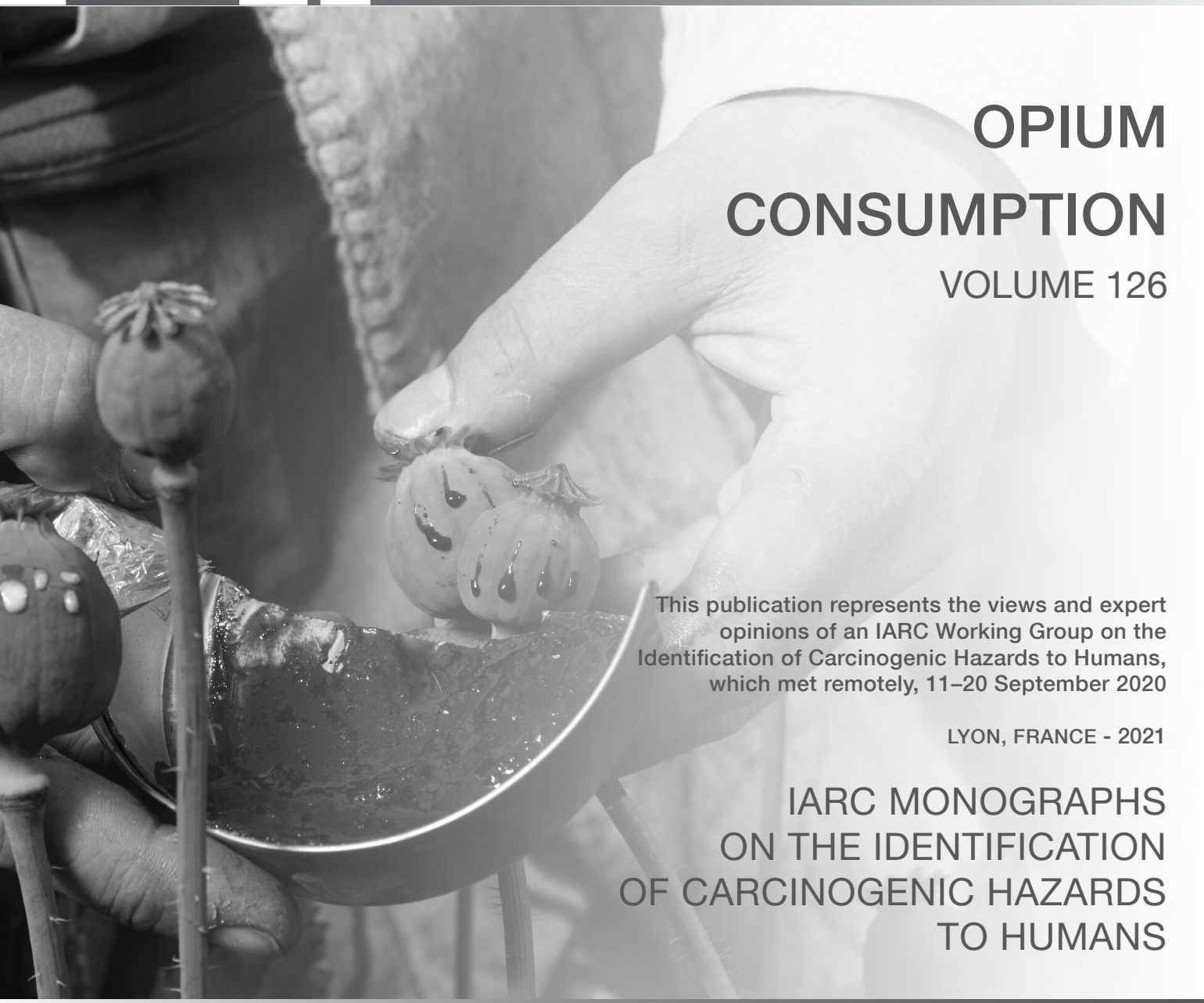
IARC MONOGRAPHS



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IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

International Agency for Research on Cancer

World Health Organization

3. CANCER IN EXPERIMENTAL ANIMALS

3.1 Mouse

See Table 3.1.

3.1.1 Subcutaneous injection

Three groups of 27–35 female CBA mice (age, 20–24 weeks) were exposed by weekly subcutaneous injection to olive oil only (vehicle control group, *n* =27) or *sukhteh* [opium dross] (collected in the Islamic Republic of Iran) at a total dose of 33 mg for 27 weeks, or to opium pyrolysates (pyrolysis of crude opium from India was carried out in the laboratory) at a total dose of 40 mg for 35 weeks. Moribund mice were killed and complete autopsies performed on all mice (Friesen et al., 1985). [The Working Group noted that reporting for this study was limited. The study duration was not reported, but the Working Group inferred that it was "for life", as with the experiment in hamsters reported in the same article. Similarly, survival was not reported, but reduced survival related to toxicity was implied.] The only results reported were "interim results" at 12 months. No tumours were reported in the control group, two mammary carcinomas were reported in mice treated with *sukhteh*, and one unspecified tumour was reported in mice treated with opium pyrolysates. [The Working Group noted that the denominators (effective number of mice) for the interim results were not provided and also that the study was limited by the low number of mice, possible decreased survival, lack of survival and body-weight data, unknown adequacy of the *sukhteh* and opium pyrolysate doses, and limited reporting.]

3.1.2 Skin application

Two groups of 30 female Swiss mice [assumed age, 52 days] were given *sukhteh* [opium dross] or opium pyrolysates at a total dose of 14.4 mg or 28.8 mg in acetone [presumed], respectively, by dorsal skin application three times per week for 50 weeks (Friesen et al., 1985). After 50 weeks, no tumours were found in mice treated with *sukhteh* or opium pyrolysates. [The Working Group noted that the study was limited by the low number of mice, short study duration, lack of an unexposed or vehicle control group, unknown adequacy of the doses of *sukhteh* and opium pyrolysates, lack of survival and body-weight data, and limited reporting.]

3.1.3 Initiation–promotion

In an initiation–promotion study, three groups of 30 female Swiss mice (age, 52 weeks) were given two doses of 1200 μg of *sukhteh* [opium dross], 200 μg of opium pyrolysates (in 0.05 mL of acetone), or 1000 μg of opium pyrolysates (in 0.05 mL of acetone), with an interval of 2 days, by dorsal skin application. Starting 10 days after initiation, these mice were given

Table 3.1 Carcinogenicity studies in experimental animals exposed to opium

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Mouse, CBA (F) 20–24 wk NR [assumed for life] Friesen et al. (1985)	Subcutaneous injection *Sukhteh* [opium dross], NR Olive oil, 0.1 mL Injections given 1×/wk for 27 wk (vehicle control); injections given 1×/wk for 27 wk, totalling 33 mg 27, 27–35 NR	Control, no tumours reported *Sukhteh*, 2 mammary carcinomas (interim results at 12 mo; denominators [effective number of mice] NR)	NA NR	Duration of experiment not explicitly reported, but "for life", as with the study in hamsters in the same article (Friesen et al., 1985), can be inferred. Survival data not reported, but reduced survival possible from reference to toxicity with respect to number of surviving mice. Principal limitations: low number of mice; survival and body-weight data not reported; extent of possible decreased survival unknown; unknown adequacy of the dose; limited reporting.
Full carcinogenicity Mouse, CBA (F) 20–24 wk NR [assumed for life] Friesen et al. (1985)	Subcutaneous injection OP, NR Olive oil, 0.1 mL Injections given 1×/wk for 27 wk (vehicle control); injections given 1×/wk for 35 wk, totalling 40 mg 27, 27–35 NR	Control, no tumours reported OP, 1 unspecified tumour (interim results at 12 mo; denominators [effective number of mice] NR)	NA NR	Duration of experiment not explicitly reported, but "for life", as with the study in hamsters in the same article (Friesen et al., 1985), can be inferred. Survival data not reported, but reduced survival inferred from reference to toxicity with respect to number of surviving mice. Principal limitations: low number of mice; survival and body-weight data not reported; extent of possible decreased survival unknown; unknown adequacy of the dose; limited reporting.

Table 3.1 Carcinogenicity studies in experimental animals exposed to opium (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Mouse, Swiss (F) NR [assumed to be 52 d] 50 wk Friesen et al. (1985)	Dorsal skin application *Sukhteh* [opium dross], NR Acetone [presumed], 0.05 mL 3×/wk for total of 14.4 mg; no unexposed or vehicle controls reported 30 NR	No tumours induced	NA	Principal limitations: lack of control group; low number of mice; survival and body-weight data not reported; only a 1-yr study; unknown adequacy of dose level; limited reporting (some details inferred from initiation–promotion study described below).
Full carcinogenicity Mouse, Swiss (F) NR [assumed to be 52 d] 50 wk Friesen et al. (1985)	Dorsal skin application OP, NR Acetone [presumed], 0.05 mL 3×/wk for total of 28.8 mg; no unexposed or vehicle controls reported 30 NR	No tumours induced	NA	Principal limitations: lack of control group; low number of mice; survival and body-weight data not reported; only a 1-yr study; unknown adequacy of dose level; limited reporting (some details inferred from initiation–promotion study described below).
Initiation–promotion Mouse, Swiss (F) 52 d 51 wk Friesen et al. (1985)	Dorsal skin application *Sukhteh* [opium dross], NR Acetone, 0.05 mL 0 (control) or 2 doses of 1200 µg (2 d apart), followed by application of 1 µg TPA 1×/wk for 50 wk, starting 10 d after initiation 30 (TPA only), 30 NR	Skin papilloma 1/30, 1/30	[NS]	Principal limitations: low number of mice; survival not reported; only a 1-yr study; unknown adequacy of dose. Positive results (skin papilloma, 23/30) with positive control of initiation with 50 µg DMBA.

Table 3.1 Carcinogenicity studies in experimental animals exposed to opium (continued)

Study design **Species, strain (sex)** **Age at start** **Duration** **Reference**	**Route** **Agent tested, purity** **Vehicle** **Dose(s)** **No. of animals at start** **No. of surviving animals**	**Tumour incidence**	**Significance**	**Comments**
Initiation–promotion Mouse, Swiss (F) 52 d 51 wk Friesen et al. (1985)	Dorsal skin application OP, NR Acetone, 0.05 mL 0 (control), 2 doses of 200 µg or 2 doses of 1000 µg (2 d apart), followed by application of 1 µg TPA 1×/wk for 50 wk, starting 10 d after initiation 30 (TPA control), 30, 30 NR	Skin papilloma 1/30, 1/30, 1/30	[NS]	Principal limitations: low number of mice; survival not reported; only a 1-yr study; unknown adequacy of dose. Positive results (skin papilloma, 23/30) with positive control of initiation with 50 µg DMBA.
Full carcinogenicity Hamster, Syrian golden (F) 8 wk Lifetime Friesen et al. (1985)	Intratracheal instillation *Sukhteh* [opium dross], NR Tricaprylin, 0.2 mL 0 (vehicle), 0.880 mg, 1×/wk 10, 10 NR	Vehicle, malignant tumours, 0/10 *Sukhteh*, malignant lymphoma, 2/10; adrenal haemangioendothelioma, 1/10	NA [NS]	No significant decrease in survival. Principal limitations: low number of mice; survival and body-weight data not reported; short lifetimes (average survival of controls, 69 wk); unknown adequacy of dose.
Full carcinogenicity Hamster, Syrian golden (F) 8 wk Lifetime Friesen et al. (1985)	Intratracheal instillation OP, NR Tricaprylin, 0.2 mL 0 (vehicle), 1.659 mg, 1×/wk 10, 10 NR	Vehicle, malignant tumours, 0/10 OP, malignant tumours, 0/10	NA	No significant decrease in survival. Principal limitations: low number of mice; survival and body-weight data not reported; short lifetimes (average survival of controls, 69 wk); unknown adequacy of dose.

d, day; DMBA, 7,12-dimethylbenz[*a*]anthracene; F, female; mo, month; NA, not applicable; NR, not reported; NS, not statistically significant; OP, opium pyrolysates; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; wk, week; yr, year.

12-*O*-tetradecanoylphorbol-13-acetate (TPA) at a dose of 1 µg by dorsal skin application once per week for 50 weeks. A control group of 30 mice was exposed to TPA only (Friesen et al., 1985). Histopathological examination was performed on gross skin tumours. After the 50 weeks of treatment with TPA, no increase in the incidence of skin papilloma was observed in the groups treated with *sukhteh* or opium pyrolysates compared with the controls. [The Working Group noted that the study was limited by the low number of mice, lack of survival data, and unknown adequacy of the *sukhteh* and opium pyrolysate doses.]

3.2 Rat

Initiation–promotion

In an initiation–promotion study, two groups of 15 male Wistar albino rats were given opium by oral administration [presumably by gavage] at a dose of 0 mg/kg body weight (bw) per day (purified water) for 20 (n = 5) or 40 (n = 5) weeks, or 300 mg/kg bw per day [presumably in purified water] for 5 days per week for 16 weeks followed by phenobarbital at a dose of 50 mg/kg bw per day for 5 days per week until the end of the experiment at 20 (n = 5) or 40 (n = 5) weeks (Alzaidi et al., 2018). [It was explicitly stated that a positive control group (diethylnitrosamine-treated) was treated by gavage, and the Working Group inferred the same route of administration for the other groups.] Histopathological examination was performed only on the liver, small intestine, and colon. No carcinogenic changes were found in opium-treated or control rats. [The Working Group noted that the study was limited by the low number of rats, short study duration, unknown adequacy of the opium dose, histopathology limited to the liver, small intestine, and colon, lack of a phenobarbital-only control, and unclear and incomplete reporting (e.g. lack of survival data). This study was deemed to be inadequate for informing the evaluation due to the low number of rats and other limitations, and it was not tabulated or considered further.]

3.3 Hamster

See Table 3.1.

Intratracheal instillation

Three groups of 10 female Syrian golden hamsters (age, 8 weeks) were given vehicle only (0.2 mL of tricaprylin), 0.88 mg of *sukhteh* [opium dross], or 1.659 mg of opium pyrolysates by intratracheal instillation, once per week for life. Moribund hamsters were killed and complete autopsies performed on all hamsters (Friesen et al., 1985). There was no significant decrease in average survival between hamsters treated with opium pyrolysates or *sukhteh* when compared with the vehicle control group. No malignant tumours were found in the control group or in hamsters treated with opium pyrolysates. Two malignant lymphomas and one adrenal haemangioendothelioma were reported in hamsters treated with *sukhteh*. [The Working Group noted that the study was limited by the low number of hamsters, lack of survival and body-weight data, short lifetimes, and unknown adequacy of the *sukhteh* and opium pyrolysate doses.]

3.4 Evidence synthesis for cancer in experimental animals

Opium, *sukhteh*, and opium pyrolysates were tested for carcinogenicity in mice, rats, and hamsters. The three studies available in mice (a study in female CBA mice treated by subcutaneous injection, a study in female Swiss mice treated by skin application, and an initiation–promotion study in female Swiss mice (Friesen et al., 1985) and the available study in Syrian golden hamsters (an intratracheal installation

study; Friesen et al., 1985) had various limitations, including low numbers of animals, lack of survival and body-weight data, unknown adequacy of the treatment doses, and limited reporting. The available study in rats, an initiation–promotion study (Alzaidi et al., 2018), was considered uninformative due to the low number of rats, and other limitations.

References

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Friesen M, O'Neill IK, Malaveille C, Garren L, Hautefeuille A, Cabral JR, et al. (1985). Characterization and identification of 6 mutagens in opium pyrolysates implicated in oesophageal cancer in Iran. *Mutat Res.* 150(1–2):177–91. doi:10.1016/0027-5107(85)90114-9 PMID:4000158