Animal Carcinogenesis Bioassays and the *IARC Monographs* Programme

Yann Grosse for the *IARC Monographs* Programme; International Agency for Research on Cancer, WHO, Lyon, France

Advisory Group to Recommend Priorities for the *IARC Monographs*

Two Advisory Groups (2010–2014 and 2015–2019)

- Provided list of specific agents with High/Medium priority

AND

- Considered that (a) agents tested in cancer bioassays could be given High priority and (b) agents being tested in cancer bioassays should be given Medium priority

Two Important Sources of Bioassays for the *IARC Monographs*

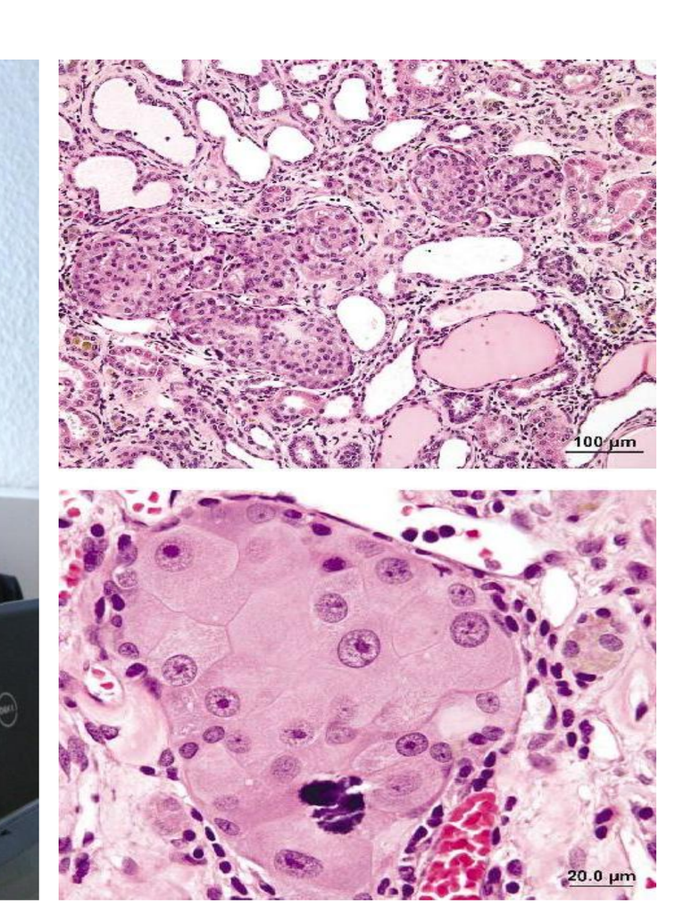
Bioassays performed by the US National Toxicology Program

Bioassays performed by the Japan Bioassay Research Center

The Animal Carcinogenicity Subgroup

Study scientists

Pathologists



References

- Preamble to the *IARC Monographs* (2019). https://monographs.iarc.fr/preamble-to-the-iarc-monographs/
- IMO Vol 123 Group (2018) Carcinogenicity of some nitrobenzenes and other industrial chemicals. *Lancet Oncol.* 19:e661–e682.

Evaluating Animal Evidence

Sufficient evidence	The agent causes increased incidence of malignant tumours or combination of benign/malignant tumours in: • Two or more studies OR • Both sexes of a single species in a well-conducted (ideally GLP) study
Limited evidence	• Increased incidence of malignant tumours or combination of benign/malignant tumours in one study only OR • Increased incidence of benign tumours only OR • Demonstration of promoting activity only OR • Unresolved questions regarding quality/interpretation of studies

Integration of Stream of Evidence in Reaching Overall Classification

Stream of evidence			Classification based on strength of evidence
Evidence of cancer in experimental animals	**Evidence of cancer in humans**	**Mechanistic evidence**	
Sufficient	***Limited***	-	**Probably carcinogenic (Group 2A)**
Sufficient	Inadequate	***Strong (in exposed human cells or tissues)***	
Sufficient	Inadequate	-	**Possibly carcinogenic (Group 2B)**
Limited/Inadequate	Inadequate	-	**Not classifiable (Group 3)**

The evidence in ***bold italic*** represents the basis of the overall evaluation.

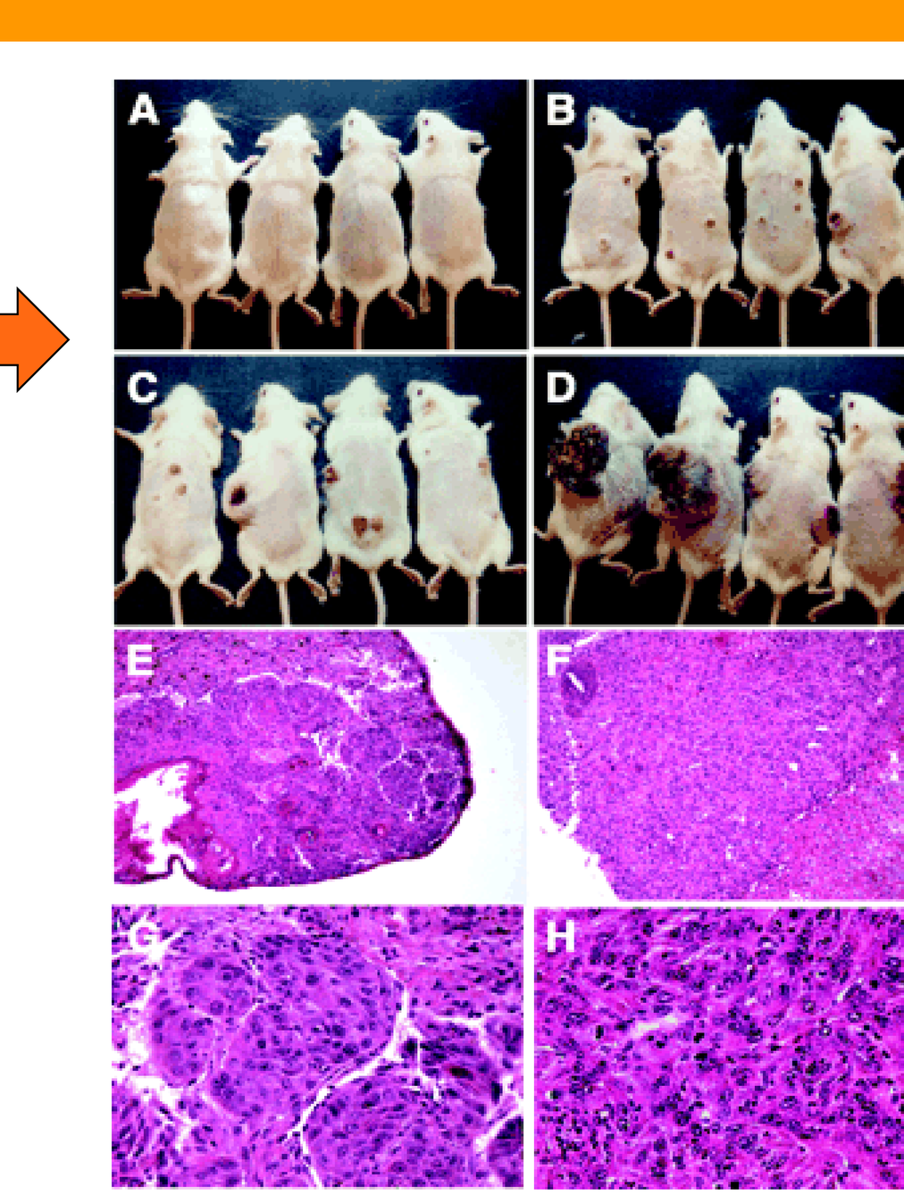
Examples of *IARC Monographs* Classifications Driven by Positive Cancer Bioassays

Agent	Evidence in experimental animals (histopathology)	Evidence in humans (organ site)	Mechanistic evidence	Eval.	Publication date Vol.
Silicon carbide whiskers	***Sufficient*** (Rat: pleural and peritoneal mesothelioma)	Inadequate	Physical properties of these fibres resemble those of asbestos	**2A**	2017 Vol. 111
Multiwalled carbon nanotube (CNT)-7	***Sufficient*** (Rat: peritoneal mesothelioma)	Inadequate	-	**2B**	2017 Vol. 111
Other multiwalled CNTs	Limited (Rat: peritoneal mesothelioma)	Inadequate	-	**3**	2017 Vol. 111
Single-walled CNTs	Inadequate	Inadequate	-	**3**	2017 Vol. 111
Hydrazine	***Sufficient*** (Mouse: bronchioloalveolar Ca, HCC; Rat: HCC; Hamster: HCC)	***Limited*** (bladder cancer)	-	**2A**	2018 Vol. 115
Tetrabromobisphenol A	***Sufficient*** (Mouse: hepatoblastoma, HCC, haemangioSa; Rat: uterine AdCa, malignant mixed Müllerian uterine tumours)	Inadequate	***Strong***	**2A**	2018 Vol. 115
Tetrachloroazobenzene	***Sufficient*** (Mouse: bronchioloalveolar Ca, urethral transitional epithelial Ca, forestomach squamous cell Ca, skin fibroSa and malignant schwannoma; Rat: skin malignant schwannoma, cholangioCa, gingival squamous cell Ca)	Inadequate	***Strong***	**2A**	2019 Vol. 117
Furfuryl alcohol	***Sufficient*** (Mouse: nasal respiratory epithelium squamous cell Ca; Rat: renal tubule Ca)	Inadequate	-	**2B**	2019 Vol. 119
Quinoline	***Sufficient*** (Mouse: haemangioSa, HCC, histiocytic Sa; Rat: haemangioSa, HCC, nasal esthesioneuroepithelioma, mediastinal Sa)	Inadequate	-	**2B**	In prep. Vol. 121
ortho-Phenylenediamine	***Sufficient*** (Mouse: HCC; Rat: HCC, urinary bladder transitional cell Ca)	Inadequate	-	**2B**	In prep. Vol. 123

AdCa, adenocarcinoma; Ca, carcinoma; HCC, hepatocellular carcinoma; Sa, sarcoma

Evaluating Animal Evidence – The New Preamble

Studies eligible to contribute to Sufficient (or Limited) evidence	• Studies in genetically modified animals such as: - Tg.AC (v-Ha-*Ras* oncogene), *Trp53*$^{+/-}$, or *ras*H2 (human *HRAS* proto-oncogene) mice - Mice with targeted expression of viral genes to animal tissue from which human cancer arises - Humanized mice implanted with human cells normally infected by the virus
Additional criteria for Limited evidence	• Increase in tumour multiplicity • Decrease in tumour latency • Positive observational studies in non-laboratory (e.g. companion) animals



B[*a*]p-induced skin tumours in wild type (A,E), Tg.AC (B,F), *Trp53*$^{+/-}$ (C,G) and Tg.AC/*Trp53*$^{+/-}$ (D,H) mice

International Agency for Research on Cancer

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Staff of the *IARC Monographs* & *Handbooks of Cancer Prevention*

Lamia Benbrahim-Tallaa, Véronique Bouvard, Marieke Dusenberg, Sandrine Égraz, Fatiha El Ghissassi, Jennifer Girschik, Fiona Gould, Yann Grosse, Kate Guyton, Amy Hall, Béatrice Lauby-Secretan, Heidi Mattock, Karen Müller, Solene Quennehen, Mary Schubauer-Berigan, Lucy Shedden

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