The IARC *Monographs* Workshops: *Tumour Concordance between Humans and Experimental Animals* and *Mechanisms Involved in Human Carcinogenesis*

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Background

- The IARC *Monographs* have been published continuously since 1971. For the 100th Volume of the Programme the evidence on all human carcinogens (Group 1) that have been identified to date has been updated
- Nearly 150 experts from 28 countries contributed to Volume 100, which was developed in six meetings from October 2008 to October 2009: A. Pharmaceuticals, 23 agents; B. Biological agents, 11 agents; C. Metals, particles and fibres, 14 agents; D. Radiation, 14 agents; E. Personal habits and indoor combustions, 11 agents; F. Chemicals and related occupations, 34 agents[1-6]
- For each agent, evaluations of the evidence of carcinogenicity in humans and in experimental animals and an overall evaluation of the human cancer hazard have been developed
- Tumour sites with *sufficient evidence* of carcinogenicity in humans or experimental animals, as well as those sites with *limited evidence* in humans were established
- The available information on the established mechanistic events and other likely mechanisms for these agents known to cause cancer in humans was also specifically summarized
- In the past, many IARC *Monographs* evaluations have been made for agents that had been tested in 2-year cancer bioassays in experimental animals, but for which epidemiological information or detailed mechanistic data were lacking. In the future, cancer-hazard identification and cancer-risk assessments will increasingly rely on molecular epidemiology and on information about mechanisms of carcinogenesis, especially for new and untested agents for which bioassays in experimental animals and classical epidemiological studies in humans are less likely to become available.
- Hence, insight into how related agents may cause cancer in humans will be particularly useful in future assessments of the IARC *Monographs*
- In addition, identification of carcinogens based on cancer studies in experimental animals should be facilitated

Objectives

- Two Workshops will synthesize the Volume 100 review information for related future IARC Scientific Publications on *Tumour Concordance between Humans and Experimental Animals* and *Mechanisms Involved in Human Carcinogenesis*
- These publications will build on the analyses of two extensive databases (see upper right-hand corner) prepared from information collected in the Volume 100 review. These analyses should address important hazard- and risk-assessment questions and cut across individual agents to discern more general principles.

As for tumour concordance between humans and experimental animals, questions and goals are:

- To determine whether particular tumours in experimental animals have predictive value for human cancer (either at an analogous site or at other sites)
- What are the circumstances under which it is reasonable to expect analogous tumour sites to occur in different species ?
- Identify human cancer sites without good animal models
- To find out whether different tumour sites tend to occur together
- The analyses may be restricted to subsets of carcinogenic agents (*e.g.*, metals, physical agents, hormonal agents, biological agents) or they may be more general in nature

As for mechanisms involved in human carcinogenesis, the Workshops will aim to:

- Compile these mechanisms that were identified in Volume 100; joint consideration of multiple agents that act through a similar mechanism could facilitate development of a more detailed description of that mechanism and its common mechanistic steps
- Identify biomarkers that could be influential in future studies; this part will identify biomarkers that could be included in future studies to provide more reliable information about whether a particular mechanism is operating in either humans or experimental animals. Detailed information from advanced toxicological analyses and results on various predictive end-points and biomarkers in short-term animal assays may allow cancer-hazard identification in the absence of classical bioassays and epidemiology.
- Identify susceptible populations and developmental stages. Because susceptibility often has its basis in a mechanism, this could also facilitate a more reliable and precise description of populations that may be susceptible to agents acting through each mechanism.
- Promote research that will lead to more reliable evaluations

Excerpt from the databases

Database on experimental animal and human tumour sites

Volume	Agent	Target site in humans	Study ID	Study reference	Species	Strain	Exposure route	Sex	Site	Histology	Neoplasm as described in the study	Dose-Response	Study details
100A	Azathioprine	Non-Hodgkin lymphoma, skin (squamous-cell carcinoma)	99	Imamura *et al.* (1973)	Mouse	C57BL	s.c.	5	Lymphoid tissue	lymphoma	8 thymic lymphomas; 1 reticulum-cell neoplasm; 2 non-thymic lymphomas.	0	25 males and 21 females. Injections of 100 mg/kg bw, 2x/wk for 2 wk and then 1x/wk for 7 months. 10 males and 6 females as controls. Males and females combined: 11/38 (29%); controls: 0/16 (p=0.022)
100A	Azathioprine	Non-Hodgkin lymphoma, skin (squamous-cell carcinoma)	100	Mitrou *et al.* (1979a)	Mouse	New Zealand Black; New Zealand White	s.c.	2	Lymphoid tissue	lymphoma	Lymphomas are 77% of all tumours in treated mice. Controls: only one malignant lymphoma.	1	4 groups (10-15 mice) NZW/NZB. 0.2 mg/mouse, 0.4 mg/mouse (6 or 12 mg/kg bw) 5x/wk, or 2.0 mg/mouse/wk beginning at 120 or 180 days of age. All tumours: 10/48 (21%); 29/48 (60.5%); 4/27 (15%). Controls: 3/96 (3%). 0.2 and 0.4 mg/mouse 5x/wk groups: p=0.001 and p=0.0001
100A	Azathioprine	Non-Hodgkin lymphoma, skin (squamous-cell carcinoma)	101	Mitrou *et al.* (1979b)	Mouse	New Zealand Black; New Zealand White	i.p.	1	Lymphoid tissue	lymphoma	Ten treated mice developed 11 tumours (9 lymphomas, and one mammary and one lung adenocarcinomas).	0	4 groups (9-10 mice) NZW/NZB mice. 0.2 mg/mouse, 5x/wk beginning at 6-12 wk of age. All tumours: 10/49 (20%). Controls: 2/93 (2%) (p<0.05)

Database on mechanisms involved in human carcinogenesis

Volume	Agent	Target site in humans (sites on which *sufficient* human evidence is based)	Other sites with *limited* human evidence	Evidence in exp. animals	Target site in experimental animals	Established mechanistic events	Other likely mechanistic events
100A	Azathioprine	Non-Hodgkin lymphoma, skin (squamous-cell carcinoma)	-	*sufficient*	Mouse: lymphoid tissue	Immunosuppression	-
100A	Azathioprine	Non-Hodgkin lymphoma, skin (squamous-cell carcinoma)	-	*sufficient*	Mouse: lymphoid tissue	DNA damage	-
100A	Diethylstilbestrol	Vagina (clear cell carcinoma, exposure *in utero*), cervix (clear cell adenocarcinoma, exposure *in utero*)	Cervix (squamous cell carcinoma, exposure *in utero*), testis (exposure *in utero*)	*sufficient*	Mouse: cervix, mammary gland, uterus Hamster: kidney	-	Epigenetic programming (perinatal exposure)

bw, body weight; dose-response (0, negative; 1, positive); i.p., intraperitoneal injection; sex (1, positive in males; 2, positive in females; 5, positive in males and females); s.c., subcutaneous injection; wk, week or weeks

The Workshops

- Preparations to organize these two Workshops have been initiated in 2011 in consultation with a core group of experts. The development of the database with the Volume 100 information on the two main topics is on-going (see above) and will be completed in April 2012. The Workshops are scheduled to take place 16–18 April and 28–30 November 2012 at the IARC. Workshop participants have been drawn largely, but not exclusively from the six Volume 100 Working Groups.
- The first meeting will discuss in subgroups and in plenary sessions:
  (1) tumour concordance and mechanisms together, to see where the two topics can benefit from each other
  (2) the databases and whether further development and refinement with respect to content and structure are needed in order to allow more detailed analysis
  (3) which data analyses should be done by participants in the intervening period until the second Workshop with the same Working Group
  (4) how the ensuing publication(s) should be structured
- During the first Workshop there will also be invited lectures on key issues and recent insights in toxicology and carcinogenesis (e.g., the hallmarks of cancer, inflammation and cancer, recent developments in toxicology, biological models for leukaemia and lymphoma, tumour (site) concordance, previous analyses of tumour (site) concordance on the basis of IARC *Monographs* data).
- The second Workshop will discuss the results of the analyses and the interpretation of the data, and aim to reach consensus on the final form and content of the publication(s).

References

[1]Grosse Y, Baan R, Straif K *et al.* (2009) A review of human carcinogens—Part A: pharmaceuticals. *Lancet Oncol*, 10: 13-14.
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[6]Baan R, Grosse Y, Straif K *et al.* (2009) A review of human carcinogens—Part F: chemical agents and related occupations. *Lancet Oncol*, 10: 1143-1144.

Recommended reading

[7]Cogliano VJ, Baan R, Straif K *et al.* (2011) Preventable exposures associated with human cancers. *J Natl Cancer Inst*, 103: 1827-1839
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[9]Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. *Cell*, 144: 646-674

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