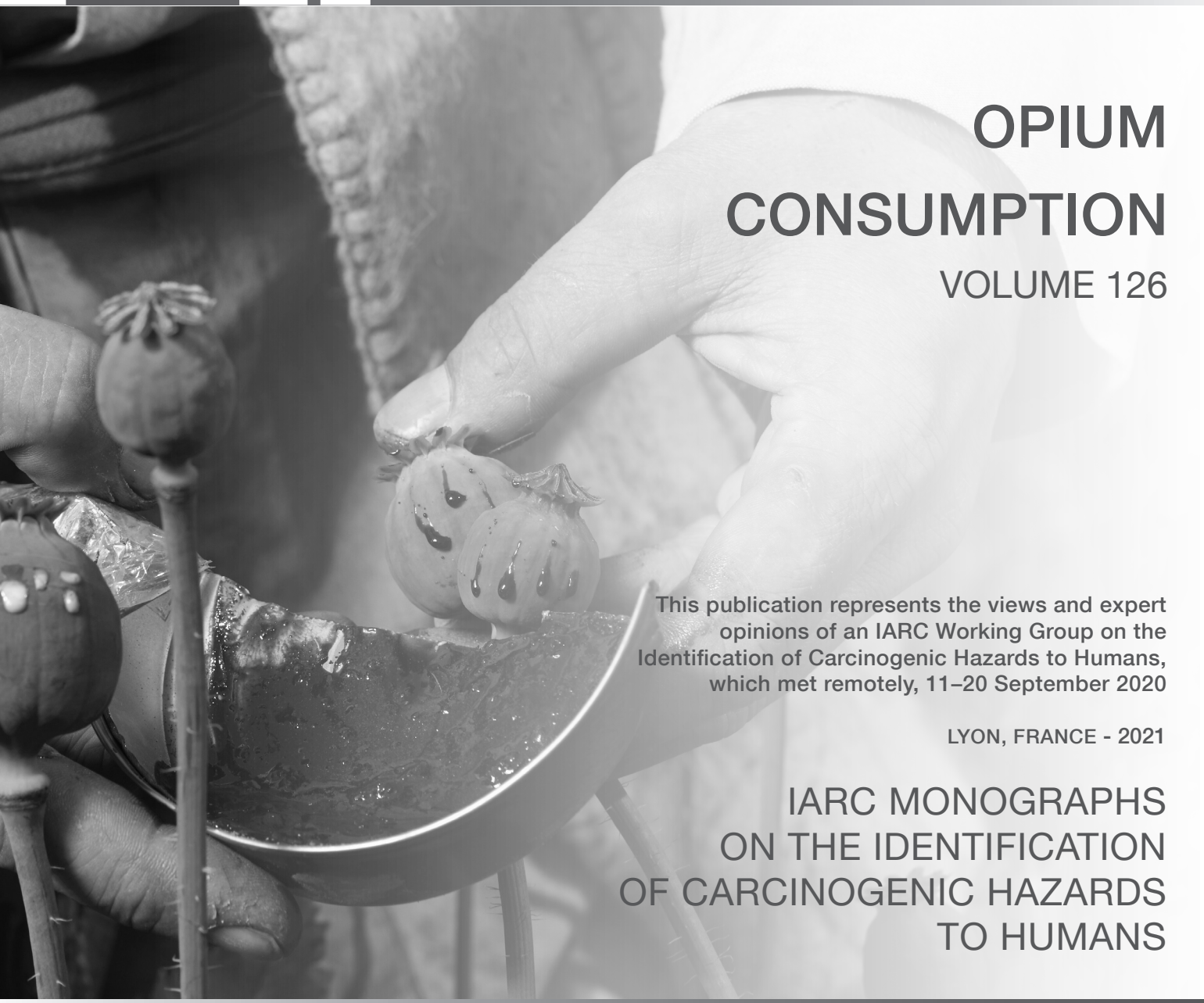
IARC MONOGRAPHS



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

LYON, FRANCE - 2021

IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

International Agency for Research on Cancer

World Health Organization

5. SUMMARY OF DATA REPORTED

5.1 Exposure characterization

Opium is a highly addictive narcotic drug that has been used for centuries for medicinal and non-medicinal purposes. It has analgesic, hypnotic, antitussive, gastrointestinal, and cognitive effects.

Opium comes from the juice (latex) of the unripe seedpod of the poppy plant (*Papaver somniferum*), and has a complex chemical composition consisting of at least 25 alkaloids (e.g. morphine, codeine, and thebaine) and other ingredients. Opium is often adulterated with compounds such as lead to enhance its weight. Illicit opium product may therefore be a combination of opium and other compounds. The types and percentages of the alkaloids in opium differ widely between different poppy cultivars. The latex can be processed by drying or boiling before consumption. Opium includes raw or crude opium, opium dross (tarry residues formed after smoking raw opium), and refined opium or opium sap (boiled opium dross with or without raw opium). All forms of opium are typically smoked or ingested. Pyrolysis products may result from combustion (smoking) of all three forms of opium. Opium derivatives (morphine, codeine, and heroin) are not considered in the present monograph.

Opium production and distribution have been controlled internationally since 1961, and 190 countries have ratified an international convention controlling the production, distribution, and use of opium.

Opium is produced illicitly in some 50 countries worldwide, and global production has increased during the last decade from 4950 to 7610 tonnes. Over 80% of the world's illicit opium comes from Afghanistan. Of the total opium produced, 15–20% is used as raw or minimally processed opium. In 2009, the Islamic Republic of Iran was estimated to be the world's largest per capita consumer of raw or minimally processed opium, representing 42% of total global opium consumption, followed by Afghanistan and Pakistan. In 2018, there were an estimated 5 million users of illicit opium worldwide.

Due to its illicit nature, "street" opium is not subject to safety standards. Legal opium is used to produce opium tincture and syrup; however, these represent a small proportion of global opium production.

Epidemiological studies have been conducted only on users of illicit forms of opium and have used questionnaires, interviews, or patient records to evaluate opium exposure. Some studies compared questionnaire/interview data on opium consumption with opium biomarkers. Opium derivatives can be detected in blood,

urine, hair, and nails for limited periods after opium exposure.

The amount of detail and the quality of exposure information varied considerably across the epidemiological studies. Some studies defined opium consumption as opium dependence using standardized tools such as those based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Multiple studies used the structured and validated Golestan Cohort Study (GCS) questionnaire (GCSQ), which defined opium exposure as use more than once per week for at least 6 months. The GCSQ incorporated questions on opium type, dose, mode of consumption, temporality of exposure, duration, intensity, and cumulative exposure. To date, cohort studies that have used the GCSQ have evaluated baseline questionnaire data only, so any time-varying changes in exposure status have not been reported. This may be important, particularly in cancers with a long latency period. Many studies asked the participants to quantify the amount of opium consumption using grams or a local unit of nokhods per day, but these estimates were likely imprecise.

The factors most strongly related to opium use across studies were sex, age, tobacco smoking, and socioeconomic status.

5.2 Cancer in humans

The studies of cancer in humans that were available for this evaluation have all investigated illicit opium consumption in the form of the minimally processed latex of the poppy plant (*P. somniferum*). Opium, as purchased and consumed by millions of people in several countries, is a complex mixture that includes alkaloids (e.g. morphine and thebaine), non-alkaloids (e.g. sugars, fats, meconic acid, and water), and impurities (e.g. lead and chromium). Several informative cohort and case–control studies have investigated the association between opium consumption (by smoking or ingestion of crude opium, opium dross, or minimally processed opium) and cancers of various sites in humans. Some of these studies, most notably the GCS, had a strong design and used several strategies to alleviate concerns about bias. Cancers of the oesophagus, urinary bladder, lung, larynx, pancreas, stomach, colon and rectum, and pharynx were studied in more depth.

A cohort study (the GCS) showed a positive association between opium consumption and risk of oesophageal cancer, with an exposure–response association. A case–control study also showed a positive association when cases were compared with neighbourhood controls, but the association disappeared when cases were compared with hospital controls. In both studies, the large majority of the oesophageal cancer cases were of squamous type. The Working Group concluded that although a positive association is credible, chance, bias, and confounding cannot be ruled out with reasonable confidence. The association observed in the cohort study was not very strong and could possibly have arisen due to residual confounding. The results of the case–control study are subject to interpretation based on the appropriateness of the control group.

The GCS found a strong association between opium consumption and risk of urinary bladder cancer, with evidence of an exposure–response relation. Likewise, nearly all eight case–control studies that studied the association between opium consumption and urinary bladder cancer found higher odds of opium use among cases than in controls, with adjusted odds ratios ranging from 2 to 5. Control selection, adjustment for confounding, and definition of exposure varied among studies; however, it was notable that all studies, regardless of design, pointed in the same direction. The Working Group concluded that despite a modest number of cases in the cohort study, a positive association has been observed and that, collectively, the most informative studies rule out confounding, bias,

and reverse causation with a reasonable degree of confidence.

The association between opium consumption and laryngeal cancer has been extensively studied in a cohort study (the GCS) and six case–control studies. The GCS found a strong positive association between opium consumption and risk of laryngeal cancer, with an exposure–response association. Likewise, all six case–control studies showed substantially increased opium use among laryngeal cancer patients compared with controls, ranging from 2- to 16-fold. The quality of these studies – including adjustment for potential confounders, excluding opium use that initiated within a few years before diagnosis, and various other sensitivity analyses – varied across studies. However, the two studies that adjusted for many confounders and analysed the data in various ways also found strong associations between opium consumption and laryngeal cancer. The Working Group concluded that a positive association has been observed. The more informative studies, collectively, rule out chance, confounding, bias, and reverse causation with reasonable confidence. This inference resulted from the observation of very strong associations, exposure–response associations, consistency across studies, availability of studies with large sample sizes, and various efforts to rule out bias and confounding in at least two key studies: the GCS and IROPICAN (the Iranian Study of Opium and Cancer).

The association between opium consumption and lung cancer has been studied in a cohort study (the GCS) and three case–control studies. The cohort study found a positive association with an exposure–response trend for increasing quartiles of consumption. These results were adjusted for cigarette smoking and other potential confounders, although adjustment for cigarette smoking might have been less than ideal due to the low number of study participants with lung cancer who used opium but never smoked cigarettes. The quality of control selection, adjustment, and exposure data collection varied across the case–control studies. However, all three case–control studies, which collectively involved a large number of cases and controls, showed a positive association between opium consumption and lung cancer, with adjusted odds ratios ranging from 2 to 6. The Working Group concluded that a positive association has been observed. Given the totality of evidence and the strong association observed in the cohort study, the Working Group concluded that chance, bias, and confounding were unlikely to explain the results.

In the GCS, ever-use of opium did not show a clear association with an increased risk of pancreatic cancer. However, there was evidence of an association for participants who had very high amounts of cumulative use. A case–control study found evidence of increased risk among opium users. The controls were from the same clinic from which the cases were recruited, therefore reducing the possibility of biased reports; however, bias from data collection on the part of interviewers cannot be entirely ruled out. However, there was no exposure–response association with either duration of opium use or cumulative opium use in this case–control study. The Working Group concluded that a credible association was observed, but chance, bias, and confounding cannot be ruled out, partly because the number of studies was small. Although the only case–control study showed some evidence to support an association, the cohort study showed an association only for very high exposures.

The association between opium consumption and gastric cancer has been studied in two cohort studies (the GCS and Ardabil cohort study) and two case–control studies. All studies showed increased risk of gastric cancer. In one study, opium consumers were observed to have an increased risk of developing precursor lesions for gastric cancer, alleviating concerns about reverse causation. The GCS results showed a positive association with opium consumption,

particularly for the noncardia subtype, but the exposure–response trend was not statistically significant. In the Ardabil cohort study, opium consumption was associated with an increased risk of baseline antral and gastric body intestinal metaplasia, which are precursor lesions for gastric cancer, and subsequent incident gastric cancer. Both case–control studies also showed strong positive associations between opium consumption and odds of gastric cancer. The Working Group's assessment was that although a positive association in the body of evidence was credible, chance, confounding, and bias from potential under-reporting in case–control studies cannot be ruled out with reasonable confidence. This decision was reached partly because of lack of a clear exposure–response relation and partly because of lack of data for *H. pylori* or diet in some of these studies, which may lead to confounded results.

The association between opium consumption and cancers of the colon and rectum has been studied in a cohort study (the GCS) and two case–control studies. The GCS found no positive association between opium consumption and risk of colon cancer, nor did it find an association with cumulative opium consumption. However, two case–control studies with similar design, conducted by some of the same investigators, found evidence of strong associations between opium consumption and risk of cancer of the colon and rectum. The Working Group concluded that an association has not been established, primarily because of conflicting evidence and the lack of any positive association in the cohort study.

Only one case–control study was considered informative for cancers of the head and neck excluding the larynx. This study had a large sample size and used a variety of methods to adjust for confounding and alleviate concerns about reverse causation and under-reporting by cases and controls. This study found a strong positive association between opium consumption and cancer of the pharynx. The Working Group concluded that a positive association between opium consumption and pharyngeal cancer was credible, but that chance, bias, and confounding could not be excluded with reasonable confidence, primarily because there was only one (well-conducted) study.

5.3 Cancer in experimental animals

The available studies on opium could not be interpreted as showing either the presence or the absence of a carcinogenic effect because of major limitations, including low numbers of animals, lack of survival and body-weight data, unknown adequacy of the treatment doses, and limited reporting.

5.4 Mechanistic evidence

Evidence of opium absorption, distribution, and metabolism in humans and rodents is provided by studies on intoxication and excretion. In humans, opium metabolites have been detected in urine, hair, and blood after ingestion or smoking of opium. In rats, metabolites have been measured in hair after oral exposure and in urine after inhalation of volatilized opium.

There is consistent and coherent evidence in experimental systems that opium exhibits key characteristics of carcinogens: it is genotoxic. There is consistent evidence for *sukhteh* (opium dross) and opium pyrolysates (solid residues of combusted opium), but not for raw opium, that such forms induce clastogenicity and mutagenicity. Studies in exposed humans were uninformative. *Sukhteh* and opium pyrolysates induced dose-related increases in sister-chromatid exchange in human primary peripheral blood mononuclear cells and Chinese hamster ovary cells, with and without metabolic activation. No data for mammalian experimental systems in vivo were available. *Sukhteh* and opium

pyrolysates consistently induced mutagenicity in multiple strains of *Salmonella typhimurium* that are indicators of base-pair substitution and frameshift mutations. The studies on genetic and related effects are not numerous. However, consistent findings were seen across several test systems in different species, indicating that forms of opium containing pyrolysates are genotoxic. In multiple experimental systems, including human cells and cells from another mammalian and non-mammalian species, forms of opium containing pyrolysates induced both clastogenicity and mutagenicity. This evidence is also coherent with what is known about the genotoxicity and mutagenicity of combustion products.

There is also some evidence of increases in the incidence of precursors to chronic inflammation; however, the data are inconsistent. Evidence pertaining to oxidative stress and antioxidant status is conflicting. Information related to other key characteristics of carcinogens was sparse.