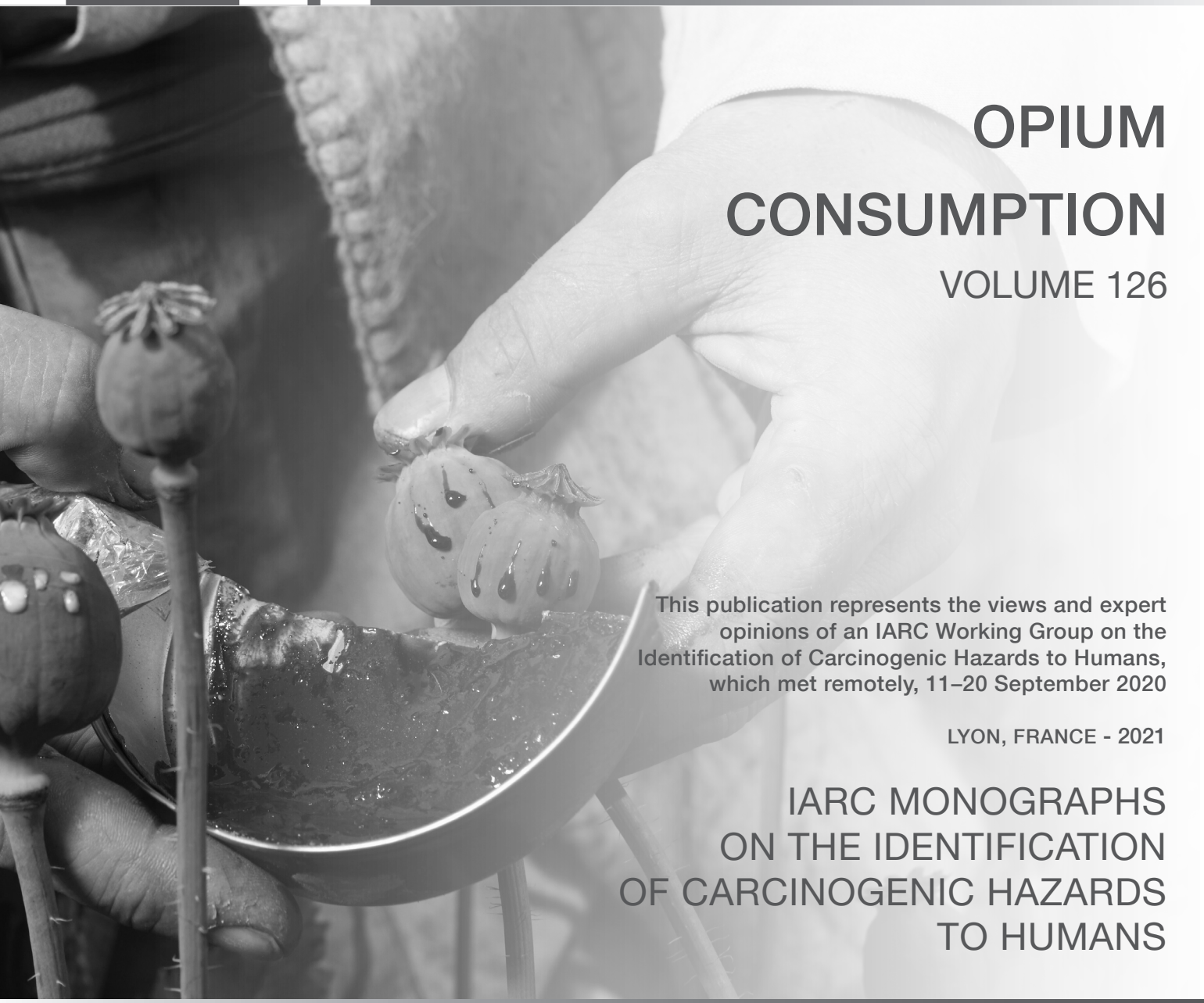
IARC MONOGRAPHS



OPIUM CONSUMPTION

VOLUME 126

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IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

International Agency for Research on Cancer

World Health Organization

1. EXPOSURE CHARACTERIZATION

1.1 Identification of the agent

1.1.1 Introduction to the agent

Opium is a highly addictive narcotic drug obtained from the juice (latex) of the unripe seedpod of the poppy plant (*Papaver somniferum*). The latex requires minimal processing before it can be consumed. The traditional practices of latex processing vary from place to place and may include air-drying, heat-drying, or boiling (DEA, 1992, 2020a; Ray et al., 2006).

Chemically, opium is a complex mixture; notably, it contains several alkaloids, including morphine, codeine, noscapine, thebaine, and papaverine. After extraction and purification (Kalant, 1997), the alkaloids may also be used as base material for the manufacture of semisynthetic opiate derivatives, such as heroin (from morphine) and oxycodone (from thebaine) (Kalant, 1997; Yaksh & Wallace, 2018). The alkaloid components of opium or their derivatives are responsible for its analgesic, hypnotic, antitussive, and antidiarrhoeal effects when consumed (Labanca et al., 2018). There are also many wholly synthetic opioid drugs available, for example, fentanyl and methadone. These drugs mimic the effects of opium on consumers but are not manufactured from opium or its alkaloids and may have chemically unrelated structures.

The agent considered in the present monograph is "opium consumption". In this context, the term opium includes raw, minimally refined, and dross types, which are derived from the poppy latex and comprise a complex chemical mixture. The agent definition also includes contaminants that are integral to the complex mixture (see Section 1.4.2(g)). The agent definition does not include the pure alkaloids that can be extracted from opium (for example, morphine or codeine), their semisynthetic modifications such as heroin, or wholly synthetic opioid compounds such as fentanyl.

1.1.2 Botanical and chemical data

(a) Nomenclature of opium and its source plant

Botanical name: *Papaver somniferum*

Family: Papaveraceae

Subfamily: Papaveroideae

Common names: opium poppy, breadseed poppy (Mahr, 2017; Labanca et al., 2018)

Opium (*lachryma papaveris* or "poppy tears", also called "raw opium") is the dried latex obtained from the unripe seedpods of the opium poppy plants (INCB, 2019).

Although, as a complex mixture, minimally processed opium has no chemical structure or formula, a highly purified form of opium does have a Chemical Abstracts Service (CAS) registry number of 8008-60-4 (Drugs.com, 2019a).

European Community/List No.: 232-368-5 (ECHA, 2019), also known as "crude opium"

WHO Anatomical Therapeutic Chemical codes: A07DA02, N02AA02 (WHOCC, 2019)

The nomenclature of certain opium products (e.g. as described in Section 1.4.1(c)) has varied over time and by country (USDA, 2020). For example, opium is called *teriak* in Persian, *afeen* in Hindi, and *afiyoon* in Urdu, while (minimally) refined (i.e. further processed, for example, condensed) opium is known as *chandu* in India and Myanmar (DEA, 1992). In the Islamic Republic of Iran (hereafter referred to as "Iran"), different types of opium are known by different terms: *teriak* for raw opium, *sukhteh* or *sookhteh* for opium dross, and *shireh* or *shire* for refined opium (Khademi et al., 2012; Nikfarjam et al., 2016). There is also a multitude of "street names", such as Aunti, Aunti Emma, Big O, Black Pill, Chinese Molasses, Dopium, Dream Gun, Fi-do-nie, Gee, Guma, Midnight Oil, and Zero (DEA, 2020a).

(b) Description of the plant and its cultivation

P. somniferum (Fig. 1.1) is a dicotyledonous, dialypetalous, superovaried annual herb, 30–150 cm long with a stem between 0.5 and 1.5 cm thick, blue-green leaves, and four white, violet, or purple petals, which is cultivated in temperate and subtropical regions. It is hardy and may be grown without fertilizers or pesticides (UNODC, 1953a; Ray et al., 2006; Pushpangadan et al., 2012). Traditionally, most highland and upland farmers in south-eastern Asia have not used fertilizers for any of their crops, but opium poppy farmers have started using both natural and chemical fertilizers to increase opium poppy yields in recent years. Chicken manure, human faeces, or bat droppings are mixed into the planting soil. Opium poppy seeds are planted by the end of October. After 1 month, some plants are removed and 8–18 plants/m^2 are left. Most opium poppy varieties in south-eastern Asia produce three to five mature pods per plant. Harvesting is done in February, about 2 weeks after the flower petals fall from the pods (DEA, 1992). All parts of plants of the *Papaver* genus are characterized by watery and milky latex, except the seeds.

1.1.3 Opium composition and forms

(a) Opium composition

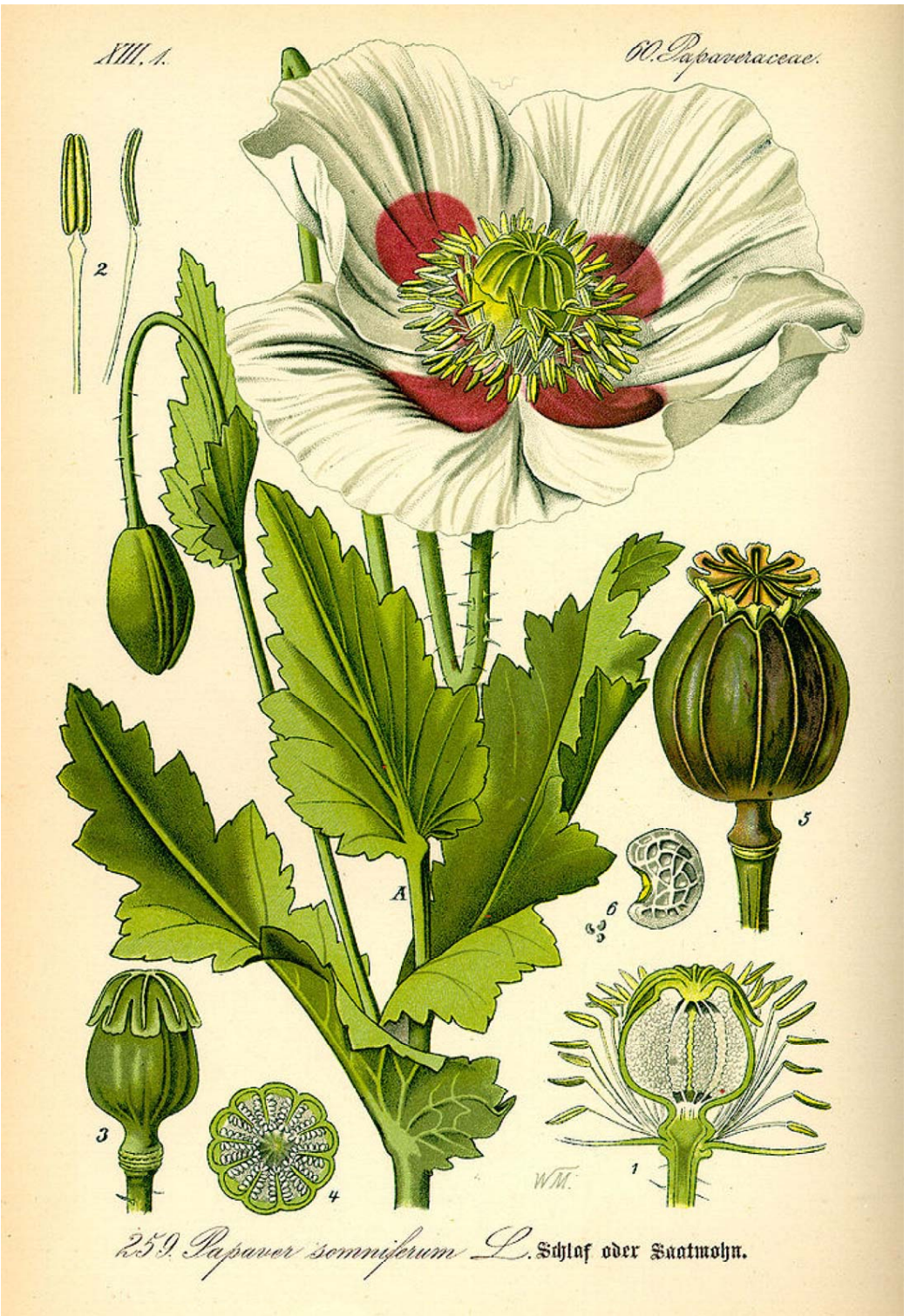
Opium has a complex chemical composition consisting of sugars, proteins, fats, water, meconic acid, plant wax, latex, gum, ammonia, sulfuric and lactic acids, and at least 25 alkaloids (Fig. 1.2; Pushpangadan et al., 2012; Labanca et al., 2018). The composition of opium is further discussed in Section 4.1. The alkaloids are categorized into two main chemical classes: phenanthrenes and benzylisoquinolines (Yaksh & Wallace, 2018). The types and percentages of these alkaloids differ widely in different poppy cultivars. Also, differences in seed yield per plant and latex yield per plant have been reported (Solanki et al., 2017; Labanca et al., 2018). The principal phenanthrenes are morphine, codeine, and thebaine (Yaksh & Wallace, 2018). Morphine is the most abundant phenanthrene in opium. The metabolites of thebaine, an intermediate of morphine biosynthesis in poppy plants, include thebaol and oripavine (WHO, 2006; Megutnishvili et al., 2018).

The principal benzylisoquinolines are papaverine and noscapine (Frick et al., 2005; Beaudoin & Facchini, 2014; Labanca et al., 2018; Yaksh & Wallace, 2018).

(b) Composition of different forms of opium

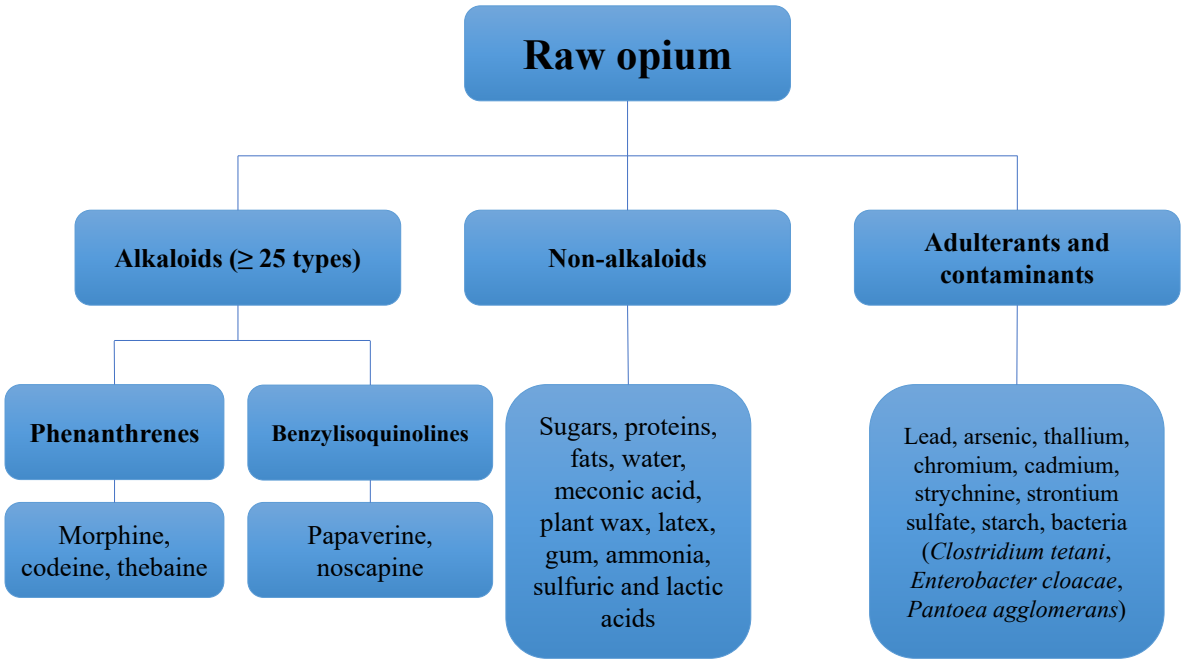
The main forms of opium are raw or crude opium, opium dross, refined opium, and other derivatives.

Fig. 1.1 Opium poppy, *Papaver somniferum*



Professor Dr Otto Wilhelm Thomé, *Flora von Deutschland, Österreich und der Schweiz*, 1885, Gera, Germany. Courtesy of Wikimedia Commons. Released under public domain.

Fig. 1.2 Schematic view of the composition of raw opium



Created by the Working Group.

(i) Raw or crude opium

Raw or crude opium is the unprocessed dried latex of the poppy seedpod and is a dark and sticky substance (Fig. 1.3; Khademi et al., 2012). Alkaloids are major components of crude opium. Among all alkaloids, the most abundant is morphine (10–12% of crude opium by weight). The other alkaloids – including thebaine, codeine, papaverine, noscapine, narcotine, and narceine (UNODC, 1953a; Labanca et al., 2018), together with morphine – make up about 25% of the weight of crude opium, as shown in Table 1.1. Sterols such as cycloartenol and β-sitosterol (Malaveille et al., 1982) are also present in raw opium. [The Working Group noted that the expression of the morphine content of opium as a percentage depends in part on the moisture content.] After the opium has been collected, the moisture content is usually ~30%. Commercial opium usually has a moisture content of ~10–15%. Opium that is apparently dry still retains considerable moisture (~6%) (UNODC, 1953a). Raw opium is often adulterated with other substances, for example, starch (37%) and strontium sulfate were reported in Mexican opium (Sodi Pallares & Meyran Garcia, 1954); arsenic in Indian opium (Datta & Kaul, 1977; Narang et al., 1987); and arsenic and strychnine in Sri Lankan opium (Wijesekera et al., 1988). More recently, traded opium in Iran has been shown to be contaminated with heavy metals such as lead, chromium, cadmium, and thallium, and bacteria such as *Clostridium tetani*, *Enterobacter cloacae*, and *Pantoea agglomerans* (Ghaderi & Afshari, 2016; Aghababaei et al., 2018; Ghane et al., 2018).

(ii) Opium dross

Dross is produced by scraping away the tarry residues that accumulate on the inside walls of the opium pipe as a result of incomplete

Fig. 1.3 Dried latex obtained from the opium poppy

DM Trott. Courtesy of Wikipedia. Released under Creative Commons Attribution-Share Alike 4.0 International.

combustion of raw opium. The dross is black, dry, and granular (Meysamie et al., 2009). Each gram of opium yields 0.3 g of dross (Siassi & Fozouni, 1980). The summary content of the five main alkaloids in opium dross is less than their summary content in raw opium (see Table 1.1). This pyrolysed opium (Meysamie et al., 2009), unlike raw opium, contains primary aromatic amines, heterocyclic (nitrogen-containing) aromatic compounds, and polycyclic aromatic hydrocarbons.

(iii) Refined opium or opium sap

Refined opium or opium sap is the (minimally) refined product of opium and is prepared by boiling opium dross with or without raw opium in water for several hours. The solution is then filtered, insoluble parts are separated, and the excess water is left to evaporate. The final product is brown, sticky, and shiny (Kalant, 1997; Meysamie et al., 2009; Khademi et al., 2012; Nikfarjam et al., 2016). The summary alkaloid content in minimally refined opium is about the same as in raw opium (see Table 1.1).

(iv) Other opium derivatives

Other opium derivatives include the pure alkaloids like morphine and codeine; semi-synthetic opiates like heroin, compact-heroin, and buprenorphine; and crystal and synthetic opioids like fentanyl, methadone, and pethidine. This group of opium derivative drugs is outside of the scope of this monograph (see Section 1.1.1, Introduction to the agent).

Table 1.1 Alkaloid content of raw, prepared, and dross illicit opium from south-eastern Asia: analysis after initial drying (weight %)

Component	Raw (n = 15)		Dross (n = 15)		Prepared[a] (n = 15)	
	Range	Mean	Range	Mean	Range	Mean
Morphine	9.8–15.0	12.2	6.8–15.4	10.2	10.5–22.7	16.2
Codeine	1.6–3.2	2.2	0.9–1.7	1.2	1.8–4.4	2.7
Thebaine	1.8–4.4	2.8	0–0.1	0.1	1.1–3.4	1.9
Papaverine	0.02–0.52	0.21	0.04–0.14	0.09	0.08–0.20	0.14
Narcotine	5.0–8.0	6.4	Not detected	NR	1–2[b]	1.5[b]
H_2O	28–36	NR	6–9	NR	7–27	NR

NR, not reported.
[a] Prepared opium is a 30–50% mixture of raw and dross opium [the Working Group noted that "prepared" opium in this reference is likely to be similar to the "refined" opium described elsewhere in the present monograph].
[b] Estimated.
From Lim & Kwok (1981). ©1981. United Nations. Reprinted with the permission of the United Nations.

1.2 Methods of measurement, detection, and analysis

Biological marker detection techniques

Biomonitoring of opium derivatives in urine, blood, hair, or other tissues provides a direct marker of an individual's opium exposure. Interindividual differences in the absorption and metabolism of opium, and the temporality or cumulative dose of opium or opium derivatives (e.g. morphine, codeine, or poppy seed paste), among other factors, can influence concentrations in body fluids or tissues.

Opium metabolites are present in urine or blood for 2–4 days after the opium is consumed (Hasselström & Säwe, 1993; Abnet et al., 2004; Rashidian et al., 2017). Methods to detect opium alkaloids in blood and urine include gas chromatography-mass spectrometry (GC-MS), high-performance liquid chromatography (HPLC), and thin-layer chromatography, among others (Dams et al., 2002; Sabzevari et al., 2004; Shamsipur & Fattahi, 2011; Gholivand et al., 2015; Bagheri et al., 2017; Rashidian et al., 2017; Megutnishvili et al., 2018). Dispersive liquid–liquid microextraction is a fast, reproducible, cost-effective, and simple technique to preconcentrate opium alkaloids in human urine or plasma, enabling subsequent quantification via HPLC or GC-MS (Rezaee et al., 2006; Ahmadi-Jouibari et al., 2013; Farahani & Sereshti, 2020).

Opium use can be determined by a rapid urine drug screen, followed by confirmatory testing methods including thin-layer chromatography, HPLC, or GC-MS (Rashidian et al., 2017). Microfluidic technologies have emerged as useful tools in solid-phase extraction methods, enhancing their simplicity, portability, and extraction yields, while reducing testing times and cost. Farahani & Sereshti (2020) recently outlined the use of microfluidic devices for solid-phase and spectrophotometric detection of opium alkaloids (morphine, codeine, and papaverine) in urine samples for point-of-care testing. Their method yielded extraction recoveries of between 66.7% and 85.0%, with limits of quantitation of 4, 4, and 1 ng/mL, and limits of detection of 1.4, 1.3, and 0.3 ng/mL for morphine, codeine, and papaverine, respectively. For blood, use of an ultrasensitive electrochemiluminescent immunoassay for morphine yielded a limit of detection of 67 pg/mL and a limit of quantification of 0.2 ng/mL (Fei et al., 2013).

Thebaine is an opium alkaloid that, if found in the body, indicates consumption of opium

or its derivatives. Thebaine can be quantified in hair using GC-MS with high validity (Lee et al., 2011). Likewise, morphine can be measured in hair at concentrations as low as 0.016 ng/mg using GC-MS. Hair may be suitable for assessing past exposure to opium by evaluating morphine or thebaine concentrations, but these measures are dependent on hair length (hair grows at a rate of 0.9–1.2 cm/month) and hair colour (higher morphine concentrations have been documented in dark hair) (Sabzevari et al., 2004). Toenails may also be suitable for the biomonitoring of opium use. A study assessing cocaine and morphine concentrations in toenails and hair showed higher concentrations in toenails than in hair. Toenails grow at a rate of about 1–2 mm/month (Yaemsiri et al., 2010), so concentrations in toenails could document past exposure to opium (Cingolani et al., 2004). To date, no studies on opium and cancer incidence have been identified that used hair samples or toenail clippings to biomonitor opium exposure, although samples were collected in some studies (Pourshams et al., 2010; Ashrafi et al., 2018). [The Working Group noted that these methods are not specific for opium exposure and may also reflect exposure to other opiates.]

1.3 Production

1.3.1 Legal production

As described in Section 1.4.1, legal opium production occurs in a few countries, as prescribed by international protocols. Such cultivation (e.g. Fig. 1.4) is used to produce the global supply of more highly processed forms of opium, such as opium tincture and morphine. India was the main producer and only licit exporter of raw opium in 2017, accounting for 432.5 tonnes (47.5 tonnes in morphine equivalent) or 98.4% of total global licit production. It was followed by China, which produced 6.4 tonnes (0.7 tonnes in morphine equivalent) and where poppy straws (dried seedpod capsules) have replaced opium as the main raw material used in the manufacture of alkaloids since 2000. The Democratic People's Republic of Korea also produced smaller amounts of opium in 2017, but exclusively for domestic consumption and use. Japan produces very small amounts for scientific purposes only (INCB, 2019). [The Working Group noted that there are large annual variations; for example, Australia was the largest producer in 2016, with 180 tonnes, followed by France, Turkey, Spain, Hungary, and India, in descending order (INCB, 2017). Most substances resulting from licit opium production are outside of the scope of this monograph (e.g. morphine and codeine). However, as noted above, opium tincture and opium syrup are within the scope of this monograph.]

1.3.2 Illicit production

Opium is illicitly produced in some 50 countries worldwide, and the area of land under illicit opium poppy cultivation (240 800 hectares in 2019, preliminary estimate) has increased substantially over the last 10 years. In addition, global potential production of oven-dry opium has shown a long-term upward trend and has increased over the last decade from 4950 to 7610 tonnes (UNODC, 2020). Afghanistan is currently the world's largest producer of illicit opium (UNODC, 2019b, 2020). Over 80% of the world's opium comes from Afghanistan, but less than 1% [0.35% in 2018, calculated by the Working Group] is seized there (UNODC, 2020), and massive volumes of illicit opiates are smuggled out of the country (Beyrer, 2011).

As noted above, opium poppies can be grown without artificial irrigation or fertilizers, and the product does not need refrigeration, can be transported by mule or camel without decaying, and has a high market price (Goodhand, 2000; Beyrer, 2011). Myanmar (7%) and Mexico (6%) are the second and third major global producers of illicit opium, respectively (UNODC, 2019b,

Fig. 1.4 Poppy field in Tasmania, Australia

2020). Of the 7610 tonnes of opium produced worldwide in 2019, it was estimated that some 1180–1480 tonnes remained unprocessed for consumption as opium, while the rest was processed into heroin (UNODC, 2020).

1.3.3 Harvesting of opium

Opium is harvested, about 2 weeks after the petals fall, in two phases: the incision of the capsule and the collection of the latex. Opium harvesting is labour-intensive (Ray et al., 2006) and poppies are still processed manually in many producer countries. The incision of the capsule requires a high level of skill: the latex is found between the epicarp and the mesocarp, and the juice channels are cut so that they run upwards from below (Fig. 1.5). A great many channels must be made, but the wall of the capsule must not be cut right through or the latex will run down inside and be lost (UNODC, 1953b). The immature seedpods (fruits) of the opium poppy are scratched and incisions are made by a special lancet called (in Afghanistan) a *nushtar* or *nishtar*. A *nishtar* carries three or four blades, 3 mm apart, and is scored upward along the seedpod. Incisions are made at sunrise or sunset, and it takes from 8 to 14 hours for the latex to exude and solidify (UNODC, 1953b). Incisions are made three or four times, 2–3 days apart. Each time, the sticky brown resin (latex) is scraped

Fig. 1.5 Poppy capsule with opium latex ("poppy tears") flowing from the immature seedpod

From iStockphoto.com/sadikgulec.

off the following morning with a blunt-bladed instrument and collected (Fig. 1.6). The latex is dehydrated by air-drying, boiling, or heating. In the legal processing of opium, scratching the pods is not done and the dried capsules (poppy straws) are processed to extract alkaloids (Ray et al., 2006).

1.4 Use and consumption

1.4.1 Opium history and description

(a) History

Opium use has been reported from several centuries BCE from several areas in the world, mainly around Mesopotamia (UNODC, 2008). The medicinal and adverse effects of opium were well described by Avicenna, the famous Persian physician, in his textbook *The Canon of Medicine* in the early 11th century CE (Heydari et al., 2013). Avicenna described analgesic,

Fig. 1.6 Harvesting of raw opium from the poppy seedpod in the field

A blunt-bladed instrument is used to scrape the solidified latex from the opium poppy seedpod.

hypnotic, antitussive, gastrointestinal, and cognitive medicinal effects, listed adverse effects such as respiratory depression, neuromuscular disturbances, and sexual dysfunction, and explained the potential toxicity of opium. Opium was used for headache, joint pain, earache, toothache, labour, and kidney and urinary bladder pain. Other indications for use included insomnia, severe cough, severe diarrhoea, and high libido. Opium was applied as oral, topical, rectal, and intranasal treatments. Forms such as syrups, tablets, smoke, and ear drops were popular (Heydari et al., 2013). From the Middle East, opium use spread to Europe, China, and India between the 11th and 15th centuries (Aragón-Poce et al., 2002), and later to the USA and Australia.

In the 17th century, the habit of opium smoking, linked to the spread of tobacco smoking, presented greater addiction potential than when the opium was ingested, which was the traditional means of consuming the drug (UNODC, 2008). After the Opium Wars of the mid-19th century, China fully legalized the importation of opium (UNODC, 2008). According to official Chinese figures, about 3.5% of the total population of China and 25% population of adult men smoked opium in 1906 (UNODC, 2008). In the USA, about 0.18% of

the adult population and up to 10% of people in the medical profession were addicted to opium in 1907–1908 (UNODC, 2008). In some other countries (e.g. Iran, Viet Nam, Laos, Cambodia, Thailand, Myanmar, Indonesia, the Philippines, India, Canada), the proportions of opium users among the total populations were estimated to vary between 0.1% and 2.9% in 1907–1908 (UNODC, 2008).

(b) Historical regulation

In Iran, royal orders for the restriction of opium use were documented as many as 400 years ago (Razzaghi et al., 2000). In China, the importation and sale of opium were banned for the first time in 1729 (UNODC, 2008). Bans on some aspects of opium use were initiated early in the 20th century in several countries, including New Zealand, Australia, and Canada (New Zealand Legal Information Institute, 1901; Australasian Legal Information Institute, 1908; Canadian Senate Special Committee on Illegal Drugs, 2002). An International Opium Convention came into force in 1928 and was eventually signed and ratified by 56 countries, which agreed to prohibit the manufacture, import, sale, distribution, export, and use of narcotic drugs, except for medical and scientific purposes (UNODC, 2008).

In 1953, an Opium Protocol was proposed, in which only seven countries – Bulgaria, Greece, India, Iran, Turkey, the former Soviet Union, and the former Serbia and Montenegro – would be authorized to produce opium for export, and opium use was limited exclusively to medical and scientific needs (UNODC, 1953c). The Protocol did not receive enough international ratifications to bring it into force until 1963, and it was superseded by the 1961 Single Convention, which came into force in 1964 (Senate of Canada, 2001) (see Section 1.5).

(c) Opium consumption and description of its forms

Globally, an estimated 1100–1500 tonnes of opium are consumed each year [76% of which is consumed in Asia] (UNODC, 2009, 2020). Annually, an estimated 450 tonnes of opium are consumed in Iran (42% of total global opium consumption) (UNODC, 2010), making this country the world's largest per capita consumer of opium (Dolan et al., 2011). After Iran, the next highest consumption occurs in Afghanistan and Pakistan, with an estimated 80 tonnes of opium (7% of the globally consumed opium) consumed annually in each of these two countries (UNODC, 2009). Among individual opium users, historical average daily doses have varied between 0.5 and 2.6 g in India and between 3.8 and 15 g in China (UNODC, 2008). In recent epidemiological (case–control) studies, the median daily consumption quantity among control groups who used opium was less than 2 g (Khademi et al., 2012; Mohebbi et al., 2021), and in a recent survey of 8696 daily opium users the mean daily dose was 3 g (Rafiei et al., 2019); these data are further described in Section 1.4.2(c) and Section 2. [The Working Group noted that few published data were found on the quantities of daily opium consumption in Iran and other countries.]

There are two main methods of consuming opium; ingestion (sometimes referred to as "eating" in the literature) and smoking (Khademi et al., 2012). Opium can be ingested through chewing, drinking, and swallowing (UNODC, 1953d). Opium can be chewed or eaten raw, dried, or after boiling or heating, and with or without being combined with substances including spices, amber, aloes, cochineal, musk, saffron, sugar, or rice (UNODC, 1953d; Westermeyer & Neider, 1982). Opium can also be ingested by pounding and mixing it with liquids – including water, tea, or wine – and then drinking (Fig. 1.7; UNODC, 1953d, 2014; Fernandez & Libby, 1998). In rural

Fig. 1.7 Preparing opium tea

north-western India, opium is traditionally consumed in the form of nuggets or powder. In contrast to the powder, which is usually smoked, the nuggets are dissolved in water, filtered, and then the extract is drunk (Ray et al., 2006). Finally, some individuals ingest opium by swallowing it in the crude form in which it is sold or as a pill (Richards, 1877; UNODC, 1953d). Liquids for oral use include opium tincture, opium wine, and opium syrup (Ray et al., 2006; Heydari et al., 2013). Opium tincture, also known as laudanum, is an antidiarrhoeal prescription drug. As a solution sold as oral drops, it is authorized in 17 European Union Member States (EMA, 2020). Opium tincture usually contains 10 mg/mL morphine and 19–33% ethanol (Drugs.com, 2019b; EMC, 2020). It is also used for the management of opium withdrawal in adults (Rahimi-Movaghar et al., 2018) and neonates (Ghazanfarpour at al., 2019) and for maintenance therapy in the treatment of opioid addiction (Jittiwutikarn et al., 2004), and has, in this context, also been referred to as opium syrup (Dahmardehei & Rafaiee, 2012). Opium wine is a solution of opium in

Fig. 1.8 A man smokes opium using a traditional tobacco pipe, Lao People's Democratic Republic

From Ivoha/Alamy Stock Photo.

aromatized sherry or diluted alcohol and has the same strength as ordinary laudanum (Merriam-Webster, 2020).

In ancient times, opium was usually taken orally (Swift et al., 1997; Heydari et al., 2013); however, after the introduction of the tobacco pipe during the 17th century, smoking opium became a popular method of opium consumption, particularly in China (Swift et al., 1997). Opium smoking (Fig. 1.8) remains a common and preferred method of consuming opium in many countries, including Afghanistan and Iran (UNODC, 2014; Sheikh et al., 2020), which could be due to the pleasurable effects of opium being achieved more rapidly by smoking opium than ingesting it (Westermeyer, 1978). Raw opium and opium dross can be ingested, or smoked with special devices (an opium pipe, called a *vafoor* in Persian), after direct heating with burning charcoal or sometimes with a hot metal rod (Siassi & Fozouni, 1980; Khademi et al., 2012; Rafiei et al., 2019). Opium is placed in a pipe, the head of the pipe is heated with charcoal, and then the smoke from the heated opium is inhaled through the pipe. Refined opium can be ingested or smoked by indirect heating using a special type of opium pipe. When the refined opium is heated indirectly, the user inhales the opium vapour, not its smoke (Khademi et al., 2012).

1.4.2 Prevalence, levels, and trends

(a) Global patterns

While the estimated global number of opiate users has increased from 15–21 million in 2007 to 30 million in 2019 (UNODC, 2009, 2016, 2020), the proportion of opiate users who used opium in 2007 is unknown. In 2008, there were an estimated 4.1 million opium users (UNODC, 2010). Currently, there are approximately 5 million regular users of opium worldwide (Rahimi-Movaghar et al., 2018), 80% of whom reside in Asia (UNODC, 2010). In opium-cultivating countries and some of their neighbours, opium is more commonly used than other opiates (UNODC, 2019b).

(b) Afghanistan

In Afghanistan, a significant increase in the use of opium was observed between 2005 and 2015 (Afghanistan Ministry of Counter Narcotics, 2015). The 2005 drug-use survey estimated that there were ~150 000 regular opium users (0.6% of the total population) in the country (UNODC, Afghanistan Ministry of Counter Narcotics and Afghanistan Ministry of Public Health, 2005); by 2009, this number had increased to 230 000 (UNODC, Afghanistan Ministry of Counter Narcotics and Afghanistan Ministry of Public Health, 2009).

In 2015, the countrywide national drug-use survey – involving 2757 randomly selected households in 11 urban centres and 52 rural villages – sampled 10 549 people, including 2711 men, 3723 women, and 4110 children (The Colombo Plan Secretariat, 2015). Biological specimens (hair, urine, and/or saliva) from 8.5% of the adults (10.3% of men and 6.7% of women) and 6% of the children tested positive for opioids. No more than 9% of children with positive results were estimated to be active users; it was estimated that 46–48% of positive results derived from adult administration and 44–45% from environmental exposure. Parents may give opium to their children to calm them down or to numb their hunger (Afghanistan Ministry of Counter Narcotics, 2013). The survey confirmed that opioids are the most common illicit drug used in Afghanistan (Afghanistan Ministry of Counter Narcotics, 2015). Similar findings were reported in a study conducted in Afghanistan between 2010 and 2012, which included 2187 randomly selected urban households representing 19 025 household members in 11 provinces. In addition to self-reported questionnaires and interviews on past and current drug use among members of their household, hair, urine, and saliva samples from 5236 people in the households were obtained and tested for metabolites of 13 drugs (Cottler et al., 2014). Not all these individuals may have been opium users. Passive opium smoke exposure in Afghan homes was assessed using hair samples, revealing high concentrations of opium products and drug metabolites in the systems of family members of opium users, including women and children (Goldberger et al., 2010).

(c) India

In India, according to a national survey conducted in 2018, 0.52% of the population, or ~1.1 million people, had used opium in the last 12 months (Ambekar et al., 2019); these results are similar to those reported in a national survey conducted in 2002 (Ray, 2004). However, there are areas with higher levels of opium use. In several provinces, it has been reported that 4.8–6.6% of individuals aged 15 years or older are current opium users (Chaturvedi et al., 2003, 2013; Chaturvedi & Mahanta, 2004). In India, ingestion of opium is more common than opium smoking. In rural areas of India, raw opium is consumed in nugget form; the nugget is dissolved in water, filtered, and then the extract is drunk (Ray et al., 2006). Among opioid-dependent patients, 27% in one state and 33% in another were found to be using opium (Gupta et al., 2019).

(d) Islamic Republic of Iran

In Iran, opium has been the most widely used illicit drug for decades. Opium use is seen across different age groups, socioeconomic classes, and regions (see Section 1.4.3). In 2001, a national survey on drug use showed that 5.5% of the adult population were current opium users and 1.5% were opium-dependent (Iranian Ministry of Health, 2002). Ten years later, the 2011 national household survey showed that opium was the main illicit drug used and led to substance-use disorders (Rahimi-Movaghar et al., 2014; Amin-Esmaeili et al., 2016). Of the population aged 15–64 years, 4.4% and 2.3% were reported to have used raw opium (*teriak*) and minimally refined opium (*shireh*), respectively, in the last 12 months, and 1.2% and 0.3% had used them daily in the last 12 months. Opium had been used in the last 12 months by 7.9% and 0.8% of men and women, respectively, which represents [2 300 000] people in the adult population. Two surveys of a rural population showed that daily raw opium and *shireh* use by people aged 12 years and above increased from 5% and 1.3% in 2000 to 15.7% and 9% in 2012, respectively (Ziaaddini et al., 2013). In two studies that assessed weekly use of opium in the population aged 40–75 years, 17% of respondents in Gonbad in 2006 and 8.4% in Valashahr in 2016 were opium ever-users. Both studies included urban and rural areas (Pourshams et al., 2010; Gandomkar et al., 2017). Opium use is also frequent among high school and university students (Rahimi-Movaghar et al., 2006; Menati et al., 2016). Opium is one of the most common substances for which individuals seek treatment for drug dependency (Jafari et al., 2010; Akbari et al., 2019; Rafiei et al., 2019). There are regional differences in the extent of opium use in Iran (Amin-Esmaeili et al., 2016; Alizadeh et al., 2020; Naghibzadeh-Tahami et al., 2020; Sheikh et al., 2020). In the Golestan Cohort Study (GCS), which was conducted in the north-east of Iran, the median cumulative amount of opium used among the cohort population was 21 nokhod-years [about 4.2 gram-years] (a *nokhod* is the standard unit of opium supply and is approximately equivalent to 0.2 g) (Sheikh et al., 2020), while in another study conducted in Kerman Province in the south-east of Iran, the median cumulative amount of opium used among the control group was 87.5 gram-years (Naghibzadeh-Tahami et al., 2020).

Comparison of the results of four national studies on drug users from 1998 to 2018 (Razzaghi et al., 2000; Narenjiha et al., 2005, 2009; Rafiei et al., 2019) shows that traditional use of opium has remained the main form of illicit drug use. In the fourth national study on drug users carried out in 2018 (n = 20 175) (Rafiei et al., 2019), daily use of opium (raw opium, opium dross, and/or *shireh*) was reported by 37.5% of participants ("drug abusers" recruited from 16 outpatient and inpatient centres, drop-in centres, shelter, prisons, and homes). Moreover, 67.1% of participants reported opium to be their dominant drug of use at the time of the interview. For those who reported daily use of opium, 85% of opium consumed was raw opium; 25% and 5% reported daily use of *shireh* and opium dross, respectively.

In Iran, the most common method of opium consumption is smoking (90.9%), followed by oral ingestion (8.8%). Smoking of *sukhteh* and *shireh* is reported to be the dominant route of use by three quarters of participants in the survey described above. The other one quarter reported ingestion as the dominant route of *sukhteh* and *shireh* use (Rafiei et al., 2019).

(e) Pakistan

In Pakistan, opium consumption has decreased over recent decades. A national survey conducted in 2013 estimated that there were 320 000 regular opium users in the previous year (0.3% of the population aged 15–64 years). In Pakistan-administered Kashmir, 0.4% of the population was using opium regularly, and the

highest proportion of opium users (1%) was in the province of Balochistan (UNODC and Government of Pakistan, 2013). Opium users were mostly married, slightly older (mostly aged 40–54 years), and were more likely to live in rural areas than were heroin users. Also, 84% of opium users versus about 60% of heroin users lived in a home (rather than a park, road, shrine, or other location). Many of the opium users had also used heroin and cannabis (UNODC and Government of Pakistan, 2013).

(f) Other countries

In China, the proportion of people consuming opium is small. In 2000, a national survey on drug use showed that ~0.14% of individuals aged 15 years and older had used opium in the previous 12 months, which showed a decreasing trend compared with surveys conducted in 1993 and 1996 (Hao et al., 2004). In China, opium is consumed mainly by smoking (Ray et al., 2006).

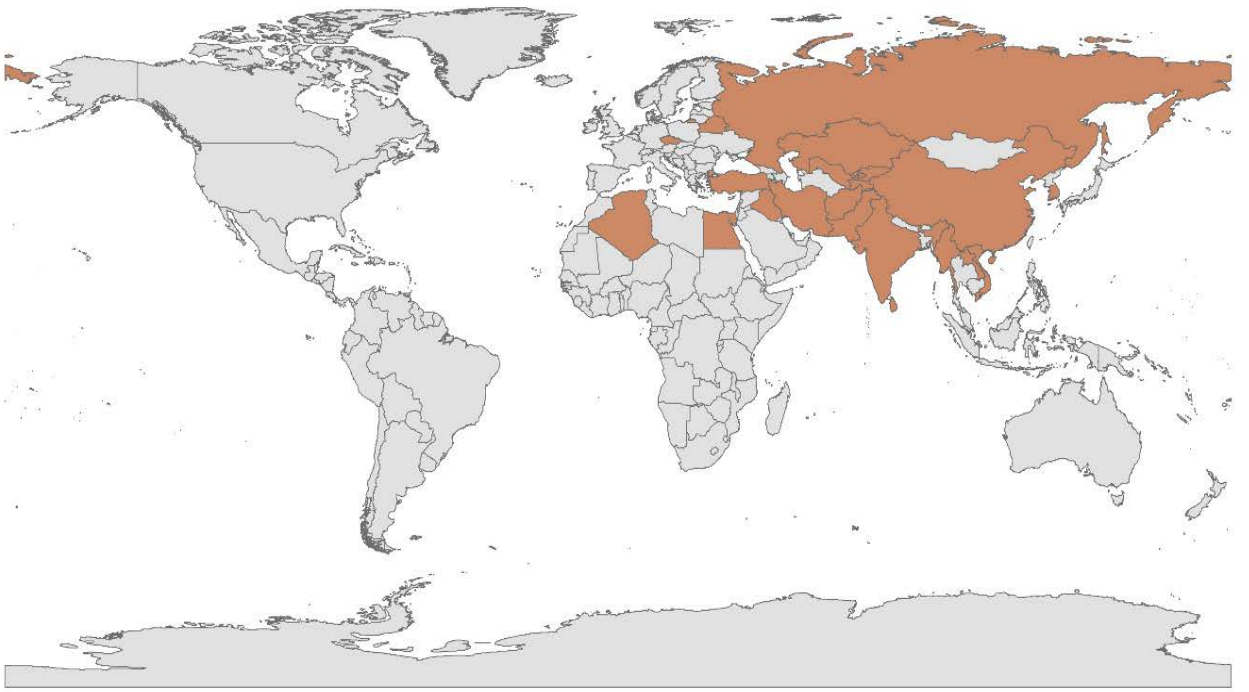
In 2018, there were 43 511 registered drug users [including more than 3100 registered opium users] in central Asia, excluding Turkmenistan (for which no data were available) (INCB, 2020). In addition, opium use has been reported in a small percentage of the population in Sri Lanka (Sri Lanka National Dangerous Drugs Control Board, 2018), Algeria (Abdennouri, 2014), Viet Nam (Thao et al., 2006), and the Democratic People's Republic of Korea (Yun & Kim, 2015). Recent data on the extent and pattern of opium use in these countries and for other parts of the world are lacking. Although most of the data on opium use come from southern and south-western Asia, the high number of countries all around the world that produce opium (either legally or illegally), the many countries that report opium seizures annually, and reported cases of opium poisoning (both in adults and in children) in other countries (Martínez & Ballesteros, 2019), suggest that opium use exists to a greater or lesser degree in many areas of the world. Fig. 1.9 indicates countries with reports of opium use during the past 20 years. Fig. 1.10 illustrates countries with reported opium seizures in 2018.

(g) Exposure to lead and other adulterants and contaminants as part of opium exposure

In the present monograph, contaminants and adulterants of opium are considered integral parts of the complex mixture to which opium users are exposed. Several studies have indicated the presence of different levels of lead contamination in tested opium samples (Aghaee-Afshar et al., 2008; Aghababaei et al., 2018; Akhgari et al., 2018; Rahimi et al., 2020). Some other studies have shown higher concentrations of lead in the blood of opium users than in non-users (Salehi et al., 2009; Amiri & Amini, 2012; Khatibi-Moghadam et al., 2016; Nemati et al., 2016; Ahmadinejad et al., 2019). Although all these reports originate from Iran, there is huge variation in the reported lead concentrations measured in opium samples, with values ranging from 1.88 ± 0.35 μg/g (Aghaee-Afshar et al., 2008) to 138.10 ± 75.01 μg/g (Aghababaei et al., 2018). Similarly, there is significant variation in reported mean blood lead concentrations among opium users (Alinejad et al., 2018; Soltaninejad & Shadnia, 2018), with major differences between opium users in different provinces of Iran (Amiri & Amini, 2012; Khatibi-Moghadam et al., 2016; Soltaninejad & Shadnia, 2018). The exact source of this contamination is not clear; however, water and soil contamination of opium poppy cultivation farms (Salamon & Fejer, 2011; Chizzola, 2012; Moghaddam et al., 2020), the use of inappropriate methods and equipment in opium production, and adulteration of opium with lead to increase its weight to raise profits are among the suggested mechanisms (Aghababaei et al., 2018; Akhgari et al., 2018; Alinejad et al., 2018; Zamani et al., 2020).

There are also reports from some countries that show other types of adulterants in opium, including arsenic (between 25 μg/100 g and 29 mg/100 g) in India and Sri Lanka (Datta &

Fig. 1.9 Countries with reports of opium use during the past 20 years, according to United Nations Office on Drugs and Crime reports, country reports, and published studies



Countries that are highlighted in the map are: Afghanistan, Algeria, Belarus, China, Czechia, Egypt, India, Iran (Islamic Republic of), Iraq, Kazakhstan, Kyrgyzstan, Lao People's Democratic Republic, Myanmar, Pakistan, the Russian Federation, Democratic People's Republic of Korea, Sri Lanka, Tajikistan, Turkey, Uzbekistan, and Viet Nam.
Data from Fan et al. (2004); Klusonová et al. (2005); Ray et al. (2006); Thao et al. (2006); UNODC (2010, 2020); UNODC and Government of Pakistan (2013); Abdennouri (2014); The Colombo Plan Secretariat (2015); Yun & Kim (2015); Amin-Esmaeili et al. (2016); Rahimi-Movaghar et al. (2018); Sri Lanka National Dangerous Drugs Control Board (2018); Ambekar et al. (2019); INCB (2019); Martínez & Ballesteros (2019).

Kaul, 1977; Wijesekera et al., 1988), strontium sulfate in Mexico (Sodi Pallares & Meyran Garcia, 1954), strychnine in Sri Lanka (Wijesekera et al., 1988), and chromium in Iran (Aghababaei et al., 2018).

1.4.3 Factors that are associated with opium use

The objective of this section is to provide information on the determinants of opium use and co-exposures to carcinogenic agents among opium users. The literature shows that sex and socioeconomic characteristics are associated with ever-using opium, and/or the intensity and duration of opium consumption (see Sections 1.6.1 and 1.6.2 for more information about these terms).

The average age of starting opium use is usually below 25 years (Haidary, 2015; Rasekh et al., 2018; Rafiei et al., 2019). Globally, opium use is much more prevalent in men than women (Dolan et al., 2011; UNODC, 2018). Surveys conducted in countries with high numbers of opium users – including Iran (Najafipour et al., 2015; Amin-Esmaeili et al., 2016), India (Mohan et al., 1986; Chaturvedi et al., 2013), and Afghanistan (Cottler et al., 2014) – have shown that men are 5- to 12-fold more likely to use opium than are women. There are also studies that show earlier age at initiating opium use (Ghaderi et al., 2017), higher cumulative opium use (Moossavi

Fig. 1.10 Seizures of opium, 2018

Created by the Working Group, with annual seizure data from UNODC (2019a)

et al., 2018), and higher rates of multiple drug use (Mohan et al., 1986; Chaturvedi et al., 2003; Ghaderi et al., 2017) among men who are opium users than among women opium users.

Opium is used across the spectrum of society. Reports from India and Iran show that opium use typically starts in social gatherings for pleasure and entertainment (Ray et al., 2006; Rahimi-Movaghar et al., 2018). Many users consume opium only occasionally and at such social events. Some people self-medicate with opium taken as a painkiller or sedative; however, this might result in regular use and dependence (Ray et al., 2006; Rahimi-Movaghar et al., 2018). Cessation of opium use by an individual who is opium-dependent gives rise to a classical opiate withdrawal syndrome of mild to moderate intensity. Opium dependence is not a benign disorder; however, opium costs less, requires fewer doses per day, and has less severe withdrawal symptoms than heroin (Westermeyer & Peng, 1977). Moreover, reports from several countries show that opium users have a more stable lifestyle and lesser degree of psychopathology than heroin users. A high proportion of opium users are married and live with their families (UNODC and Government of Pakistan, 2013; Rahimi-Movaghar et al., 2018; Gupta et al., 2019; Rafiei et al., 2019).

Reports from Afghanistan, India, and Iran indicate that opium use is more prevalent in populations with lower socioeconomic status (Gobar, 1976; Afghanistan Ministry of Counter Narcotics, 2013; Chaturvedi et al., 2013; Amin-Esmaeili et al., 2016). Socioeconomic status is a complex concept, and it has traditionally been defined by education, wealth, and occupation. Therefore, the selection of the socioeconomic indicator of the study population varies in different studies. Some indicators that have revealed significant correlations with opium use include income (Griffith & La France, 2018), employment (Chaturvedi et al., 2013; Haidary, 2015; Amin-Esmaeili et al., 2016; Griffith & La France, 2018), education (Chaturvedi et al., 2013; Haidary, 2015; Amin-Esmaeili et al., 2016), marital status (Chaturvedi et al., 2013; Amin-Esmaeili et al., 2016), wealth score (Sheikh et al., 2020), and urban or rural residence (Shiri et al., 2006; Khademi et al., 2012; Sheikh et al., 2020). There are also reports from Iran that have shown higher opium consumption among specific occupations, such as those involving long-distance driving (Rajabizade et al., 2004; Souri et al., 2016) and welding (Saberi-Zafarghandi et al., 2010).

Many opium users are also tobacco smokers; however, the percentages of opium users who also smoke tobacco vary across subgroups of men and women in the studied populations. In the GCS, which includes more than 50 000 residents of Golestan Province in the north-east of Iran, 8486 participants reported using opium, and of these 4475 (52.7%) also reported smoking cigarettes (Sheikh et al., 2020). In the GCS, opium users who also smoked cigarettes had significantly higher levels of cumulative opium use than opium users who did not smoke cigarettes (Moossavi et al., 2018). Similarly, in other studies that were conducted in different populations and geographical regions, the prevalence of ever-smoking tobacco among opium users was reported to be as high as 60–70%, and was more common among men than women (Mohan et al., 1986; Chaturvedi et al., 2003; Nasrollahzadeh et al., 2008; Ghaderi et al., 2017).

Evidence from the GCS shows that opium users are more likely to chew tobacco (Sheikh et al., 2020) and drink alcohol than non-users (Sheikh et al., 2020). The GCS also shows some evidence of slightly higher rates of drinking very hot tea (Islami et al., 2020), having an unhealthy diet, burning biomass as the main household fuel, and using water pipes to smoke tobacco among opium users than among non-users (Sheikh et al., 2020).

1.5 Regulation and legislation

The first international conference to discuss the global narcotics problem was the Opium Commission in Shanghai in 1909 (UNODC, 2008). Subsequent international conferences were held in 1924–25 and 1953 to prohibit the manufacture, import, sale, distribution, export, and use of narcotic drugs, except for medical and scientific purposes (UNODC, 2008). More information on international regulations before 1961 is presented in Section 1.4.1.

The current Single Convention on Narcotic Drugs (UNODC, 1961), which came into force in 1964 and was subsequently ratified by 190 countries (INCB, 2020), aims to prohibit the production and supply of named narcotic drugs and prevent drug abuse by coordinated international action (United Nations Treaty Collection, 1975). This Convention includes opium in Schedule I of international control. Parties to the Convention are committed to limit the possession, use, trade, distribution, import, export, manufacture, and production of opium exclusively to medical and scientific purposes. Morphine and thebaine, the main alkaloids that can be purified from opium, are also listed independently in Schedule I. Preparations of opium or morphine containing not more than 0.2% morphine are included in Schedule III of the Convention.

After endorsement of the Single Convention, countries individually developed national legislation to regulate access to the internationally controlled substances. Differences in substance classifications in these national laws may slightly affect the status of opium. For example, the UK has placed opium in class A of its three classes (UK Government, 2019), Canada in Schedule I of its six classes (Minister of Justice Canada, 2019), the USA in Schedule II of its five classes of controlled substances (DEA, 2020b), and Iran in class II of its two classes for illicit substances (Drug Control Law, 2010). However, all countries can prosecute individuals for illegal production, trafficking, and distribution of opium, and most countries can prosecute for possession of opium.

Global licit production of opium was about 30 000 tonnes in 1907–1908 before the international commitment to limit opium production to medical and scientific purposes (UNODC, 2004, 2008). Global illicit opium production decreased by about 25% between 2017 and 2019 (UNODC, 2020). The reduction might reflect the effectiveness of control measures in restricting the production and availability of opium and other opiates for use. Nevertheless, the continuing production of opium and the high number of users reflect partial effectiveness of the international conventions and national laws.

1.6 Quality of exposure assessment in key epidemiological studies of cancer and mechanistic studies in humans

Epidemiological studies have used various exposure assessment methods to investigate the association between opium and cancer incidence. Optimal exposure assessment should consider:

- the type of epidemiological study
- the source of the opium exposure data, such as from a validated and structured interview, a clinical interview, or from patients' records, etc.
- a clear definition of opium use
- the age or date of first use of opium
- the average daily dose of opium (intensity)
- the duration of exposure in months or years
- the cumulative exposure (intensity multiplied by duration)
- the temporality of the exposure (when it occurred relative to the study end-point)
- the type(s) of opium consumed (raw, dross, or minimally refined; see Section 1.1.2)

- the mode of consumption (smoking or ingestion).

The intensity, modes, and type of opium use may change between data collection at baseline and at the time of end of follow-up, which is particularly important for cancers with long latency. The manner of data collection should minimize the potential for under-reporting of opium, which can occur because of its illicit nature. Where possible, the accuracy of the exposure ascertainment should be checked (see Section 1.2). However, opium metabolites in urine can only indicate recent exposure to opium (Abnet et al., 2004). Furthermore, as outlined in Sections 1.1.3(b), 1.4.2(g), and 1.6.2, the opium product may be adulterated or contaminated by potentially carcinogenic impurities [the Working Group noted that the extent of and components of adulteration have varied by time and geographical area, which makes exposure assessment difficult].

1.6.1 Exposure assessment methods in epidemiological studies of cancer and mechanistic studies in humans

The Working Group evaluated 5 publications from cohort studies (4 of which were conducted within the same cohort), 27 case–control studies, and 1 meta-analysis investigating the association between opium consumption and cancer incidence or mortality (see Tables S1.6.2A–D, Annex 1, Supplementary material for Section 1, web only; available from: https://publications.iarc.fr/600; and Section 2, Tables 2.1–2.5). One study did not mention how exposure data were ascertained (Khoo, 1981). The remainder of the studies ascertained data on opium exposure via patient records or by questionnaires or interviews.

The Working Group identified 13 mechanistic studies in humans. Most mechanistic studies compared opium users with non-users, and examined various biological outcomes other than cancer (e.g. Asgary et al., 2008; Ghazavi et al., 2013a, b; Hashemipour et al., 2013; Nabati et al., 2013; Ayatollahi-Mousavi et al., 2016; Dwivedi et al., 2019).

As outlined in Section 1.2, biomarkers were used to evaluate the quality of the questionnaire data. The reliability of questionnaire data was assessed using test–retest methods.

The extent of exposure assessment varied across studies. Some studies incorporated "ever" versus "never" opium consumption without collecting other data on opium exposure (type, mode of ingestion, duration, intensity, or temporality of use) (see Tables S1.6.2A–E, Annex 1, Supplementary material for Section 1, web only; available from: https://publications.iarc.fr/600). In the GCS, comprehensive exposure assessment was obtained via an interview-based structured and validated questionnaire administered by trained staff, including general practitioners and nutritionists. Multiple studies used the GCS Questionnaire (GCSQ) (see Section 2).

The GCSQ ascertained information on age at starting opium use, daily amount consumed, frequency of use, route of administration (smoking or ingestion), opium type, and age at stopping use (Rahmati et al., 2017; Sheikh et al., 2019). "Ever" use of opium was defined as opium use at least once per week for at least 6 months (Malekzadeh et al., 2013). Opium was quantified via nokhods, and cumulative use was calculated in "nokhod-years" based on nokhods per day multiplied by the number of years of consuming opium (Moossavi et al., 2018; Sheikh et al., 2020).

In a case–control study of gastrointestinal cancers (oesophageal, gastric, pancreatic, and colon and rectum), Vazirinejad et al. (2020) defined opium use as mesghals per day. A *mesghal* (also known as a *mithkal*) is a unit of weight used to quantify precious materials such as gold and saffron. One mesghal is equal to 4.55 g (Houtsma et al., 1993).

In Golestan Province, opium is primarily either smoked or ingested. The GCS (Sheikh et al., 2020) evaluated opium consumption on

the basis of quartiles of cumulative nokhod-years of consumed opium compared with never consumption of opium (where "never" was defined as not having consumed opium at least once per week for at least 6 months). In addition, smoking opium and ingesting opium were separately evaluated in the GCS. Opium smoking was evaluated on the basis of quartiles of cumulative nokhod-years of smoking opium compared with never-smoking opium. Opium ingestion was evaluated on the basis of quartiles of cumulative nokhod-years of ingested opium compared with never-ingestion of opium. For individuals who smoked and ingested opium, cumulative exposure was calculated separately and included in the corresponding smoked and ingested exposure categories. A study by Mohebbi et al. investigated the validity of perceived and reported opium use across Iran using a modelling clay-like material to demonstrate the amount of opium used (Mohebbi et al., 2019). The study showed that estimating the amount of opium on the basis of nokhods or grams was inaccurate and varied by geographical region, and that people had a tendency to underestimate the actual amount of opium consumed (Mohebbi et al., 2019). Experimentally, the median perceived weight for 1 g of opium by the participants was lower than the expected standard (0.24 g instead of 1 g; interquartile range, 0.16) (Mohebbi et al., 2019). Similarly, the participants perceived the median weight of one nokhod as lower than the expected standard (0.16 g instead of 0.20 g; interquartile range, 0.16). (Mohebbi et al., 2019). [The Working Group noted that this suggests that the amounts of opium consumed may have been underestimated in studies reporting opium use in grams and in studies reporting exposure intensity as nokhods per day.]

Information on opium exposure from the GCSQ was validated for 150 participants by means of quantification of opium alkaloids (codeine and morphine) in urine (Abnet et al., 2004). The validity of self-reported opium use was high (sensitivity, 93%; specificity, 89%). The GCS study also assessed the reliability of the questionnaire by reinterviewing 130 participants 2 months after they initially completed the questionnaire. The comparison yielded kappa values of 0.96 for ever-use of opium and 0.74 for duration of opium use (Abnet et al., 2004). Tables S1.6.2A–D (Annex 1, Supplementary material for Section 1, web only; available from: https://publications.iarc.fr/600) shows that a minority of case–control studies assessed opium exposure via structured, validated questionnaires. The remaining case–control studies ascertained exposure information from patient records, telephone calls, interviews, or public demographic information. The questionnaires were administered in various ways in the case–control studies. To minimize variation across interviews, some studies used a single interviewer for all study participants (see, for example, Naghibzadeh Tahami et al., 2014; Akbari et al., 2015). However, others used multiple interviewers, so may be prone to random variation in exposure assessment (Bakhshaee et al., 2017). To quantify the amount of opium used, some studies categorized opium exposure on the basis of never versus low versus high use, using median use in the control population as a cut-off point for low versus high, thereby reflecting levels in the background population.

To date, one meta-analysis has investigated the association between opium consumption and cancer risk: Afshari and colleagues investigated the association between opium use and the incidence of urinary bladder cancer, aiming to distinguish between exposure to opium alone and exposure due to concurrent use of opium and cigarettes (Afshari et al., 2017). Two researchers extracted data from the eligible studies; a third researcher acted as an adjudicator in case of disagreement. The meta-analysis included 11 case–control studies, 1 cohort study, and 5 cross-sectional studies, all from Iran. The included studies evaluated exposure on the basis of structured validated questionnaires

(Hosseini et al., 2010; Shakhssalim et al., 2010; Akbari et al., 2015; Lotfi et al., 2016) or patient records (Sadeghi et al., 1979; Aliasgari et al., 2004; Nourbakhsh et al., 2006; Salehi et al., 2011; Karbakhsh et al., 2013; Aliramaji et al., 2015). One study had limited information on how exposure data were ascertained (Ketabchi et al., 2005). The five cross-sectional studies investigated the frequency of opium consumption. Two studies evaluated the dose of opium, and five studies included the duration of opium consumption. The meta-analysis did not provide a clear definition of opium use and did not distinguish the type of opium used or method of consumption. One study included in the meta-analysis (Tootoonchi et al., 2000) was excluded from the present monograph because it lacked sufficient detail for evaluation (see Section 2.2), and two studies were excluded from consideration for the present monograph because they were case series (Ghavam-Nasiri et al., 2002; Mohseni et al., 2005). The varying methods of exposure ascertainment in the meta-analysis should be considered when interpreting the study findings.

1.6.2 Critical review of exposure assessment

(a) Studies of cancer in humans

This section reviews the exposure assessment methods and quality in the cancer epidemiology and human mechanistic studies for the primary exposure of interest, opium consumption. It also provides an assessment of potential confounders of associations of opium use with cancer (notably tobacco) (see Section 1.4.3). The quality assessment findings are summarized in Tables S1.6.2A–E (Annex 1, Supplementary material for Section 1, web only; available from: https://publications.iarc.fr/600) and, for cancer in humans, in Tables 2.1–2.5.

To assess the quality of the exposure assessment, the cancer epidemiology studies and mechanistic studies carried out in people exposed to opium were reviewed and tabulated (see Tables S1.6.2A–E, Annex 1, Supplementary material for Section 1, web only; available from: https://publications.iarc.fr/600). A high-quality exposure assessment would include the list of data elements provided at the start of Section 1.6.1. The presence of these data was tabulated for each study (see Tables S1.6.2A–E, Annex 1, Supplementary material for Section 1, web only; available from: https://publications.iarc.fr/600). It was noted whether the exposure data were collected before or after the disease outcome was identified, and whether the reference group might contain opium-exposed individuals. The study definition of the opium user was examined (e.g. "addict") and whether the study reported a minimum intensity or duration of exposure for an individual to be included as an exposed individual. Data relating to other exposures reported in the paper were also identified and are included in Tables S1.6.2A–E (Annex 1, Supplementary material for Section 1, web only; available from: https://publications.iarc.fr/600). The reported co-exposures varied with each paper and could include smoking and chewing of tobacco, use of alcohol, tea temperature, food, cooking methods, occupational exposures, and others.

(i) Golestan cohort and case–control studies and opium exposure

The majority of the data relating to cancer and opium use that were identified were from Iran, particularly from the Golestan cohort of over 50 000 people recruited between January 2004 and June 2008 (Khademi et al., 2012). More detail about the GCS is provided in Section 2.1. This cohort examined opium use and reported that the consumption of *sukhteh* [opium dross] and use of opiates such as heroin were uncommon in this cohort (Khademi et al., 2012).

Each participant in the GCS was interviewed at baseline by a trained general physician (Pourshams et al., 2010; Sheikh et al., 2020), using a structured and validated questionnaire

(the GCSQ), which gathered exposure history, including that of opium use. Opium use was defined as ever-used, encompassing opium use at least weekly over a 6-month period (Abnet et al., 2004). Those who used opium occasionally were included in the unexposed group. The age of starting consumption, intensity, and duration at each dose level, type of opium, and mode of consumption (smoking only, ingestion only, or both) were collected.

[The Working Group considered the data collected using the GCSQ to be systematic, detailed, and comprehensive.] The GCSQ allows the assessment risk of average daily intensity in nokhods, duration of use, and cumulative exposure. Exposure metric(s) can be lagged for cancers with a long latent period because the temporality of the exposure is known. The prospective nature of the exposure assessment means that recall bias is less likely than when exposure data are collected after diagnosis. In addition, reverse causation and protopathic bias can be discounted (see Annex 2, Methodological considerations for epidemiological studies on opium consumption and cancer). This occurs, for example, when the development of a perhaps painful disease precipitates the use of opium. A minimum level of exposure (less than weekly over a 6-month period) was defined, and individuals with such low exposure were excluded from the exposed group because their inclusion could reduce the strength of any observed association. However, these individuals may have been included in the reference or unexposed group, which could also reduce the observed association. The daily opium dose was validated by comparing the questionnaire responses with measurements of urinary metabolites (Abnet et al., 2004). [The Working Group noted that the few Golestan cohort participants who reported using only heroin at the time of enrolment were past users of opium and were included in the exposed group.]

The GCSQ has been used in several publications from the GCS (Pourshams et al., 2005; Khademi et al., 2012; Malekzadeh et al., 2013; Rahmati et al., 2017; Moossavi et al., 2018; Sheikh et al., 2019, 2020). The GCSQ has also been used in several case–control studies, including some conducted in Golestan Province (Shakeri et al., 2012, 2013) and some in other regions in Iran (Naghibzadeh Tahami et al., 2014, 2016; Shakeri et al., 2016, in which the questionnaire was modified for pancreatic cancer; Akbari et al., 2015; Iankarani et al., 2017; Alizadeh et al., 2020). While the GCSQ differentiates between modes of opium consumption, some studies using this questionnaire combined the different modes for their analyses.

The GCS collected exposure data at baseline (Pourshams et al.; 2005). These prospectively collected data have been used in later studies (Khademi et al., 2012; Moossavi et al., 2018; Sheikh et al., 2019, 2020). Although the cohort exposure data, such as on opium smoking, have been updated since the data collection at baseline, they have not been published (Pourshams et al., 2010). [The Working Group noted that, while the duration of use and cumulative exposure to opium may increase after baseline, the study classified cohort members with respect to opium use at baseline.]

[The Working Group noted that, as discussed in Section 1.4.2, secondhand opium exposure can occur. Exposure among non-user family members of users has been observed in Afghanistan (Goldberger et al., 2010) and Iran (Ghadirian et al., 1985). Hair samples showed that non-users may be exposed if they are domiciled with opium users (Goldberger et al., 2010).]

Some studies that used the GCSQ were case–control studies, which were not nested in the Golestan cohort, and where the opium exposure data were collected after diagnosis (Nasrollahzadeh et al., 2008; Shakeri et al., 2013, 2016; Naghibzadeh Tahami et al., 2014, 2016). [The Working Group noted that if exposure data were collected at or after diagnosis, particularly in a clinical setting, cases may be more willing

to report opium use than controls. This would result in recall bias, and exposure among controls would be more likely to be underestimated than that of cases.]

Some of the illicit opium supply may have been adulterated (see Sections 1.1.2 and 1.4.2(g)), resulting in a reduced proportion of active ingredients (Aghababaei et al., 2018). The adulterants may themselves be toxic (e.g. lead, Aghababaei et al., 2018). [The Working Group considered it likely that long-term opium consumers could obtain supplies of less-adulterated opium and that they may adjust the amount of opium consumed to experience the effects of a standard amount of the active ingredients.]

(ii) Other studies

Some case–control studies have collected data on opium exposure by structured or semi-structured interview or questionnaire (Mousavi et al., 2003; Hosseini et al., 2010; Sadjadi et al., 2014; Ghadimi et al., 2015; Bakhshaee et al., 2017; Alizadeh et al., 2020; Vazirinejad et al., 2020); others have used data from patient records (Aliasgari et al., 2004; Aliramaji et al., 2015; Berjis et al., 2018).

The definition of what is meant by opium consumption was clear in some papers, for example, diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) as opium dependence and abuse, followed up with urinary testing for opiates (Hosseini et al., 2010). In other papers, the definition was "drug abuse" (Ghadimi et al., 2015), "opium addict" (Sadeghi et al., 1979), or "opium consumer" (Aliasgari et al., 2004).

[The Working Group noted that the lack of documented detail in some studies means that there is uncertainty about the systematic nature and reliability in the collection of opium exposure data. If exposure data were collected at or soon after diagnosis, particularly from an unstructured interview, then there is the possibility of information bias. Cases may have been probed more strongly and/or may have been more willing to report opium use than controls, particularly in a clinical setting. Therefore, the control group would be more likely to contain unidentified opium users. This would create differential misclassification and could lead to overestimation of any risk. However, according to investigators, opium in Iran is a "traditional medicine in this population, and possibly because of the setting and personnel completing the interview, we suspect that there was little social pressure to deny use" (Abnet et al., 2004). The extent to which this applies to all the studies presented here was not clear.]

[The Working Group noted the possibility of a further reporting bias in case–control studies, in that opium users may under-report the amount of opium use as the number of nokhods or grams per day (see Section 1.6.1 for a discussion of the accuracy of exposure estimates in nokhods and grams). It is less likely that they would over-report the extent of exposure. This could lead to misclassification, in that exposure may be higher than reported for at least some users. This misclassification would likely lead to overestimation of the risk associated with a particular level of opium consumption. If there is a threshold of exposure below which risk is undetectable, underestimation of exposure in cases and controls could result in identification of a lower than actual threshold.]

A case–control study by Vazirinejad et al. (2020) reported opium exposure as mesghals per day. [The Working Group noted that this measure was used in a single study, but that the validity of this unit of exposure is not clear.]

[The Working Group noted that opium consumption, like tobacco smoking, may extend over many years with varying intensity over the period. Data from investigation of the reliability of the recall of tobacco smoking show that recall over many years of duration or intensity may not be reliable (Bernaards et al., 2001).]

The differences in cancer risk arising from the mode of consumption have been examined in some studies (e.g. Nasrollahzadeh et al., 2008; Hosseini et al., 2010; Malekzadeh et al., 2013; Rahmati et al., 2017; Sheikh et al., 2020). [However, the Working Group noted that even where exposure is quantified and the mode of consumption considered, no difference in the amount of exposure between the different consumption modes has been considered. It is not clear whether ingested opium is more or less carcinogenic or biologically active than the same quantity of inhaled opium. When smoked, the dross is often eaten so that all the opium is consumed, but what proportion of the opium or its metabolites reaches a critical organ, for example, the urinary bladder, has not been considered.]

[The Working Group further noted that there is no agreed standard summary measure of exposure or agreed "ideal metric" for opium exposure. In epidemiological analyses, the exposure is often presented as ever/never, so individuals with long-term, low-level exposure may be combined with those with shorter-term, perhaps higher-intensity exposure; and opium smoking and ingestion are often combined in analyses, although it would be desirable to analyse these modes of exposure separately. The GCSQ data allowed analyses by intensity, duration, and cumulative exposure. Cumulative exposure was calculated in some studies (Khademi et al., 2012; Naghibzadeh Tahami et al., 2014; Akbari et al., 2015; Moossavi et al., 2018; Sheikh et al., 2019, 2020; Alizadeh et al., 2020).]

Cancers typically develop after long periods of latency; it is therefore important to evaluate associations between exposures and their effects by evaluating exposures occurring at different time periods before the onset of disease. Exposure lagging was possible with data from the GCSQ, but explicit lagging was not identified in any of the studies. Some studies separately examined risk from distant past exposure and from all exposure (e.g. Malekzadeh et al., 2013; Moossavi et al., 2018; and Sheikh et al., 2020) or from recent and all exposure (e.g. Pourshams et al., 2005).

Reverse causation or protopathic bias could occur if opium use started, or the extent of use increased, in response to disease symptoms such as pain (see Annex 2, Methodological considerations for epidemiological studies on opium consumption and cancer). This could have occurred in studies that included recent exposures (e.g. Hamrah et al., 2017), or where the whole exposure period was included or the period of opium use was not defined. Most analyses of the Golestan cohort have evaluated reverse causation in the sensitivity analyses by excluding the first 2 years of follow-up (Khademi et al., 2012; Rahmati et al., 2017; Sheikh et al., 2019, 2020).

Studies of cancer in humans have focused on individuals who deliberately consumed opium by smoking or ingestion (injection of opium is unusual). Section 1.4.1 presents some traditional and prescription medicines that contain opium, but these are not considered in most epidemiological studies. Secondhand exposure is not considered in the present monograph, although there is evidence for such exposure in family members of users (Ghadirian et al., 1985; Goldberger et al., 2010; Afghanistan Ministry of Counter Narcotics, 2013; Vazirinejad et al., 2020). As noted in Section 1.4.2, in a community survey in Afghanistan, 10.3% of men, 6.7% of women, and 6% of children tested positive for opioids (Afghanistan Ministry of Counter Narcotics, 2015).

[In summary, the Working Group noted that epidemiological studies on opium almost all rely on self-reported exposure, which may be more reliable when collected prospectively than when collected after diagnosis of cancer. Recall bias and reporting bias cannot be ruled out in these studies. The GCS stands out as having prospectively collected detailed data on the intensity and duration of exposure, and on the type of opium and modes of exposure. Several case–control

studies outside this cohort had limited data on when the exposure occurred relative to diagnosis and on the type of opium, and did not identify the mode(s) of use.]

(iii) Quality of co-exposure data

As outlined in Section 1.4.3, there are several other exposures that co-occur with opium consumption and that may increase or decrease cancer risk (for example, the use of tobacco, alcohol, consumption of hot tea, some occupational exposures, indoor air pollution, and some foods). Most of the studies reviewed here collected information about at least some of these risk factors. Some studies excluded participants with particular exposures and some studies used co-exposures as adjustment factors.

Most studies collected tobacco-smoking history, with some reporting cumulative exposure, such as pack-years (e.g. Akbari et al., 2015; Sheikh et al., 2019, 2020); and others reporting status as never/ever smoker (Khademi et al., 2012), or never/current/ex-smoker (Ghadimi et al., 2015). Some studies collected data on the use of a hookah, which may entail exposure to a large amount of tobacco (Nasrollahzadeh et al., 2008; Shakeri et al., 2013; Sadjadi et al., 2014; Pournaghi et al., 2019). Opium may also be smoked with a water pipe, not just with dedicated opium pipes (Chaouachi, 2009).

Some studies also gathered data on nass consumption. Nass is a tobacco, lime, and ash mixture that is chewed. The tobacco-smoking or nass use reported in the GCSQ correlated with urinary cotinine levels (Pourshams et al., 2005).

The validity and reliability of the Golestan food frequency questionnaire (FFQ) was tested. The FFQ was repeatable and was correlated with 24-hour food recall, but correlation with specific nutrients measured in urine and blood was lower (Malekshah et al., 2006). FFQ use was reported by Akbari et al. (2015) and Sheikh et al. (2019, 2020). Data on food were collected using other instruments in several other studies, but were not mentioned in the analyses except as a factor to be controlled for (e.g. Nasrollahzadeh et al., 2008; Iankarani et al., 2017; Vazirinejad et al., 2020). [The Working Group noted that details about these instruments were sparse.]

The temperature of tea is a possible risk factor for oesophageal cancer and was measured by Sheikh et al. (2019). Pourshams et al. showed that the reported tea temperatures from the GCSQ were repeatable despite interindividual variability (Pourshams et al., 2005).

A history of alcohol use was collected in most studies (see Tables S1.6.2A–E, Annex 1, Supplementary material for Section 1, web only; available from: https://publications.iarc.fr/600), but is usually reported as ever or never, because it is a relatively uncommon exposure. [The Working Group noted that there could be under-reporting of alcohol use, because this is seen as socially undesirable (Naghibzadeh-Tahami et al., 2016).]

The job histories or occupational exposures gathered in the GCS do not appear to have been used in any analyses. Other studies are likely to have gathered occupational data using different questionnaires. One study of urinary bladder cancer excluded those with occupational risks (definition unclear) (Hosseini et al., 2010), while others coded jobs to International Standard Classification of Occupations codes and/or analysed risk for some industry groups (Shakhssalim et al., 2010; Ghadimi et al., 2015). A case–control study of lung cancer also excluded individuals if there had been a significant history of exposure to a list of known occupational carcinogens, such as arsenic, asbestos, and radon (Safari et al., 2016).

(b) Mechanistic studies in humans

Summaries of the exposure methods and exposure assessment quality of the human mechanistic studies are found in Tables S1.6.2E (Annex 1, Supplementary material for Section 1,

web only; available from: https://publications.iarc.fr/600).

There were limited details about how the opium exposure data were collected in many studies (e.g. Azarang et al., 2007). In most cases, data were drawn from a questionnaire and/or interview (Asgary et al., 2008; Nabati et al., 2013; Safarinejad et al., 2013a; Salarian et al., 2018). One paper used patient records (Firouzeh et al., 2016), while another used cases from the Golestan cohort and so probably used opium exposure data from the validated structured questionnaire (the GCSQ), but this was not explicitly stated in the paper (Abedi-Ardekani et al., 2011). [The Working Group noted that lack of information about how the exposure data were collected means that it is unclear how systematic the data collection was, and suggests that information bias, particularly under-reporting, and/or observer bias cannot be excluded.]

About one half of the evaluated studies used "opium user" or "opium addict" to define the exposed individuals, with no identified minimum opium exposure duration or intensity. Some studies had more specific definitions, e.g. clinic attendees (Dwivedi et al., 2019) or a DSM-IV diagnosis (Ghazavi et al., 2013a, b; Hashemipour et al., 2013). A few studies set a minimum exposure intensity and/or duration for the opium addiction (e.g. Ghazavi et al., 2013a, b; Hashemipour et al., 2013; Ayatollahi-Mousavi et al., 2016; Dwivedi et al., 2019). Some studies validated recent opium exposure by urine analysis (Nabati et al., 2013; Safarinejad et al., 2013a, b; Salarian et al., 2018). In all these studies, the non-exposed groups may have included people who used opium but did not meet the criteria for an exposed person.

A few studies reported intensity of exposure in nokhods per day (Safarinejad et al., 2013a, b). Others reported duration of addiction (Hashemipour et al., 2013; Safarinejad et al., 2013a, b). Ayatollahi-Mousavi et al. (2016) excluded those with less than 3 years of opium use, while others only included individuals who consumed more than 2 g of opium per day for at least 1 year (e.g. Ghazavi et al., 2013a, b; Hashemipour et al., 2013).

[The Working Group noted that a minimum exposure amount or time may be more important to some end-points than others. A wide range of cumulative exposure is likely between individuals in most studies; however, such individuals have been grouped in the analysis. Insufficient data were presented in most papers to evaluate this potential, but variability in intensity and duration can be seen in at least one study (Naghibalhossaini et al., 2004). Lack of a minimum exposure intensity or duration meant that individuals with a trivial intensity or duration of exposure could have been included in the exposed group. Inclusion of the intensity or duration means that the exposed individuals could be grouped and dose–response relations examined (e.g. Hashemipour et al., 2013). See also Section 1.6.1 for discussion of the relative inaccuracy of recalled grams or nokhods as weight measures of opium (Mohebbi et al., 2019). The Working Group also considered it possible that opium addicts may be exposed to opiates such as methadone when recruited from addiction clinics, but this was not identified in the literature.]

Few studies explicitly stated whether they considered temporality of exposure; Hashemipour et al. (2013) was the exception. Recent exposure was assumed when addicts were studied. [The relevance of recent or past exposure will vary depending on the outcome being assessed.]

Most of the mechanistic studies identified neither the type of opium nor the mode of consumption. Where these were identified, the analyses usually combined the different types and modes as "opium user" (Naghibalhossaini et al., 2004; Abedi-Ardekani et al., 2011; Ayatollahi-Mousavi et al., 2016; Dwivedi et al., 2019). [The Working Group noted that this was

the case even where it might be expected that there would be a difference in the effects from smoking and ingestion, for example, lesions in oral mucosa (Mansour Ghanaei et al., 2013).]

[Overall, the Working Group noted that the mechanistic studies seldom described the exposure data or collection methods in sufficient detail for them to be critically evaluated.]

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