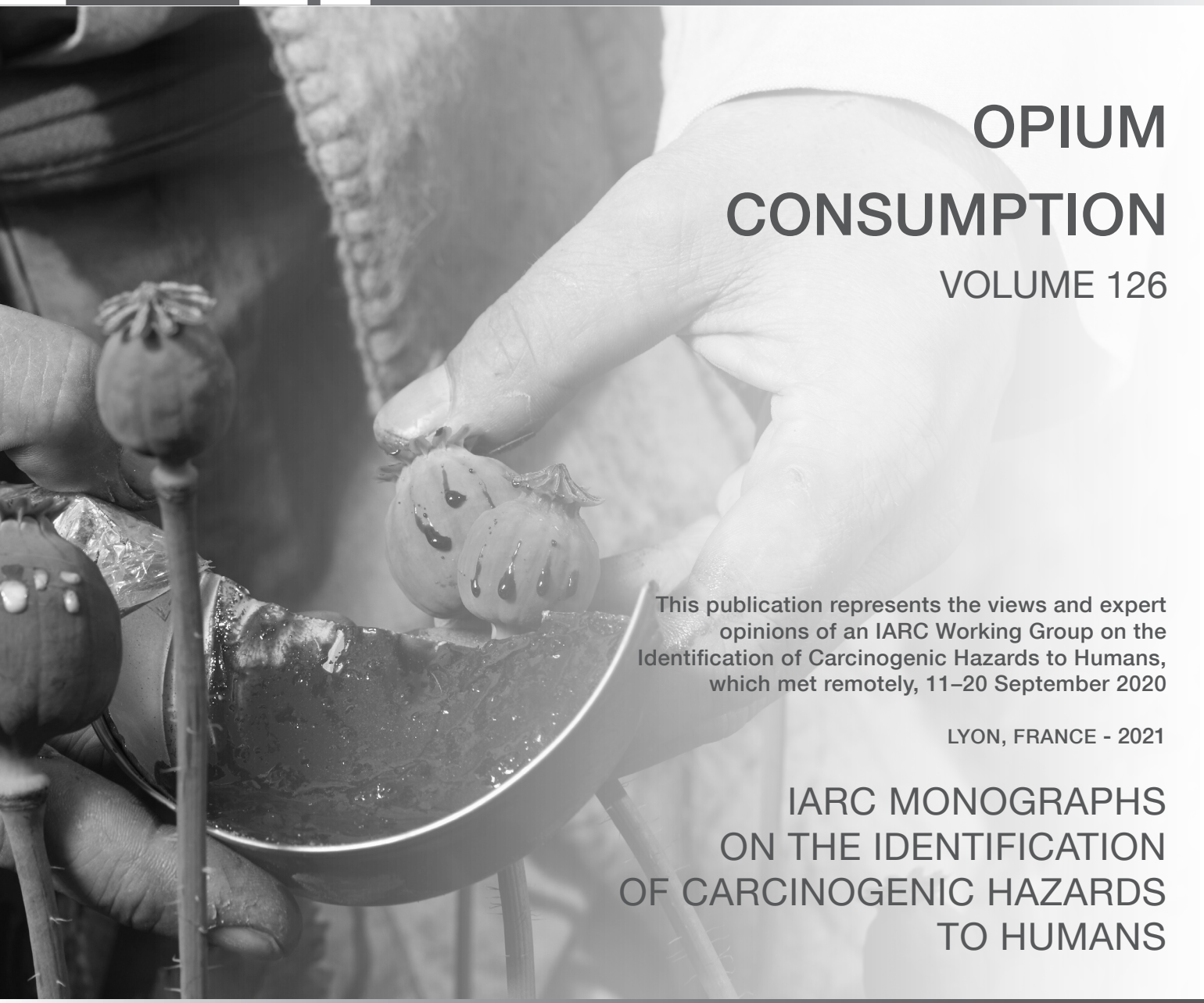
IARC MONOGRAPHS



OPIUM CONSUMPTION

VOLUME 126

This publication represents the views and expert opinions of an IARC Working Group on the Identification of Carcinogenic Hazards to Humans, which met remotely, 11–20 September 2020

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IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

International Agency for Research on Cancer

World Health Organization

GENERAL REMARKS

This one-hundred-and-twenty-sixth volume of the *IARC Monographs* contains an evaluation of the carcinogenic hazard to humans of opium consumption. Due to the coronavirus disease (COVID-19) pandemic, this meeting, which was scheduled to be held in Lyon, France, in March 2020, was held remotely in September 2020.

This agent has not been previously evaluated by the *IARC Monographs* programme. The Advisory Group to Recommend Priorities for the *IARC Monographs* programme that met in 2014 accorded high priority to the evaluation of opium consumption on the basis of new studies of cancer in humans (Straif et al., 2014).

A summary of the findings of this volume appears in *The Lancet Oncology* (Warnakulasuriya et al., 2020).

Definition and scope of the agent

The Working Group carefully considered the applicable scope of the agent under evaluation in this monograph. The agent was therefore defined as the consumption (via ingestion or smoking) of minimally processed forms of opium, including raw, dross, and "refined" opium. Opiates (narcotics derived from opium, such as codeine, heroin, and morphine) and opioids (narcotics not derived from opium, such as fentanyl and oxycodone) were expressly excluded from this evaluation.

The Working Group noted inconsistencies in the published literature in descriptions of the agent with respect to opium as a subcategory of opiates. Terms for "opium" and "opiates" are sometimes used interchangeably in scientific publications, making it difficult to understand what was studied. Sometimes "opium" is used erroneously to refer to opiates – see, for example, the publication by Hosseini et al. (2010), which includes heroin as a category under "types of opium" and "intravenous injection" as a category under opium consumption. It is generally accepted that opium is not consumed intravenously because it contains a high proportion of insoluble material. Heroin, on the other hand, is readily consumed by intravenous injection. In another example, Ketabchi et al. (2005) discuss opium use throughout their article, but – in some instances – indicate that they studied opium and its derivatives. This imprecision in agent definition creates issues both for identifying studies for inclusion and for characterizing the exposure. There are additional uncertainties in agent definition in some hospital-based case–control studies, for example, due to the secondary use of data captured from hospital records, resulting in questions about agent definition and reporting in these records.

Comments on exposure assessment

The Working Group noted numerous data gaps in the characterization of the composition of opium forms that are predominantly used throughout the world. For example, little information was available on the constituents of illicitly traded ("street") opium, and the role of the potentially carcinogenic components of street opium in contributing to its carcinogenicity was therefore unclear. Accordingly, the Working Group considered that lead and other heavy metals were part of the complex mixture that is opium, rather than co-exposures or confounders. No information was found on whether lead is a contaminant in soil used to grow poppies or is added as an adulterant to increase the weight of the traded product.

The impact of routes of opium consumption on carcinogenic hazard is not well understood, nor is the carcinogenic hazard posed by licit opium use (usually in the forms of tincture or syrup). Biomarkers of opium are not well-characterized and have seldom been directly employed in studies.

The Working Group noted the use of non-standard units (non-SI, International System of Units) in most research studies, which sometimes led to difficulties in directly comparing quantitative estimates of risk per unit of consumption across different studies.

The Working Group concluded that updating the opium consumption data for participants in the Golestan Cohort Study would add value to this already important study.

Gaps in the epidemiological literature on opium consumption and cancer

Minimally processed opium is consumed by millions of people worldwide, especially in populations concentrated in the Middle East and south-eastern Asia. Despite this widespread use, the Working Group noted substantial gaps in the epidemiological literature on opium consumption. The studies of cancer in humans were conducted almost entirely in the Islamic Republic of Iran, where approximately 40% of global consumption of opium occurs. While no other country has consumption at this level, the lack of epidemiological evidence from the countries responsible for the remaining 60% of consumption was notable, particularly in Afghanistan (responsible for > 80% of opium production), Pakistan, India, and south-eastern Asia. Although most of the studies were conducted in the Islamic Republic of Iran, where opium use is common, considering the totality of evidence the Working Group concluded that data generated from these cancer epidemiology studies were likely generalizable to other populations that consume opium in similar forms.

The Working Group considered it likely that combustion of opium would produce different levels and profiles of potential carcinogens, such that the observed carcinogenic hazards might be different for smoked and for ingested opium. However, the cancer evidence in humans did not support this view, and the overall evaluation, accordingly, did not differ by either route of consumption or form of opium consumed.

The Working Group noted that in some of the available epidemiological studies a substantial effort had been made to differentiate the carcinogenic effect of opium consumption from that of tobacco consumption, in order to control for potential confounding. However, a substantive gap in studies on the interactive effect of both

tobacco and opium consumption was noted. Joint effects of opium and tobacco smoking that are greater than additive could have important public health implications. Beyond confounding by tobacco consumption, several other potential specific methodological sources of bias in the identified literature, of relevance for the evaluation here, were also outlined by the Working Group, with detailed consideration given to their impact on the identification of the carcinogenic hazard presented by opium consumption (see Annex 2, Methodological considerations for epidemiological studies on opium consumption and cancer).

Specific data gaps in the available studies included a general lack of evaluation of latency, including differences between cancer sites and the impact on study conclusions and evaluation (for example, including irrelevant exposure in unlagged analyses may tend to bias results towards the null). Most epidemiological studies could not differentiate between important morphological subtypes (e.g. squamous cell carcinoma and adenocarcinoma of the oesophagus or urinary bladder). The identification of mutational signatures of opium exposure in different cancer tissues is an area of active research, but published findings were not available to the Working Group. Data gaps were also noted regarding the relative potency of opium consumption in different tissues or organs, as well as the need for an updated systematic review and meta-analysis including newly published literature at multiple cancer sites.

Role of evidence from bioassays in experimental animals

There was sparse evidence on carcinogenicity of opium consumption from bioassays in experimental animals. The Working Group considered that, because such studies are typically conducted to identify hazards to humans, additional bioassay studies may not be warranted for an agent classified in Group 1 as *carcinogenic to humans*. However, additional bioassays may be useful in identifying the specific components of the complex mixture of opium, or aspects of route of consumption, that contribute most to its carcinogenicity.

Scope of systematic review

Standardized searches of the PubMed database (National Library of Medicine, 2021) were conducted for the agent and for each outcome (cancer in humans, cancer in experimental animals, and mechanistic evidence, including the key characteristics of carcinogens). The Web of Science database (Clarivate, 2021) was also searched for studies of tumours in humans and experimental animals. The literature trees for the agent, including the full set of search terms for the agent name and each outcome type, are available online.[1]

[1] The literature searches for the present volume are available from: https://hawcproject.iarc.fr/assessment/612/.

References

Clarivate (2021). Web of Science [online database]. Available from: https://www.webofscience.com/wos/woscc/basic-search.

Hosseini SY, Safarinejad MR, Amini E, Hooshyar H (2010). Opium consumption and risk of bladder cancer: a case-control analysis. *Urol Oncol*. 28(6):610–6. doi:10.1016/j.urolonc.2008.10.016 PMID:19110453

Ketabchi A, Gharaei M, Ahmadinejad M, Meershekari T (2005). Evaluation of bladder cancer in opium addicted patients in the Kerman Province, Iran, from 1999 to 2005. *JRMS*. 10(6):355–7. https://doaj.org/article/d91b96931e3d4fe88d6df5f759e7739c

National Library of Medicine (2021). PubMed [online database]. Bethesda (MD), USA: National Library of Medicine. Available from: https://pubmed.ncbi.nlm.nih.gov/.

Straif K, Loomis D, Guyton K, Grosse Y, Lauby-Secretan B, El Ghissassi F, et al. (2014). Future priorities for the IARC Monographs. *Lancet Oncol*. 15(7):683–4. doi:10.1016/S1470-2045(14)70168-8

Warnakulasuriya S, Cronin-Fenton D, Jinot J, Kamangar F, Malekzadeh R, Dar NA, et al.; IARC Monographs Vol 126 group (2020). Carcinogenicity of opium consumption. *Lancet Oncol*. 21(11):1407–8. doi:10.1016/S1470-2045(20)30611-2 PMID:33038940