# Animal Carcinogenesis Bioassays and the IARC Monographs Programme

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# 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

- 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** 

Future priorities for	the IARC Monograph	ıs			
An Advisory Group of 21 scientists from 13 countries met in April, 2014, to recommend topics for assessment in 2015-19 and to discuss strategic matters for the International Agency for	Research on Cancer (IARC) Monographs programme. IARC periodically convenes such advisory groups to ensure that the Monographs reflect the current state of priorities for public health.	The Advisory Group assessed the responses to a call for nominations on the IARC website and recommended a broad range of agents and exposures for assessment with high or medium			
Panel: Agents recommended by the IARC	Advisory Group for assessment		3		
Aspartame and sucralose—widespread use Beta-carotene—chemoprevention trials pro exposed workers) who were exposed to hig Bisphenol A—widely used in epoxy resins a Coffee—numerous case-control and cohort	nd plastics; ongoing cancer bioassays of perina studies have been published since the IARC M	city ups (cigarette smokers and asbestos- atal exposure lonograph	Published Online May 6, 2014 http://dx.doi.org/10.1016/ S14/70-2045/14/70168-8 Upcoming meetings June 3-10, 2014, Volume 110- Perfluoro-octanok ackd, tetrafluoro-ethylene, dichloromethylene,		
Dirnethylformamide—widespread contami Disinfected water used for showering, bath of specific disinfection by-products, includi Ethyl acrylate—new mechanistic studies w	1,2-dichloropropane, and 1,3-propane suitone September 30-October 7, 201. Volume 111: Some nanomaterials and some fibre				
Human cytomegalovirus—herpes virus ubiquitous worldwide: recent human studies suggest potential role in glioblastoma Indium-tin oxide—used in production of liquid crystal displays (LCDs) and touch screens; new cancer bioassay and mechanistic data Iron (in food and as supplements)—daily iron intake exceeds recommended levels in manywomen; epidemiological studies of					
haem iron intake and colon and other cancers are available Mate drinking—new epidemiological studies suggest an association with oesophageal squamous cell carcinoma Methyl tertiary butyl ether (MTBE), ethyl tertiary butyl ether (ETBE), and tert-butyl alcohol—widespread exposure due to use of					
ongoing: mechanistic similarities with asbe Nicotine—increasing population exposure with DNA damage and other pathways of o Obesity and being overweight—high and in Phenyl and octyl tin compounds—used as a	cassay data are available from intraperitoneal istos have been noted ira electronic nicotine delivery systems; recent arcinogenesis icreasing prevalence; many epidemiological st ntifouling agents; new cancer bicassay data a g-term trends of decrease in physical activity,	mechanistic data suggest an association udies of several cancer types are available re available	ARC Monographs Advisory Group Members C J Porties (USA) – Chair, B Stewart (Australia) B Stewart (Australia) B Stewart (Australia) B Stewart (Australia) Grandi) M Gal (unable to attend, China K Hungafwel-Puntainen, HV air (Firland) G Lastrangous (France H Bott (Germany); PF Copta (india) + H Suda (Japan); E Redsal (Nowa); V Sowany E Needal (Nowa); V Sowany		
Pesticides (including carbary), diazinon, lindane, malathion, pendimethalin, and permethrin)—current or former widespread global use; substantial data from new epidemiological studies and recent high throughput screening. Processed and unprocessed red meat—consumed worldwide, several epidemiological studies of colorectal and some other cancers Shift work that involves circadian disruption—several new epidemiological studies, including ongoing studies with more detailed					
information on exposure and cancer outco Styrene—new epidemiological studies and Welding—common workplace exposure; m	(USA) Invited Specialists None Representatives				
reported an association with ocular melano Agents recently tested in cancer bioassays-	oma -new bioassay data for several widely used che	emicals have been published (including	R Johnson (USA) Observers		
2-amino-4-chlorophenol, 1-bromopropan 1,4-dichloro-2-nitroberzene, 2,4-dichloro- (MBT), ortho-phenylenediamine dihydroch	None  IARQWHO Secretariat  I. Bentrahim-Tallas, V Bouward  F El Ghissassi, S Franceschi,				
beta-myrcene; other pesticides (including a	blockers, coal dust; hydrazine; lead; metal wor strazine, chlorpyrifos, DDT, S-ethyl-N,N,-dipro	pylthiocarbamate [EPTC], fonofos,	Y Grosse, N Guha, K Guyton, B Lauby-Secretan, M Leon Rou D Loomis, H Mattock, E Paunovic, K Straff F Sylla, A Tritscher, C Vickers		
glyphosate, pentachlorophenol and 2.4.6-trichlorophenol, terbufos), beta-picoline; riddelline; Sdmonell otyphi and porotyphi (chronic infection); salt; stress; talc; trimethylolpropane triacrylate; zidovudine; agents in ongoing cancer bioassays (allyl chloride, anthracene, and N.N-dimethylacetamide)					

# Two Important Sources of Bioassays for the IARC Monographs

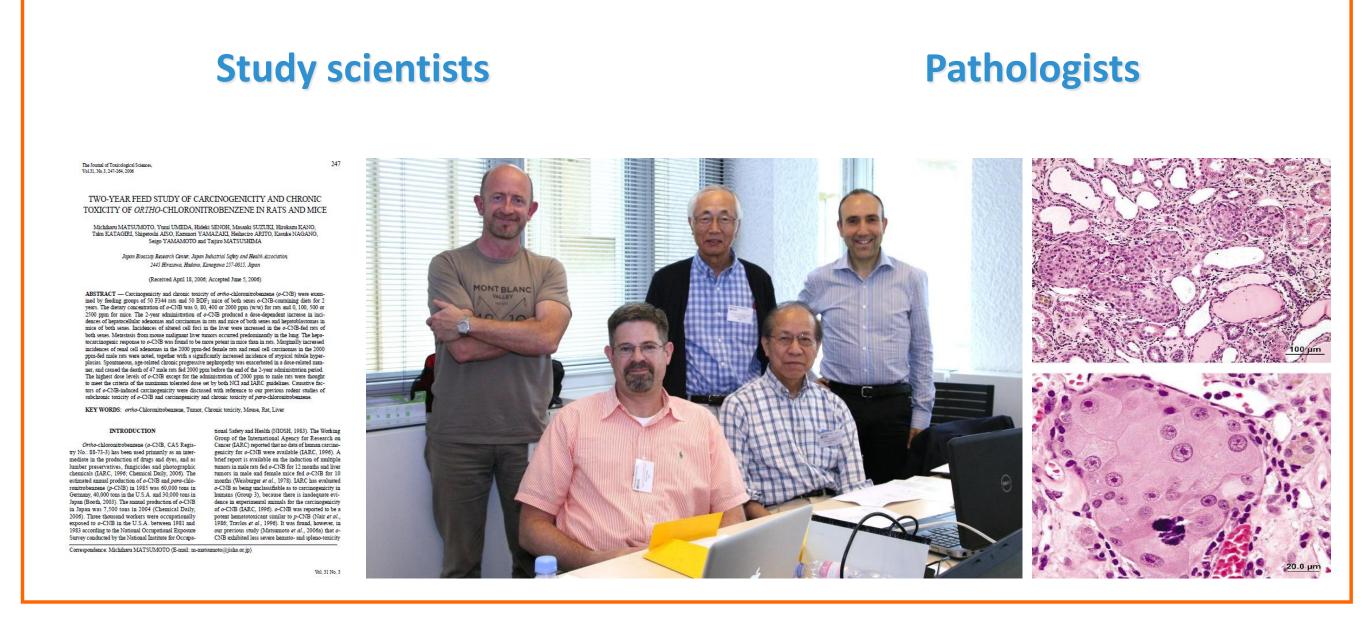
### Bioassays performed by the US National Toxicology Program



#### Bioassays performed by the Japan Bioassay **Research Center**



## The Animal Carcinogenicity Subgroup



- Preamble to the IARC Monographs (2019). <a href="https://monographs.iarc.fr/preamble-to-the-iarc-monographs">https://monographs.iarc.fr/preamble-to-the-iarc-monographs</a>, • IMO Vol 123 Group (2018) Carcinogenicity of some nitrobenzenes and other industrial chemicals. Lancet Oncol. 19:e661–e682.
- International Agency for Research on Cancer



# **Evaluating Animal Evidence**

Sufficient evidence The agent causes increased incidence of malignant tumours or combination of benign/malignant tumours in:

Two or more studies

 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
- Increased incidence of benign tumours only
- Demonstration of <u>promoting activity only</u>
- Unresolved questions regarding quality/interpretation of studies

## Integration of Stream of Evidence in Reaching Overall Classification

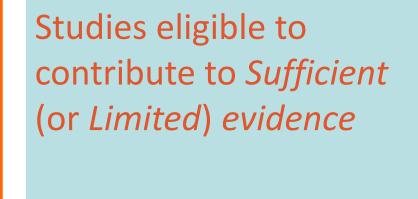
Stream of evidence			Classification based on	
Evidence of cancer in experimental animals	Evidence of cancer in humans	Mechanistic evidence	strength of evidence	
Sufficient	Limited	_	Probably carcinogenic (Group 2A)	
Sufficient	Inadequate	Strong (in exposed human cells or tissues)		
Sufficient	Inadequate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

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

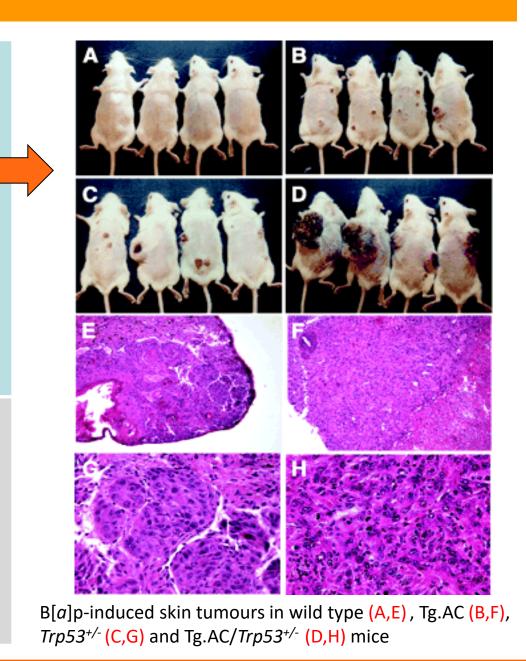
# Examples of IARC Monographs Classifications Driven by Positive Cancer Bioassays

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	<b>2A</b>	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	<b>2A</b>	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	<b>Sufficient</b> (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	<b>Sufficient</b> (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



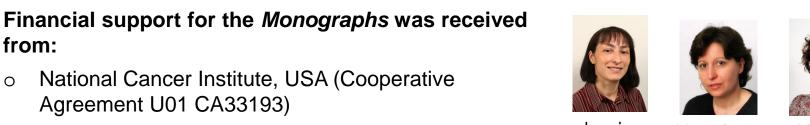
- Studies in genetically modified animals such as:
- Tg.AC (v-Ha-*Ras* oncogene), *Trp53*+/-, or *ras*H2 (human HRAS proto-oncogene) mice - Mice with targeted expression of viral genes to
- animal tissue from which human cancer arises - Humanized mice implanted with human cells normally infected by the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



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  - Centers for Disease Control and Prevention, USA

















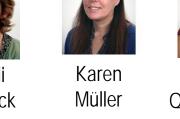




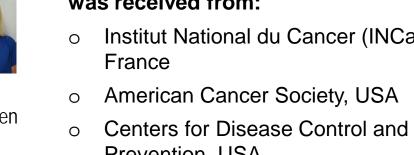


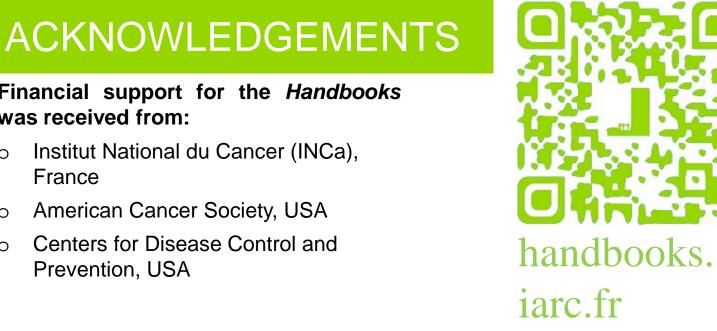














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