La monografia sui PCB: PCB e melanoma

International Agency for Research on Cancer
Lyon, France

Béatrice Lauby-Secretan, PhD
Section of the IARC Monographs
http://monographs.iarc.fr/

International Agency for Research on Cancer

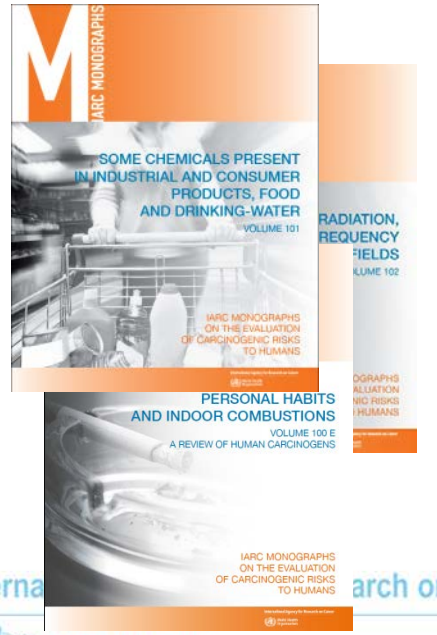
World Health Organization

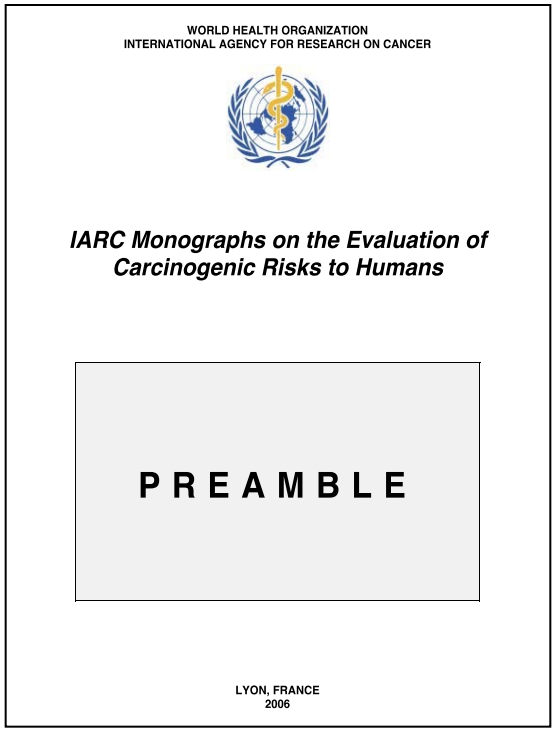
Outline

- The *IARC Monographs*
  - Procedure
  - Evaluation
- PCB and melanoma
  - Cohort studies
  - Case-control studies
  - Mechanistic data
  - Evaluation

How are evaluations conducted?

??





Published guidelines & procedures

- Participant selection
- Conflict of interest
- Data eligibility
- Review of evidence
- Decision process for overall evaluations
- Public participation

Interna arch on Cancer

World Health Organization

http://monographs.iarc.fr/ENG/Preamble/index.php

Who does the evaluation?

Attend meetings but do not write reviews or contribute to evaluations

IARC Secretariat
Coordinates all aspects of the evaluation

Working Group
Independent scientists without conflict of interest
Review science and develop evaluations

Invited Specialists
Scientists with relevant knowledge but a competing interest

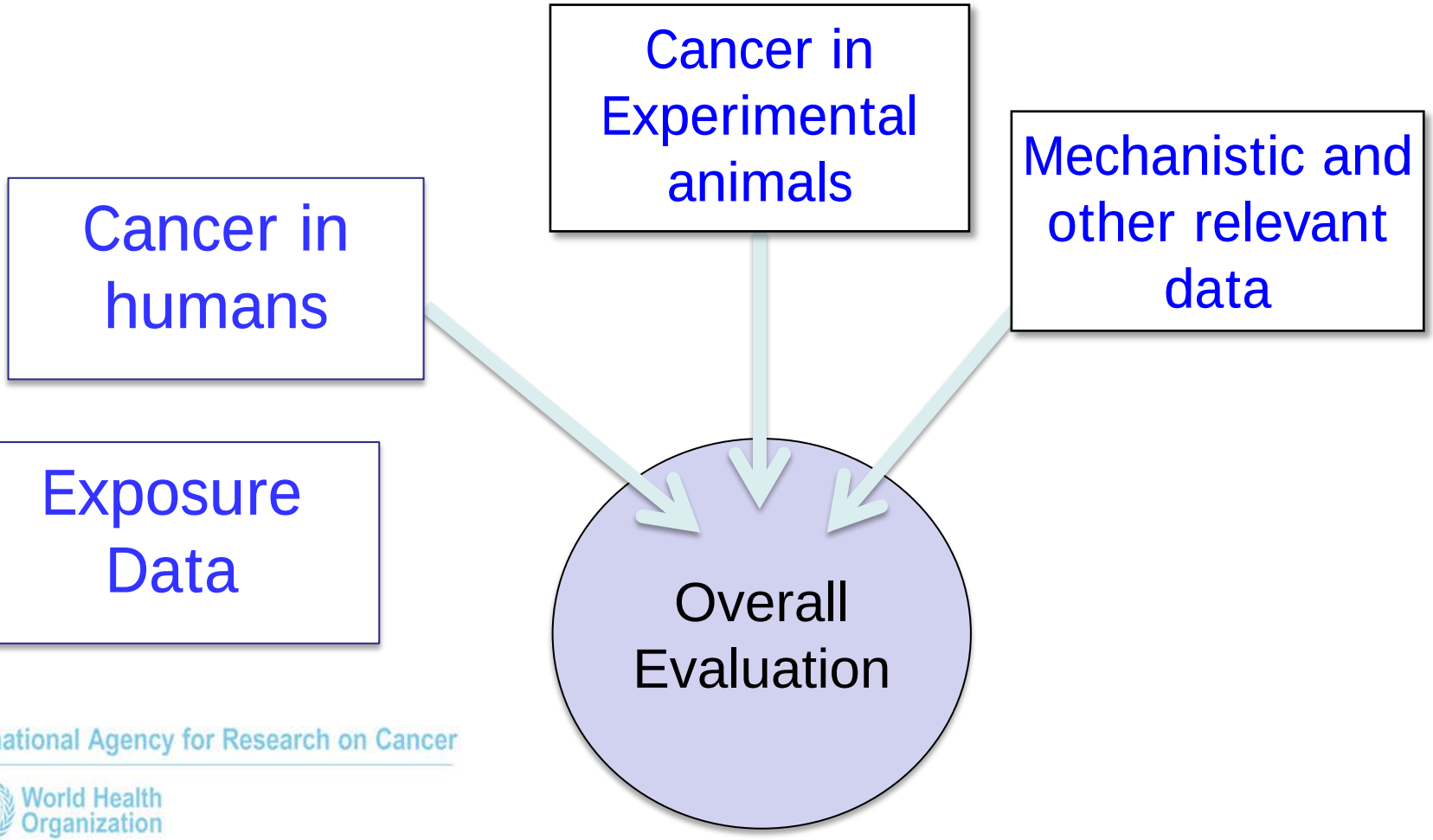
Representatives
of governments and health agencies

Observers
Scientists with a competing interest: observe but do not influence outcomes

What evidence is considered?

Publicly available scientific data

- Peer-reviewed articles
- Government reports
- Available in enough detail for critical review



International Agency for Research on Cancer

World Health Organization

What are the IARC classifications?

Carcinogenic to humans	Group 1
Probably carcinogenic to humans	Group 2A
Possibly carcinogenic to humans	Group 2B
Not classifiable as to carcinogenicity	Group 3
Probably not carcinogenic to humans	Group 4

- IARC classifications refer to the strength of scientific evidence (the level of certainty that the agent causes cancer)
- They DO NOT reflect the level of carcinogenic risk

How are the data evaluated?

Cancer in humans	Cancer in Experimental animals	Mechanistic and other relevant data

❑ *Sufficient evidence*	Causal relationship has been established Chance, bias, and confounding could be ruled out with reasonable confidence
❑ *Limited evidence*	Causal interpretation is credible Chance, bias, or confounding could not be ruled out
❑ *Inadequate evidence*	Studies permit no conclusion about a causal association
❑ *Evidence suggesting lack of carcinogenicity*	Adequate studies covering the full range of exposure are consistent in not showing a positive association at any level of exposure

How are overall evaluations determined?

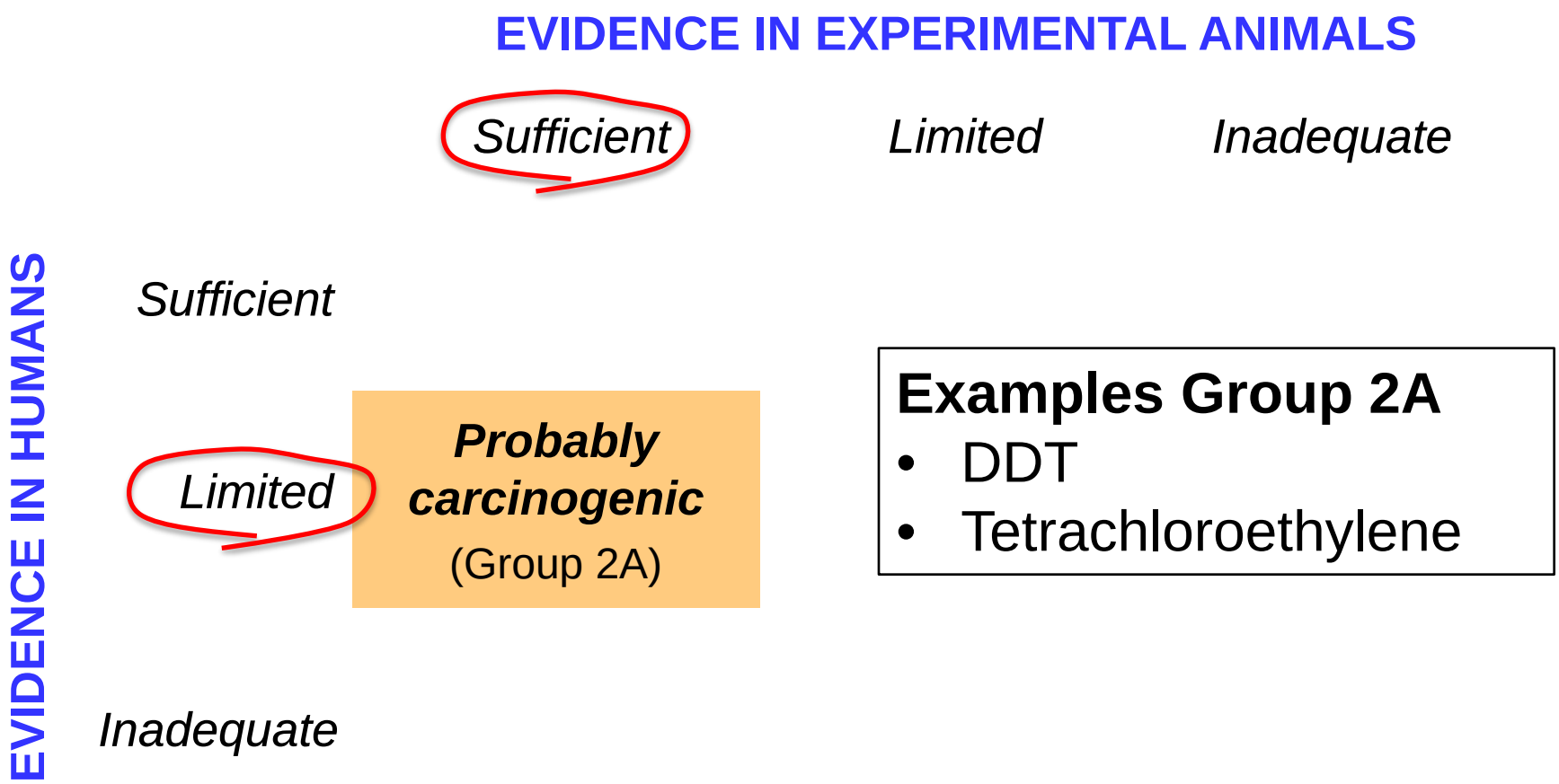
EVIDENCE IN EXPERIMENTAL ANIMALS

EVIDENCE IN HUMANS	*Sufficient*	*Limited*	*Inadequate*
Sufficient	***Carcinogenic to humans*** (Group 1)		
Limited			
Inadequate			

Examples Group 1

- Asbestos
- Tobacco smoking

How are overall evaluations determined?



Examples Group 2A

- DDT
- Tetrachloroethylene

How are overall evaluations determined?

EVIDENCE IN EXPERIMENTAL ANIMALS

Sufficient *Limited* *Inadequate*

EVIDENCE IN HUMANS

Sufficient

Limited

Possibly carcinogenic
(Group 2B)

Inadequate

Possibly carcinogenic
(Group 2B)

Examples Group 2B
- Chloroform
- Styrene

International Agency for Research on Cancer

World Health Organization

How are overall evaluations determined?

EVIDENCE IN EXPERIMENTAL ANIMALS

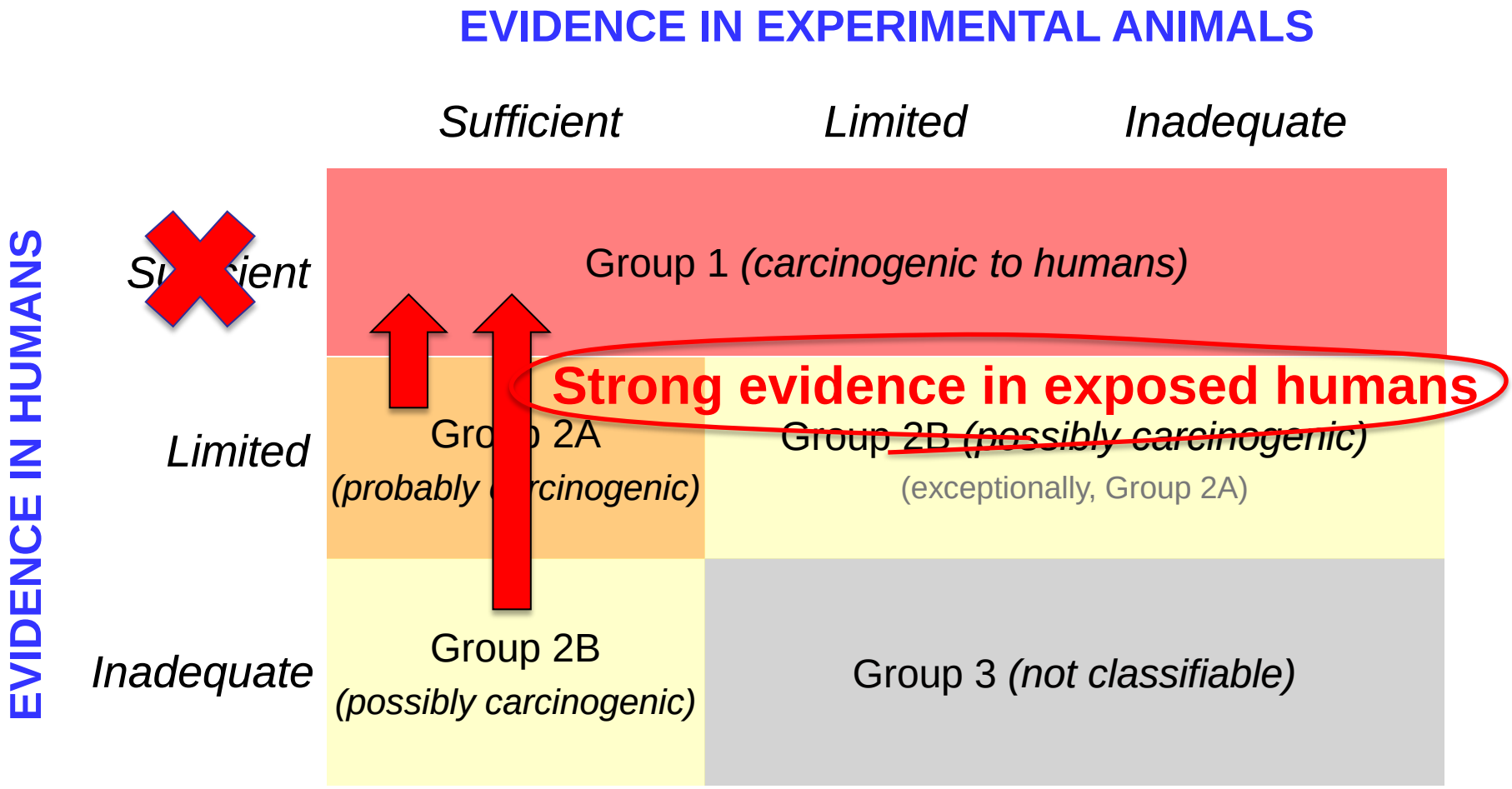
EVIDENCE IN HUMANS	*Sufficient*	*Limited*	*Inadequate*
Sufficient			
Limited			
Inadequate			

Not classifiable (Group 3)

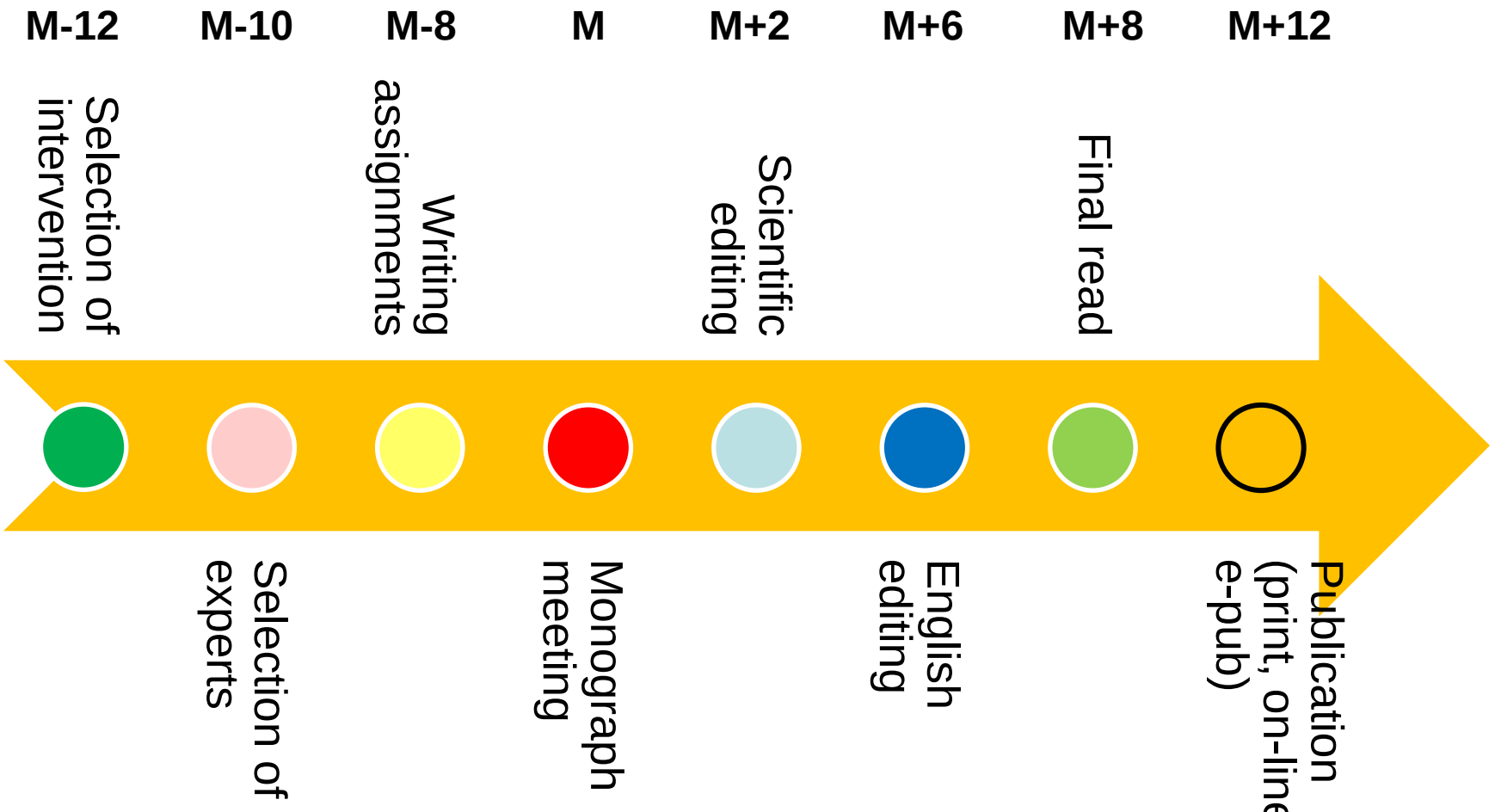
International Agency for Research on Cancer

World Health Organization

How are overall evaluations determined? Mechanistic modifications



The *IARC Monographs* process



International Agency for Research on Cancer

World Health Organization

Outline

- The *IARC Monographs*
  - Procedure
  - Evaluation
- PCB and melanoma
  - Cohort studies
  - Case-control studies
  - Mechanistic data
  - Evaluation

Skin toxicity of PCBs

- Studies on exposure of capacitor workers to PCBs suggested that these compounds are well absorbed by skin contact
- Chloracne and other dermal alterations are well known effects of long-term exposure to PCBs and related compounds
- Interference of PCBs with the metabolism of vitamin A in the skin, resulting in disturbances of the epithelial tissues of the pilo-sebaceous duct (Coenraads et al., 1994).

Studies assessing the link between exposure to PCBs and cancer (≤ 2012)

Cohorts

- Occupational cohort studies (n=13)
- Cohorts of accidental exposure (*Yusho*, *Yucheng*, with 4 follow-up each)
- Cohorts of high dietary exposure (fishermen's wives) (n=5)
- General population cohorts (n=15)

Case-controls

- Non-Hodgkin lymphoma (n=17)
- Breast (n=32)
- Other sites (prostate, testis, lung, pancreas, biliary tract, colorectum, endometrium, **skin**, uveal melanoma, children leukemia)

1.a Cohort studies in capacitor-manufacturing workers

Ruder et al. (2006), Indiana, USA, 1957–1998	3569	Melanoma	Cumulative exposure		
			Lowest tertile	5	SMR, 3.7 (1.2–8.7)
			Middle tertile	2	SMR, 1.5 (0.2–5.4)
			Highest tertile	9	SMR, 2.4 (1.1–4.6)
Prince et al. (2006b), Massachusetts & New York, USA, 1939–1998	14 458	Melanoma	Cumulative exposure		Sex, age, race, calendar period
			< 150 unit-yr		1
			150 to < 620 unit-yr	2	RR, 0.3 (0.1–1.3)
			> 620 unit-yr	6	RR, 0.7 (0.2–1.9)
			Workers employed ≥ 90 days		
			All workers	19	SMR, 1.26 (0.76–1.97)
			Male	14	SMR, 1.66 (0.91–2.79)
			Female	5	SMR, 0.75 (0.24–1.75)
			New York	14	SMR, 1.79 (0.98–3.00)
			Massachusetts	5	SMR, 0.69 (0.22–1.61)
Kimbrough et al. (2003), New York, USA, 1946–1998	7075	Skin, including melanoma	Hourly workers (employed ≥ 90 days as non-salaried workers)	9	[SMR, 1.2 (0.6–2.4)]
			Salaried workers	6	[SMR, 2.1 (0.8–4.7)]

Sex, age, race, calendar period	
Results for 0-yr lag	
P for trend = 0.83	
Sex, age, race, calendar period	
Same plant as Prince et al. (2006b)	

World Health Organization

1.b Cohort study in transformer -manufacturing and -repair workers

Yassi et al. (1994, 2003), Manitoba, Canada, 1946–1995; 1950–1995 (mortality); 1969–1995 (incidence)	2222 men	Melanoma	Duration of employment:			
			> 6 mo	8	SMR, 1.8 (0.2–6.4)	13% excluded from original mortality study because of missing identifiers. Total of deaths until 1995: 261 in cohort, 104 in subcohort, 31 in transformer-assembly department
			> 1 mo	10	SIR, 2.2 (1.1–4.0)	

1.c Cohort studies in electric-power and telecommunications workers

De Guire et al. (1988, 1992), Montreal, Canada, 1976–1983	9590	> 6 mo employment. Exposed to polyvinyl chloride, soldering fumes, and PCBs	Men	3	SMR, 3.0 (0.6–8.8)	
			Women	1	SMR, 4.8 (0.1–27)	
			Men, < 20 yr latency	2	SMR, 9.4 (1.1–34)	
			Men, > 20 yr latency	1	SMR, 1.3 (0.0–7.1)	
			Women, < 20 yr latency	1	SMR, 12.1 (0.0–67)	
Tynes et al. (1994), Norway, 1920–1991; 1953–1991	5088 men	Worked ³ 1 yr at any of eight hydroelectric-power companies	Employment > 1 yr	19	SIR, 1.1 (0.7–1.8)	
			Ever exposed to PCBs	9	SIR, 1.8 [0.8–3.4]	Incidence of other cancers not analysed in association with PCB exposure
			Ever exposed to PCBs, 0–15 µT-yr	0		
			Ever exposed to PCBs, > 15 µT-yr	9	SIR, 2.7 [1.2–5.2]	

1.c Cohort studies in electric-power and telecommunications workers (contnd)

Loomis et al. (1997), California, North Carolina, Pennsylvania, Tennessee, Virginia, USA, 1950–1988	138 905 men	Potential PCB exposure:			Age, calendar time, race, social class, active work status
		0 to < 5 yr	25	RR, 1.3 (0.6–2.6)	
		5 to < 10 yr	9	RR, 1.1 (0.5–2.7)	
		10 to < 20 yr	11	RR, 1.4 (0.6–3.3)	
		³ 20 yr	8	RR, 1.6 (0.6–4.2)	
		Cumulative PCB exposure (h), 0-yr lag:			
		> 0–2000	73	RR, 1.2 (0.6–2.5)	
		> 2000–10 000	12	RR, 1.7 (0.7–7.1)	
		> 10 000	3	RR, 1.9 (0.5–7.1)	
		Cumulative PCB exposure (h), 20-yr lag:			
		> 0 to 2000	42	RR, 1.3 (0.8–2.2)	
		> 2000–10 000	8	RR, 2.6 (1.1–6.0)	
		> 10 000	1	RR, 4.8 (1.5–15)	
		RR per 2000 h cumulative PCB exposure (continuous variable):			
		0-yr lag	-	RR, 1.02 (0.99–1.05)	
		20-yr lag	-	RR, 1.05 (1.01–1.09)	

1.d Cohort studies with other industrial exposures to PCBs

- Robinson et al., 1999
  - Proportional mortality study among 31’000 electrical workers employed in the construction industry
  - Excess mortality: PMR, 1.23 (1.02-1.47)
  - Exposure to PCB could not be confirmed (also exposure to other agents)
- Bahn et al., 1976
  - 2 cases of melanoma among 31 workers in research and development and refinery industry
  - SIR, 50.0 (95% CI, 5.6 – 217)

1.e Cohort studies with high dietary intake of PCBs

Reference, location, follow-up period	Total No. of subjects	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Mikoczy & Rylander (2009) Sweden 1968–2002 (east coast) 1965–2002 (west coast)	2042 (east coast) and 6674 (west coast) fishermen's wives	Dietary intake of fatty fish from Baltic Sea (east coast)		Comparison with national rates		SIR (95% CI)	Age Possible coexposure to PCDDs and PCDFs
		West Coast	Melanoma		38	1.03 (0.73–1.41)	
			Skin		60	1.43 (1.09–1.84)	
		East coast	Melanoma		8	0.76 (0.33–1.49)	
			Skin		9	0.95 (0.43–1.80)	
Helmfrid et al. (2012) Gusum, Sweden 1960–2003	Residents in contaminated area (number not given)	Consumption of foods from contaminated local river		Overall, compared with national death rates		SIR (95% CI)	Age, time period; Possible coexposure to metals because of industrial activities
		Men	Melanoma		15	1.56 (0.87–3.94)	
		Women	Melanoma		11	1.22 (0.60–2.19)	

2. Population-based case-control study

Gallagher et al. (2011)
British Columbia, Canada
2000–2004
80 Cases
310 controls

Exposure assessment:
Lipid-adjusted concentrations of 14 PCBs (units NR):
PCB 28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183, and 187.

Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
			Age, sex, education, skin reaction to repeated sun exposure, and total recreational sun exposure
Total PCBs			
98.01–148.71	11	1.36 (0.45–4.09)	
148.72–213.44	12	1.27 (0.39–4.12)	
> 213.44	29	6.02 (2.00–18.17)	P for trend < 0.001
DL-PCBs			
9.37–15.10	8	0.31 (0.10–0.98)	
15.11–22.57	16	1.16 (0.41–3.26)	
> 22.57	25	2.84 (1.01–7.97)	P for trend = 0.003
NDL-PCBs			
86.68–133.66	12	2.05 (0.66–6.39)	
133.67–192.39	11	1.19 (0.36–3.90)	
> 192.39	30	7.02 (2.30–21.43)	P for trend < 0.001
PCB-118			
> 4.90–8.16	13	0.89 (0.34–2.34)	
> 8.16–13.32	14	1.13 (0.40–3.23)	
> 13.32–46.19	23	3.04 (1.05–8.74)	P for trend = 0.012
PCB-138			
> 12.79–20.76	19	1.89 (0.68–5.28)	
> 20.76–30.65	8	1.30 (0.37–4.56)	
> 30.65–104.49	28	4.91 (1.69–14.32)	

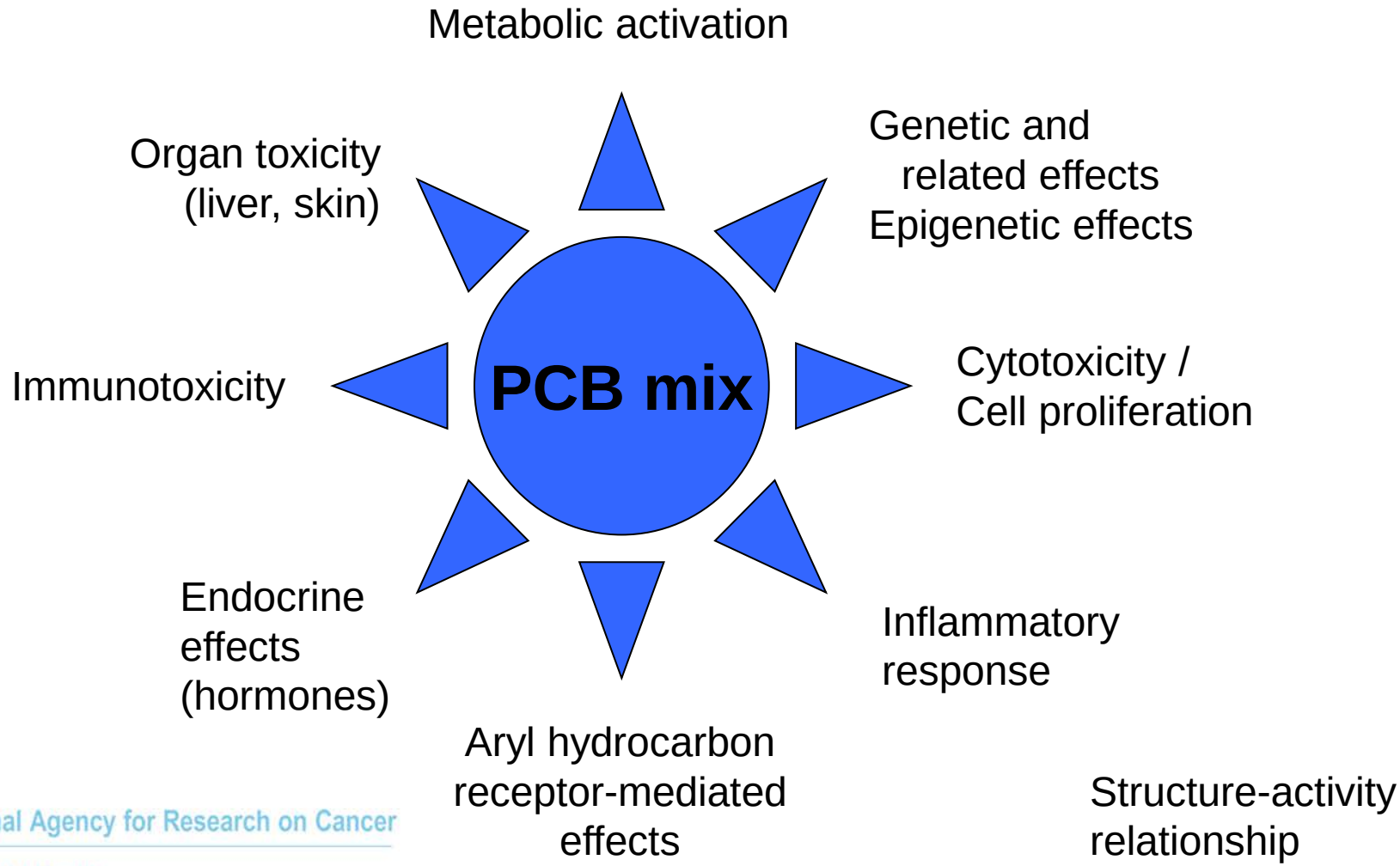
Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
PCB-153			
> 27.75–42.07	14	2.01 (0.70–5.77)	
> 42.07–60.43	12	1.35 (0.43–4.25)	
> 60.43–735.90	27	4.86 (1.68–14.08)	P for trend = 0.002
PCB-156			
> 4.09–6.07	13	1.04 (0.36–2.97)	
> 6.07–8.65	13	1.48 (0.49–4.45)	
> 8.65–113.32	29	4.22 (1.51–11.78)	P for trend = 0.001
PCB-170			
> 7.97–12.16	13	1.50 (0.53–4.29)	
> 12.16–18.51	13	1.10 (0.32–3.77)	
> 18.51–901.52	29	4.60 (1.60–13.22)	P for trend = 0.001
PCB-180			
> 25.20–38.16	12	1.46 (0.49–4.37)	
> 38.16–59.40	14	1.55 (0.44–5.43)	
> 59.40–3786.60	30	5.89 (1.87–18.50)	P for trend = 0.001
PCB-183			
> 1.87–84.86	54	4.27 (1.71–10.68)	
PCB-187			
> 6.64–10.45	11	2.54 (0.75–8.58)	
> 10.45–16.10	15	2.56 (0.76–8.62)	
> 16.10–833.15	30	11.47 (3.32–39.68)	P for trend < 0.001

3. Evaluation

- Elevated number of cancers observed consistently in studies of:
  - workers (cohorts in North America and Europe)
    - Manufacture of capacitors & transformers (four studies)
    - electric power and telecommunication workers (three studies)
    - equipment maintenance (two studies)
  - the general population, with measures of PCB levels in blood (case-control study in Canada)
- In the largest study, the risk increased with the dose
- Increase of uveal melanoma (cancer of the eye) in workers exposed to PCB oils

➢ There is *sufficient* evidence in humans for an association between exposure to PCBs and malignant melanoma

4. Relevant biological effects



The *IARC Monographs* Section

The *IARC Monographs* and Handbooks are supported by grants from:

- U.S. National Cancer Institute (since 1982)
- European Commission, DG Employment, Social Affairs and Inclusion (since 1986)
- U.S. National Institute of Environmental Health Sciences (since 1992)
- Institut National du Cancer (INCa), France
- U.S. Center for Disease Control (CDC)
- American Cancer Society

Molto grazie per l’invito