QUINACRINE STERILIZATION: A 2-PAGE EVIDENCE SUMMARY

Why the FDA hold on QS rests on science the FDA itself would now reject

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BOTTOM LINE Quinacrine sterilization (QS) — a non-surgical transcervical pellet procedure delivering 504 mg cumulative quinacrine hydrochloride (QH) — has been used by more than 200,000 women in 54 countries since 1977, with no treatment-related deaths. Quinacrine hydrochloride (QH) is not genotoxic. The two animal studies that found tumors (Cancel 2006, 2010) overdosed every animal to the point of lethal injury — 75–106× above the human QS clinical dose and 25–35× above the maximum tolerated dose (MTD) required by ICH S1C(R2). Under FDA's own current ICH S1B(R1) integrated weight-of-evidence framework (2022), those findings do not add value to the human carcinogenic risk assessment. Three independent lines of evidence — genotoxicity, carcinogenicity bioassay context, and human epidemiology across 47,101 women — converge: human carcinogenic potential at QS clinical exposures is UNLIKELY.

1. QH is not genotoxic

Genotoxicity is whether a chemical damages DNA. The complete picture for QH:

- In vivo (the test that matters): mouse micronucleus assay negative at doses up to the MTD. Neonatal mouse model — specifically optimized to detect DNA-reactive carcinogens — negative even at doses producing lethal systemic toxicity (Cancel 2006).
- In vitro (Clarke 2001 — the study FDA relied on): every positive result was generated at concentrations beyond the ICH S2(R1) cytotoxicity limits, where the guideline specifies results are unreliable. No positive call occurred within the reliable assay window.
- Modern human-cell platform: Chapman et al. (2021, 2024) integrated multi-endpoint TK6 human lymphoblastoid testing classifies QH as a non-genotoxin in vitro at clinically relevant concentrations and a non-carcinogen.

Figure 2. *Clarke et al. (2001) in vitro positive calls vs. ICH S2(R1) cytotoxicity thresholds — every positive arose outside the reliable assay window:*

Assay	ICH S2(R1) limit	Where positives occurred	Verdict
Mouse lymphoma (MLA, L5178Y, −S9)	RTG ≥ 10–20%	Positives only at RTG = 18.5% and 9.5%	**Outside reliable range**
CHO chromosome aberration	MI inhibition ≤ 50–55%	4 of 5 positives at 67–85% MI inhibition; 5th borderline	**Outside reliable range**

2. Cancel 2006 and Cancel 2010 overdosed every animal to produce the tumors

Carcinogenicity bioassays must dose to (but not beyond) the MTD — defined by ICH S1C(R2) as the dose that causes minimal toxicity, not lethal injury. The Cancel studies exceeded the MTD by 25–35-fold.

- At the doses that produced tumors, 31–36% of the rats died from the dosing itself. Every tumor-bearing animal had severe uterine necrosis and chronic inflammation — the toxicologic signature of non-genotoxic, injury-driven carcinogenesis.
- Two independent peer-reviewed re-analyses (Regul. Toxicol. Pharmacol.) confirmed MTD exceedance and an injury–inflammation–regeneration mode of action. The same pathology is seen with any caustic agent at toxic doses.
- At the MTD-appropriate 10 mg/kg dose (≈3× clinical) — Cancel observed no carcinogenic effect.

Figure 3. *QH dose levels across animal and human exposure groups. Red = tumor-associated (MTD-exceeded); green = no effect:*

Group	Dose (mg/kg)	Tumors?	× human QS dose
Human QS clinical dose (U.S. 77 kg adult)	3.3	—	**1×**
MTD-appropriate rat dose (ICH S1C(R2))	~10	**No**	~3×
Cancel 2010 — 10/10 group	10	**No tumors**	3×
Cancel 2010 — 70/250 group	250 (paired)	**Tumors + 31% mortality + severe necrosis**	**75×**
Cancel 2010 — 70/350 group	350 (paired)	**Tumors + 36% mortality + severe necrosis**	**106×**

3. Human evidence: 47,101 women. No cancer signal.

- 47,101 QS-treated women in 42 cohorts (107,548 woman-years) — no cancer signal in any cohort (Mumford & Collins 2023).
- Pooled HR across 8 controlled cohorts (197,040 woman-years): HR 1.20, 95% CI 0.93–1.55 — not statistically significant; CI includes 1.0.

- Higher-dose comparators — three independent populations, no cancer signal in any: (1) oral QH for cutaneous lupus/dermatology (~180,000 cumulative U.S. women, 100 mg/day for months–years, Cmax 3× above QS; Wallace 1989, Mittal 2017); (2) giardia treatment courses (~10 million courses, 1945–1995, 2,100 mg/course; Ehsanian 2011); (3) WWII antimalarial prophylaxis (~3M men, 100–140 mg/day, up to 4 years). Combined: ~13.2 million unique patient-courses, ~5.1 × 10^{11} mg-years cumulative systemic exposure — ~378 million-fold the Cancel rat bioassay.

Table 3 (from paper). *Pooled cancer-incidence analysis, 8 controlled QS cohorts (Mumford & Collins 2023):*

Study (country)	QS women	Controls	Cancer QS / ctrl	HR	Woman-yrs
Dabancens 1995, Chile	1,000	1,000	2.6 / 1.6	1.62	3,668
Tice 1999, Chile	785	785	17 / 12	1.42	7,852
Sokal 2000, Chile	1,492	1,492	25 / 22	1.14	13,444
Zipper 2004, Chile	3,285	12,355	8 / 22	1.37	42,705
Sokal 2008, Vietnam	2,735	1,623	23 / 13	1.05	28,697
Sokal 2010 CC, Vietnam	1,029	2,999	12 / 33	1.06	32,224
Sokal 2010 cohort, Chile	1,492	1,492	12 / 17	0.71	23,894
Jones 2017, Vietnam	10,503	9,203	12 / 8	1.31	173,146
POOLED — 8 cohorts	**22,321**	**30,949**	**111.6 / 128.5**	**1.20 (0.93–1.55) NS**	**197,040**

Table 4 (from paper). *Integrated ICH S1B(R1) weight-of-evidence summary:*

Evidence domain (ICH S1B(R1))	Key finding	Weight
Target biology / pharmacology	*Tumor-suppressive NF-κB/p53 activity; no class signal; species-specific QS mechanism*	**HIGH — against risk**
Genotoxicity (ICH S2(R1))	*In vitro positives are cytotoxicity artifacts; in vivo negative; TK6 platform: QH non-genotoxin, non-carcinogen (Chapman 2021, 2024)*	**MODERATE — against**
Carcinogenicity bioassay	*Rat tumors only at 75–106× clinical dose (25–35× MTD); 31–36% excess mortality; 10 mg/kg group: no tumors*	**LOW — does not add value**
Human epidemiology	*47,101 women / 107,548 woman-years; no cancer signal; pooled HR 1.20 (95% CI 0.93–1.55), NS*	**HIGH — against risk**
INTEGRATED CONCLUSION	**Human carcinogenic potential of QH at QS clinical exposures: UNLIKELY (ICH S1B(R1) Pathway 2)**	**UNLIKELY**

4. Why the FDA hold rests on science FDA itself would now reject

The 2007 clinical hold on IND 074802 was imposed before ICH S1B(R1) — the 2022 Addendum formalizing how rodent findings should be weighed within the totality of evidence. Applied under that framework, the Cancel bioassay falls into **Pathway 2**: the 2-year rat study ***does not add value*** to the human risk assessment and cannot justify a clinical hold.

The 2015 dispute-appeal denial characterized a non-significant HR 1.4 (95% CI 0.6–3.4) as evidence of harm because the cohort "failed to exclude a two-fold increase" — a logical inversion: a CI spanning 1.0 is absence of evidence of risk, not evidence of risk.

5. The ask

Re-engage FDA review of IND 074802 under the agency's own current framework via a **Type C meeting with CDER** if required. Proposed Phase III: 400 completers across 36 investigators, two 252 mg transcervical insertions, 24-month follow-up with pre-specified cancer safety monitoring board. Non-pivotal study; Phase III is the confirmatory study supporting a 505(b)(2) NDA.

The science FDA relied on in 2007 is science FDA's own 2022 framework now treats as unreliable. The women dying in the meantime are real, and the meter does not stop while the file sits closed.

THE HUMAN COST Using two independent methods anchored to Cleland et al. (Lancet 2012), global QS availability could plausibly avert approximately 11,000–19,000 maternal deaths annually. Net-of-cancer-risk: the pooled HR 1.20 (95% CI 0.93–1.55) is not statistically significant; worst-plausible-case upper CI translates to ≤5–8 cancer deaths per 100,000 QS users over 10 years — an order of magnitude below the maternal-mortality benefit.