to combine individual pesticide exposures
  - However there are 100s of pesticides with different chemical structures and it wouldn't be expected that they would all act in the same way on the human body

Why is it so hard to determine carcinogenicity? (2)

- Pesticide use is difficult to assess
  - Multiple pesticide use
  - No validated biomarkers
  - Difficult to remember
  - Changes over time
  - Dose depends on a huge range of factors most of which are impossible to measure

An example – glyphosate and non-Hodgkin lymphoma (NHL

- Glyphosate is a broad-spectrum herbicide
- Highest production volume of all herbicides
- Increase in use because of genetically modified glyphosate-resistant crop varieties.

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Human data = limited evidence

Study	Number of exposed cases	Number of exposed controls	OR	95%CI
McDuffie et al, 2001, Canada	51	133	1.2	0.83-1.74
De Roos et al, 2003, US	36	61	2.1	1.1-4.0
Eriksson et al, 2008, Sweden	29	18	2.0	1.1-3.7
Agricultural Health **Cohort,** 2005 US			1.1	0.7-1.9

Combining the human and experimental evaluations

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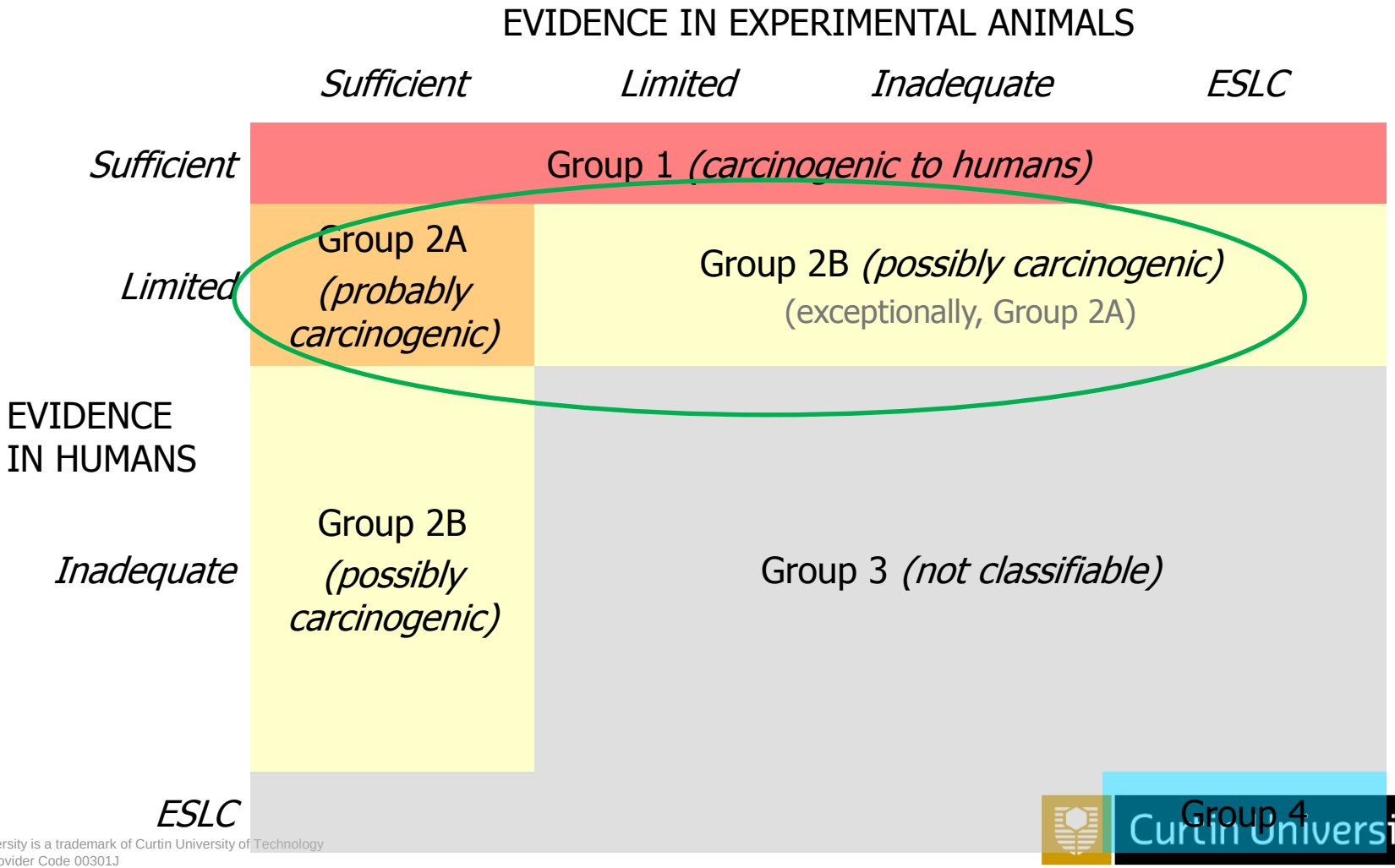

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Animal studies = sufficient evidence

- CD-1 mice, positive trend in the incidence of a rare tumour, renal tubule carcinoma.
- Male mice, positive trend for haemangiosarcoma
- Male rats (2 studies) increased rate of pancreatic islet-cell adenoma
- A glyphosate formulation promoted skin tumours in an initiation-promotion study in mice.

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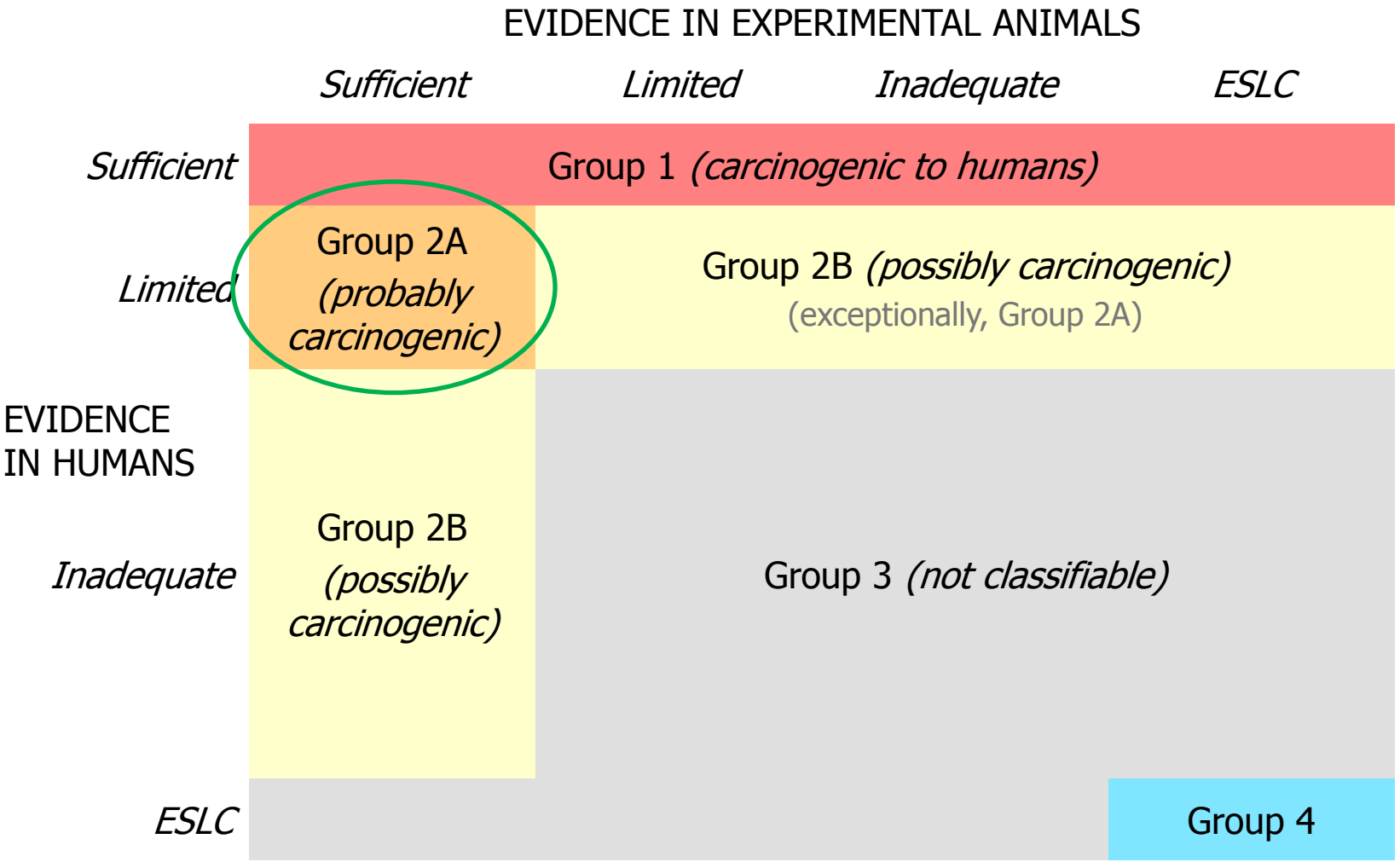

Mechanistic evidence = strong

- Has been detected in the blood and urine of exposed people, indicating absorption.
- Can induce DNA and chromosomal damage.
- Can induce oxidative stress
- One study reported increases in blood markers of chromosomal damage (micronuclei) in residents of several communities after spraying of glyphosate formulations.
- Bacterial mutagenesis tests were negative.

Mechanistic data can be pivotal

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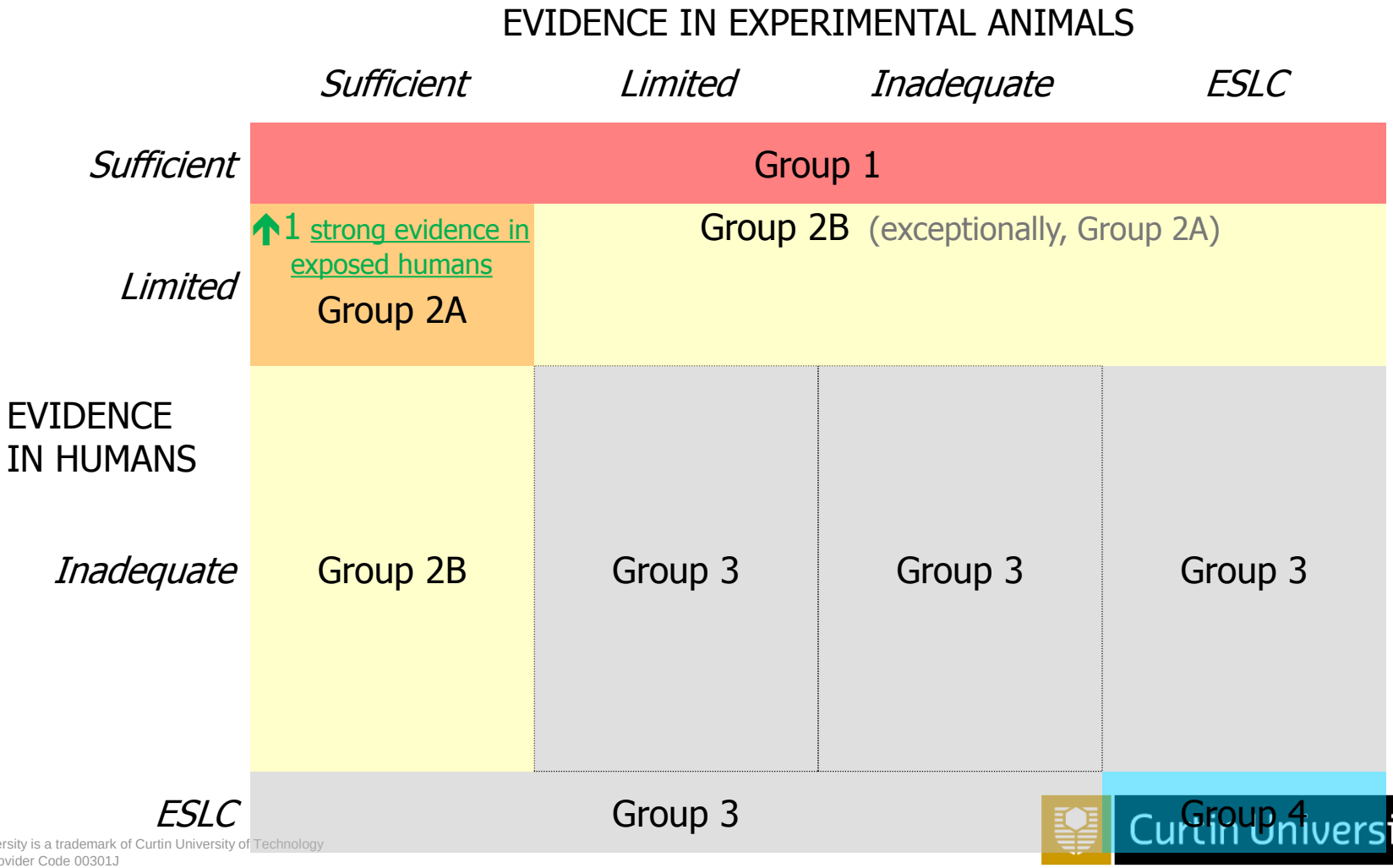

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So, what to do?

- No compensation so far in the Australian system for glyphosate and NHL
- Potentially a larger effect, no evidence regarding dose-response
- Agricultural and services users are likely to have highest exposures
- Why not take precautions?

  Minimize use

  Wear masks, wear gloves and wash hands before eating or drinking

Guidelines in the presence of uncertainty

- How strong is the possible effect?
- Is there a dose-response effect?
- Who is highest at risk?
- What harm would come from using preventive measures?

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