

Development of a data set on tumours and tumour sites in humans and in experimental animals for Group 1 agents identified up to and including Volume 109 of the *IARC Monographs*

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Introduction

Since its establishment in the early 1970s, the *IARC Monographs Programme* has conducted hazard evaluations of agents that may increase the risk of cancer in humans. The reviews of the relevant literature and the ensuing evaluations are

conducted by international Working Groups of expert scientists according to a well-established and rigorous protocol that is described in the Preamble to the *IARC Monographs* (IARC, 2006). The reviews and evaluations are published as the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*.

For Volume 100 of the *IARC Monographs*, a review was undertaken of relevant information on all the agents classified in Group 1 (*carcinogenic to humans*). For convenience, Volume 100 was organized in six parts (100A–100F), covering pharmaceuticals (IARC, 2012e); biological agents (IARC, 2012b);

arsenic, metals, fibres, and dusts (IARC, 2012a); radiation (IARC, 2012f); personal habits and indoor combustions (IARC, 2012d); and chemical agents and related occupations (IARC, 2012c). The reviews and analyses were discussed during a two-part Workshop on Tumour Site Concordance and Mechanisms of Carcinogenesis, which was convened by IARC on 16–18 April 2012 and 28–30 November 2012 in Lyon.

The data set described in this Annex also includes information on five additional human carcinogens that were added to Group 1 after completion of Volume 100, i.e. diesel engine exhaust (Volume 105; IARC, 2013), trichloroethylene (Volume 106; IARC, 2014), polychlorinated biphenyls (Volume 107; IARC, 2016b), and outdoor air pollution and particulate matter in outdoor air pollution (Volume 109; IARC, 2016a). For ease of reference, these five agents are included in an expanded group of chemical agents and related occupations denoted by Volume 100F*. Although additional Group 1 agents have been identified in subsequent volumes of the *Monographs*, the current data set extends only up to and including Volume 109, the last *Monograph* for which final results were available at the time this Annex was completed.

The reviews and updates in Volumes 100A–F specifically focused on identification of tumours, both in humans and in experimental animals, resulting from exposure to each of the Group 1 agents. In addition, the organs where the tumours were reported to arise were documented where possible. The availability of this information on the more than 100 human carcinogens in Group 1 prompted an investigation of

what level of concordance may exist between humans and experimental animals with respect to tumours and tumour sites. To this end, the pertinent information in Volume 100 was captured in a comprehensive table (Table A1; online only; available from: <http://publications.iarc.fr/578>) that could then serve as a basis to develop a database on tumour sites in animals and humans. The creation of such a database – designed to be amenable to biostatistical analysis (see Chapter 21, by Krewski et al.) – was motivated by the interest in a statistical assessment of the degree of concordance between animal and human tumour sites. This important scientific question bears upon the extent to which the animal cancer data collected here may be extrapolated to humans. It is anticipated that the database will also find other applications, including in the development of human tumour profiles to assist in the identification of additional Group 1 agents.

It should be noted that for agents classified in Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) the information on cancer in humans may often be lacking or may not be strong enough for a proper interspecies comparison to be made. For this reason, the concordance analysis (see Chapter 21, by Krewski et al.) is focused on agents in Group 1. In addition, it was decided that *sufficient evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals were required for an agent to be included in the statistical concordance analysis; with less than *sufficient evidence* of carcinogenicity, in humans or in animals, the definition of a tumour site in either species would

become less reliable or impossible. Therefore, although the data set described in this Annex (Table A1; online only; available from: <http://publications.iarc.fr/578>) provides information on all the Group 1 agents, the actual database of human carcinogens eligible for the concordance analysis is appreciably smaller (see Chapter 21, by Krewski et al.).

Methods

In making an evaluation of the evidence of carcinogenicity to humans, an *IARC Monographs Working Group* is generally asked to identify organ sites in humans for which there is *sufficient evidence* of carcinogenicity of the agent under study. However, the Working Group is not required to identify organ sites for carcinogenicity in experimental animals at the time of the evaluation, but is required more simply to assess the overall weight of the evidence in experimental animals. Consequently, for the purpose of this IARC Scientific Publication, the species-specific tumour sites in experimental animals needed to be identified for each Group 1 agent before proceeding to explore concordance between animal and human cancers.

During the six meetings for Volumes 100A–F, the respective Working Groups identified studies in experimental animals that provided results on species-specific tumour sites. This was based on criteria adapted from the Preamble to the *IARC Monographs*. It was considered that there is *sufficient evidence* for identifying a species-specific tumour site in experimental animals under any one of the following three conditions:

- An increased incidence of malignant neoplasms or an appropriate

combination of benign and malignant neoplasms *originating from the same organ (or tissue)* is identified in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols.

- An increased incidence of malignant neoplasms or an appropriate combination of benign and malignant neoplasms *originating from the same organ (or tissue)* is identified *in both sexes* of one species in one well-conducted study, ideally performed under good laboratory practice (GLP).
- A single study in one species and sex might be considered to provide *sufficient evidence* for a specific organ site when malignant neoplasms occur to an unusual degree with regard to incidence, type of tumour, or age at onset.

Confirmation of the tumours and tumour sites identified in Volume 100 was performed by one member each from the IARC secretariat and from the project team at the University of Ottawa, Canada, who systematically consulted the original publications describing the studies cited in the Volume 100 reviews. It was decided by the Workshop participants that extraction of the following information was required for each study: species, strain, sex, route of exposure, and tumour site including histology. Further information would be recorded as “study details”, for example dose, number of test animals, number of control animals, age at start of exposure, duration of exposure, duration of follow-up, and statistical analyses. The two team members independently captured the information, and any disagreements were resolved in a group discussion. Tables summarizing this information were created to enable peer review by the

Workshop participants to confirm the entries. Ultimately, more than 2000 studies were reviewed, and more than 1000 of these contributed to the identification of species-specific tumour sites in experimental animals. Studies were not considered if any one of the following exclusion descriptors was applicable:

- initiation–promotion studies;
- co-carcinogenicity studies;
- studies in genetically modified animals;
- studies with precancerous lesions as the outcome;
- studies on the carcinogenicity of metabolites and derivatives;
- studies with non-laboratory animals (livestock; companion animals);
- studies with analogous agents (similar chemical structure or similar virus type).

Results

Table A2 illustrates the format of the data set on tumours and tumour sites, with one agent from each of Volumes 100A–F. From epidemiological studies, human tumour sites with *sufficient evidence* and those with *limited evidence* are mentioned. For experimental animals, tumour sites are recorded only for agents that demonstrate *sufficient evidence* of carcinogenicity, as indicated above. Strain, sex, and route of exposure reported for each animal study are also captured. Comments are provided as appropriate. For example, no human tumour site is specified for aristolochic acid, because this agent was placed in Group 1 on the basis of the classification of plants containing aristolochic acid as a Group 1 agent, supported by mechanistic data on genotoxicity (IARC, 2012e). Together with other “mechanistic upgrades”, this agent is listed in the complete

data set (see Table A1; online only; available from: <http://publications.iarc.fr/578>) but is not included in the statistical analysis of concordance (see Chapter 21, by Krewski et al.).

All the information on tumours and tumour sites in humans and in experimental animals from *IARC Monographs Volumes 100–109* is given in Table A1 (online only; available from: <http://publications.iarc.fr/578>).

Observations

For some Group 1 agents, there were only a few studies that contributed to the identification of a tumour site in experimental animals, and frequently the studies did not enable the definition of an organ site, as a result of inadequate reporting. There were many instances where the reported tumour incidences were uninformative, possibly as a result of the small number of animals tested. In other cases, studies reported an increased incidence of tumours but without mention of malignancy or proper description of histopathological details. Also, some reports did not specify the purity of the administered agent. In these cases the experts in the *Monographs Working Groups* and the two team members (one member each from the IARC secretariat and from the project team at the University of Ottawa, Canada) had to consider the possibility of confounding, because the existence of other agents in the administered sample could have contributed to the outcome. In some studies, animals were followed up for only short periods of time after treatment, especially in studies investigating acute adverse effects, which precluded observation of carcinogenic outcomes that may take longer to develop.

Table A2. Template for presentation of data on tumours and tumour sites in humans and in experimental animals from the *IARC Monographs*

Volume 100 part Agent number	Agent	Sites with sufficient evidence in humans	Sites with <i>limited</i> evidence in humans	Agent tested in experimental animals	Species Site	Histology	Study, sex, strain, exposure route	Comments
A 1	Aristolochic acid			Aristolochic acid	Rat Forestomach	Squamous cell carcinoma	Mengs et al. (1982) (Volume 82; Volume 100A), MF, Wistar, g.; Mengs (1983) (Volume 82; Volume 100A), M, Wistar, g.; Schmeiser et al. (1990) (Volume 100A), M, Wistar, d.w.; Hwang et al. (2006) (Volume 100A), M, Sprague-Dawley, g.	The experts consider concordance when an agent in humans such as <i>Plants containing</i> <i>aristolochic acid</i> is tested in animals by one of its main components such as <i>Aristolochic acid</i> .
A 1	Aristolochic acid			Aristolochic acid	Rat Renal pelvis	Transitional cell carcinoma	Mengs et al. (1982) (Volume 82; Volume 100A), M, Wistar, g.	The experts consider concordance when an agent in humans such as <i>Plants containing</i> <i>aristolochic acid</i> is tested in animals by one of its main components such as <i>Aristolochic acid</i> .
B 24	<i>Clonorchis</i> <i>sinensis</i> (infection with)	Cholangiocarcinoma						No data on animal experiments listed because of <i>limited evidence</i> of carcinogenicity.

Table A2. Template for presentation of data on tumours and tumour sites in humans and in experimental animals from the *IARC Monographs* (continued)

Volume 100 part Agent number	Agent	Sites with sufficient evidence in humans	Sites with limited evidence in humans	Agent tested in experimental animals	Species Site	Histology	Study, sex, strain, exposure route	Comments
C 35	Arsenic and inorganic arsenic compounds	Lung, urinary bladder, skin	Kidney, liver, prostate	Dimethylarsinic acid [DMA(V)], Monomethyl- arsonous acid [MMA(III)], Sodium arsenite	Mouse Lung	Bronchiolo- alveolar carcinoma	DMA(V): Tokar et al. (2012a), M, CD1, d.w.; Sodium arsenite: Waalkes et al. (2003), F, C3H/HeNcr, in utero; Waalkes et al. (2006a, b), M, CD1, in utero; Tokar et al. (2011), MF, CD1, in utero + p.o.; Tokar et al. (2012a), M, CD1, in utero; MMA(III): Tokar et al. (2012b), M, CD1, in utero	
C 35	Arsenic and inorganic arsenic compounds	Lung, urinary bladder, skin	Kidney, liver, prostate	Sodium arsenite, Monomethyl- arsonous acid [MMA(III)]	Mouse Liver	Hepatocellular carcinoma	Sodium arsenite: Waalkes et al. (2003), M, C3H/HeNcr, in utero; Waalkes et al. (2004a), M, C3H/HeNcr, in utero; Waalkes et al. (2006a, b), M, CD1, in utero; Tokar et al. (2011), MF, CD1, in utero + p.o.; Tokar et al. (2012a), M, CD1, in utero; MMA(III): Tokar et al. (2012b), M, CD1, in utero	
C 35	Arsenic and inorganic arsenic compounds	Lung, urinary bladder, skin	Kidney, liver, prostate	Dimethylarsinic acid [DMA(V)]	Rat Urinary bladder	Transitional cell carcinoma	Wei et al. (1999, 2002), M, F344/DuCrj, p.o.; Arnold et al. (2006), F, F344, p.o.	
D 45	Fission products including Sr-90	Solid cancers, leukaemia		Sr-90	Mouse Bone	Osteosarcoma	Nilsson (1970, 1971), M, CBA, i.p.; Nilsson et al. (1980), F, CBA, i.p.	

Table A2. Template for presentation of data on tumours and tumour sites in humans and in experimental animals from the *IARC Monographs* (continued)

Volume 100 part Agent number	Agent	Sites with sufficient evidence in humans	Sites with limited evidence in humans	Agent tested in experimental animals	Species Site	Histology	Study, sex, strain, exposure route	Comments
D 45	Fission products including Sr-90	Solid cancers, leukaemia		Sr-90	Dog Bone	Osteosarcoma	Gillett et al. (1992), MF, beagle, i.v.; White et al. (1993), MF, beagle, p.o.; Gillett et al. (1987), MF, beagle, inh.	
E 63	Acetaldehyde associated with consumption of alcoholic beverages	Oesophagus and upper aerodigestive tract combined						Sufficient evidence in experimental animals but no organ sites identified due to the absence of two (or more) studies of adequate design and quality pointing at the same organ site (with a similar histological origin) in the same species.
F 75	Acid mists, strong inorganic	Larynx	Lung					No animal data available.

b.pouch, buccal pouch; d.w., drinking water; F, positive female; g., gavage; i.col., intracolonic; i.f., intrafetal; i.m., intramuscular; i.mam., intramammary; inh., inhalation; i.p., intraperitoneal; i.pulmo., intrapulmonary; i.t., intratracheal; i.v., intravenous; M, positive male and female; MF, positive male and female; NR, not reported; per., perinatal; p.o., feeding; s.c., subcutaneous; skin, skin application.

Conclusions

The data set developed here to define tumour sites for carcinogenicity in humans and in experimental animals summarizes all available data on Group 1 agents identified in Volumes 100–109 of the *IARC Monographs*. At the time of completion of Volume 109, a total of 111 Group 1 agents had been identified, and these are included in the list presented in Table A1 (online only; available from: <http://publications.iarc.fr/578>). This comprehensive set of data constitutes a unique basis for

addressing the important scientific question, i.e. to which extent these animal cancer data are comparable with human cancer data. The value of this data set is demonstrated by the initial concordance analyses that have been conducted with the database derived from it (see Chapter 21, by Krewski et al.).

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