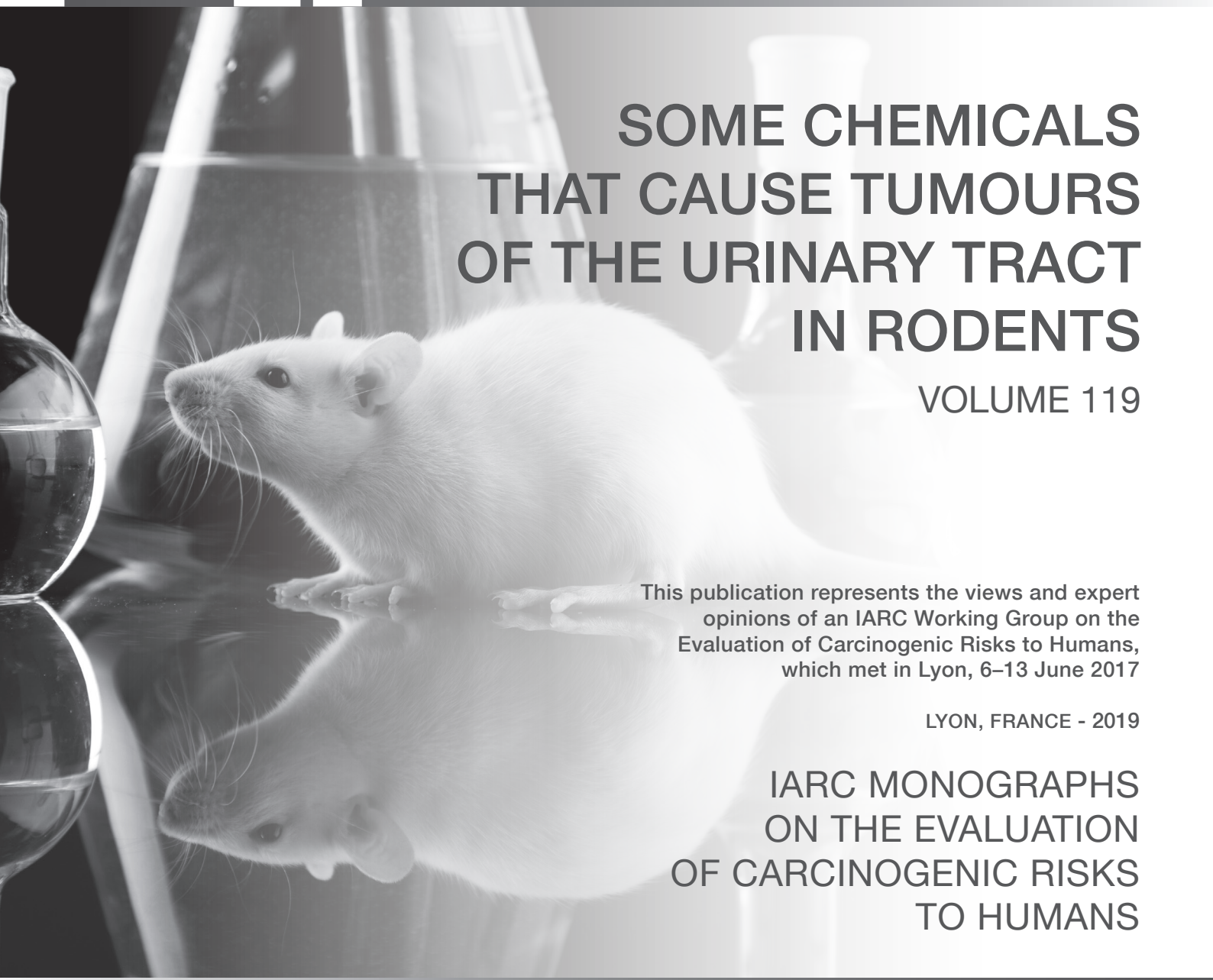
IARC MONOGRAPHS



SOME CHEMICALS THAT CAUSE TUMOURS OF THE URINARY TRACT IN RODENTS

VOLUME 119

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 6–13 June 2017

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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

GENERAL REMARKS

This one-hundred-and-nineteenth volume of the *IARC Monographs* contains evaluations of the carcinogenic hazard to humans of seven industrial chemicals (melamine, 1-*tert*-butoxypropan-2-ol, β-myrcene, furfuryl alcohol, pyridine, tetrahydrofuran, and vinylidene chloride) to which workers or the general population are or can potentially be exposed. These chemicals have been recommended for evaluation primarily because of new data on cancer in experimental animals. Epidemiological data for each of the chemicals included in Volume 119 are either lacking or scant.

Vinylidene chloride, melamine, pyridine, and 1-*tert*-butoxypropan-2-ol were evaluated previously in Volumes 71, 73, 77, and 88 of the *IARC Monographs* (IARC, 1999a, 1999b, 2000, 2006), respectively, as *not classifiable as to* their *carcinogenicity to humans* (Group 3). Apart from the availability of new data, a separate consideration pertaining to experimental data for chemicals subject to re-evaluation (e.g. 1-*tert*-butoxypropan-2-ol, pyridine) is that certain criteria for specification of *sufficient* and *limited* evidence of carcinogenicity in experimental animals (as detailed in the Preamble to the *IARC Monographs* as amended in January 2006) had changed since the previous evaluation. In relation to experimental data, administration of all seven compounds to rats and mice of both sexes resulted, in at least some instances, in an increase in the incidence of urological tumours, that is tumours of the kidney or urinary bladder. A summary of the findings of this volume appears in *The Lancet Oncology* (Grosse et al., 2017)

High production volume chemicals, and quantification and relative contributions of sources of exposure

Five "high production volume" chemicals (melamine, furfuryl alcohol, pyridine, tetrahydrofuran, and vinylidene chloride) were evaluated. The Working Group noted that most of the agents reviewed in this volume do not have a single source of exposure, and humans may be exposed occupationally or through food and beverages, drinking-water, and the environment. Quantitative determination of the most important sources of human exposure is relevant and was attempted by the Working Group when valid information was available in the scientific literature. However, for many of the agents, quantitative information on many – if not all (e.g. 1-*tert*-butoxypropan-2-ol) – sources of exposure was lacking or inconclusive.

α_{2u}-Globulin-associated kidney tumours in male rats

Of the seven chemicals under review in this volume, four (1-*tert*-butoxypropan-2-ol, β-myrcene, pyridine, and tetrahydrofuran) caused renal tubule tumours in male rats. With each of these four chemicals, the concentration of α_{2u}-globulin was increased in the rat kidneys. The induction of α_{2u}-globulin nephropathy and carcinogenesis is a male-rat-specific disease; thus, if the induction of renal tubule tumours in male rats can be attributed to an α_{2u}-globulin-associated mechanism, the induction of these kidney tumours may not be relevant for humans. IARC established seven criteria that need to be met in order to conclude that renal tubule tumours arising in male rats are due to an α_{2u}-globulin-associated mechanism (Capen et al., 1999). Although each of the four chemicals caused an accumulation of α_{2u}-globulin and most caused a characteristic sequence of histopathological changes associated with α_{2u}-globulin accumulation, many of the other five criteria were not determined or were not met, or the experimental data were inconsistent; thus, the available evidence did not fully satisfy an α_{2u}-globulin-associated mechanism for the induction by these four chemicals of renal tubule tumours in male rats.

Transgenic mouse models

The Working Group noted the difficulty in evaluating a short-term study in transgenic mice (Spalding et al., 2000; see also Tennant et al., 1996) in light of the article by Pritchard et al. (2003) on "The role of transgenic mouse models in carcinogen identification", which states that although they have great promise, transgenic models also have actual or potential limitations for use in a carcinogen identification effort. Many transgenic models have mutations in only one pathway that may or may not be relevant to human cancer processes for a given chemical. In addition, the specific gene defect may influence tumour development and type, increasing the difficulty of modelling the human response. It is also of concern that the genetic background can influence tumour type, incidence, and location. Thus, short-term, gene-specific transgenic assays may not be able to assess critical information that can be obtained in longer-term bioassays (e.g. multiple target organ effects, interactions of time and age). These issues do not preclude the use of transgenic models, but they must be considered in the selection and interpretation of data obtained using such models.

Evaluation of data on the mechanisms of cancer

In its evaluation of data on mechanisms of carcinogenesis, the Working Group used the procedures first introduced in Volume 112 of the *IARC Monographs* for assessing the strength of evidence with respect to 10 key characteristics of carcinogens (Smith et al., 2016) and for reviewing data from large-scale toxicity testing programmes (IARC, 2017).

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