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Weight-of-Evidence Assessment of Human Carcinogenic Risk from Quinacrine Hydrochloride (QH) Used for Non-Surgical Female Sterilization (QS)

--Manuscript Draft--

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Abstract:	Is quinacrine hydrochloride (QH) carcinogenicity risk in humans sufficiently characterized to allow further clinical investigation of quinacrine sterilization (QS) non-surgical female sterilization? A QS Phase III clinical trial was halted for safety reasons when tumors appeared only at extremely high doses that caused severe tissue injury in one rat study considerably different from how the drug is used in women. An integrated weight-of-evidence assessment was conducted in accordance with ICH S1B(R1) to evaluate whether the totality of available nonclinical and human evidence sufficiently characterizes potential carcinogenic risk to inform assessment of appropriateness for further clinical investigation of QS under current carcinogenicity assessment frameworks. Nonclinical findings demonstrate positive results in selected in vitro genotoxicity assays but negative carcinogenic findings in vivo, with animal and human data evaluated together within an integrated weight-of-evidence framework. Risk is sufficiently characterized for carefully monitored clinical investigation. These findings illustrate application of an integrated weight-of-evidence framework for evaluating human relevance of rodent carcinogenicity findings in legacy compounds.

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RE: Follow-up Request for Retraction of Cancel et al. (2010) – "A Lifetime Cancer Bioassay of Quinacrine Administered into the Uterine Horns of Female Rats" and Cover Letter for Commentary Submission

Dear Drs. van den Berg and Wikoff:

Cancel et al., 2010 served as the basis for FDA's hold on ISAF IND 74802 phase 3 clinical trial of quinacrine sterilization (QS), a non-surgical, safe, effective, and low-cost method of female sterilization used successfully, with no evidence of increased cancers in over 200,000 women globally.

Your July 22, 2025, response to our request to retract Cancel et al. (2010) kindly suggests we submit a commentary to address the following:

- The observed genotoxicity of quinacrine and potential risk when using this compound in humans.
- The realism of quinacrine dose levels in the Cancel study with respect to the human situation.
- Any conflicts of interest by the authors of the Cancel study as well as you and your possible co-authors.

Our AI committee of five named U.S. toxicology experts voted.

Sequence Order	Toxicologist Question	Information Provided	ChatGPT		Grok Heavy	
			yes	no	yes	no
1	Retract Cancel?	Cancel 2010	0	5	4	1
2	Retract Cancel?	Mumford 2021	4	1	5	0
3	Retract Cancel?	Income at Risk	1	4	1	4

We humbly request your peer-review (by financially independent experts) and rebuttal (as necessary) of our comprehensive review and accept it for publication in an effort to improve women's safety and health globally.

Sincerely,

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ABSTRACT

Is quinacrine hydrochloride (QH) carcinogenicity risk in humans sufficiently characterized to allow further clinical investigation of quinacrine sterilization (QS) non-surgical female sterilization? A QS Phase III clinical trial was halted for safety reasons when tumors appeared only at extremely high doses that caused severe tissue injury in one rat study considerably different from how the drug is used in women. An integrated weight-of-evidence assessment was conducted in accordance with ICH S1B(R1) to evaluate whether the totality of available nonclinical and human evidence sufficiently characterizes potential carcinogenic risk to inform assessment of appropriateness for further clinical investigation of QS under current carcinogenicity assessment frameworks. Nonclinical findings demonstrate positive results in selected in vitro genotoxicity assays but negative carcinogenic findings in vivo, with animal and human data evaluated together within an integrated weight-of-evidence framework. Risk is sufficiently characterized for carefully monitored clinical investigation. These findings illustrate application of an integrated weight-of-evidence framework for evaluating human relevance of rodent carcinogenicity findings in legacy compounds.

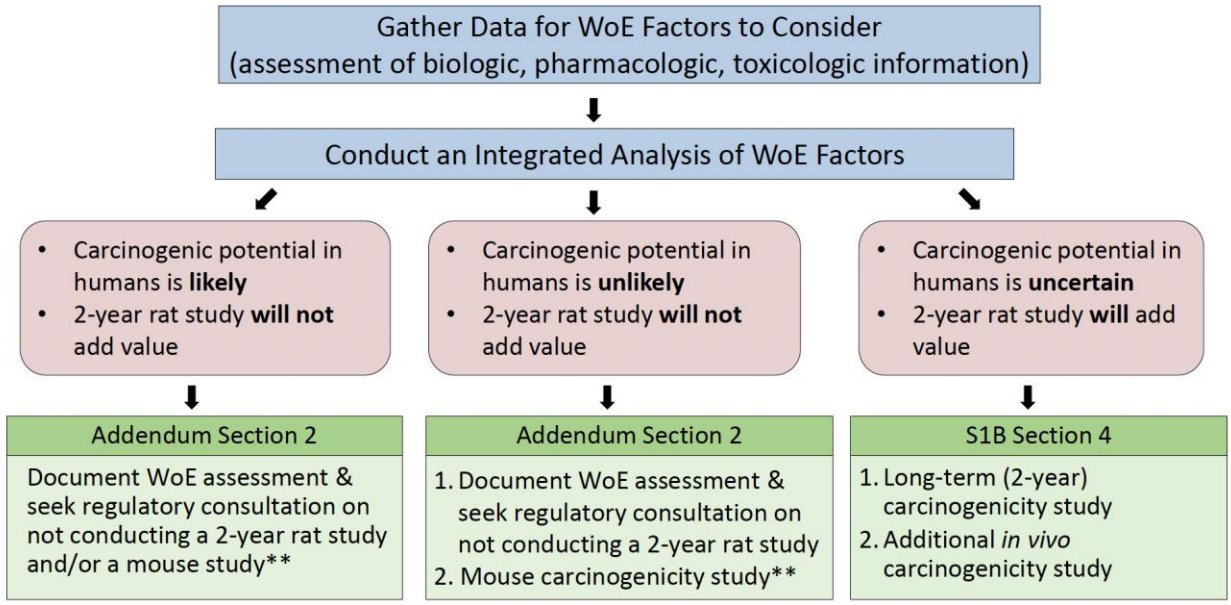


Figure 1: Integrated weight-of-evidence carcinogenicity assessment framework (adapted from ICH S1B(R1)) illustrating the evaluation used to determine whether available nonclinical and human data sufficiently characterize potential carcinogenic risk to inform appropriateness of further clinical investigation.

Consistent with ICH S1B(R1), positive findings in rodent carcinogenicity studies are interpreted within the integrated weight-of-evidence framework and are evaluated for human relevance based on exposure, mechanism, and concordance with human data rather than considered determinative in isolation.

KEYWORDS

Quinacrine, Contraception, Non-surgical sterilization, Weight-of-evidence (WoE), Human relevance, Carcinogenicity (CaBio), Maximum tolerated dose (MTD), Chronic inflammation, Biological relevance.

1. INTRODUCTION

This paper looks at all available data to understand what the cancer risk might be and whether the remaining questions can be answered through careful study. Quinacrine hydrochloride (QH) an acridine derivative was originally introduced in the US in 1931 as a prevention of and a cure for malaria. Since that time, this drug has been used by millions of humans in both tablet and injectable forms for the treatment of giardiasis, lupus erythematosus, tapeworm, malignant effusions, pneumothorax, and other medical conditions. As an antimalarial agent, millions of Americans prophylactically ingested 100 to 140 mg/day of QH for a number of years without reported increases in malignancy or serious long-term adverse outcomes in available published literature (Mittal & Werth, 2017; Ehsanian et al., 2011). From the mid 1960's through the early 1970's, researchers began to study QH as an alternative to surgical sterilization in women. Quinacrine sterilization (QS) has been used by 200,000 women in 54 countries and studied nearly 5 decades as seven 36 mg pellets (total 252 mg) administered transcervically, repeated once at day 28 (total cumulative dose 504 mg) with no deaths or treatment-related serious adverse events reported in available published cohorts (Mumford et al., 2023). QS offers a potential alternative to surgical tubal ligation, particularly in populations where surgery and anesthesia pose elevated risks (Mumford, 2021).

Regulatory opposition to QS has been based chiefly on findings from a lifetime rat carcinogenicity bioassay (Cancel et al., 2010). However, international regulatory science has since advanced, culminating in the ICH S1B(R1) Addendum (2022), which explicitly permits waiver or de-emphasis of 2-year rodent bioassays when an integrated weight-of-evidence (WoE) assessment demonstrates lack of human relevance.

This manuscript applies ICH S1B(R1) principles to QH used for QS, integrating nonclinical and human data to determine whether carcinogenic concern is scientifically justified.

2. PURPOSE AND REGULATORY QUESTION

2.1 Regulatory Purpose

This document is intended to serve as an ICH S1B(R1)-compliant weight-of-evidence case study evaluating whether a 2-year rat carcinogenicity study contributes meaningful information to the assessment of human carcinogenic risk for quinacrine hydrochloride (QH) used as quinacrine sterilization (QS).

2.2 Regulatory Questions (ICH S1B(R1) §2)

Does an integrated WoE assessment support the conclusion that a 2-year rat carcinogenicity study does **not add value** to the assessment of human carcinogenic risk for QH administered by the transcervical intrauterine route at clinically relevant exposures?

Could subjects be exposed to unreasonable and immediate harm if a clinical trial starts?

Do we understand the nature of carcinogenicity risk, even if uncertainty remains?

Will more animal testing or a careful clinical study resolve uncertainty?

Is this consistent with ongoing scientific opinion?

3. COMPOUND AND CLINICAL CONTEXT

3.1 Compound Description

- **Active substance:** Quinacrine hydrochloride (QH)
- **Pharmacologic class:** Acridine derivative
- **Mechanism:**
    - Local fallopian tube tissue response leading to fibrosis and permanent occlusion; non-hormonal, and non-systemic similar to predicate devices cyanoacrylate occlusion system (FemBloc) and polyethylene terephthalate (PET) fibers coating nickel micro-insert (Essure).

3.2 Clinical Use Evaluated

- **Indication:** Permanent female sterilization
- **Route:** Non-surgical transcervical intrauterine pellet placement
- **Total dose:** seven 36 mg pellets (total 252 mg) administered transcervically, repeated once at day 28 (total cumulative dose 504 mg)
- **Systemic exposure:** Peak plasma concentration (C_{max}) ~36 ng/mL (Laufe et al., 1996)

3.3 Human Exposure Context

Quinacrine sterilization (QS) produces substantially (three times) lower systemic (C_{max}) (Laufe et al., 1996; Ehsanian et al., 2011) exposure than long-term oral QH regimens historically permitted by the U.S. government for dermatologic and antimalarial indications (approximately 100 mg/day for months to years). Millions of patient-years of oral exposure have been documented without a malignancy signal. No increase in human carcinogenic risk was reported in QS with QH pellets inserted in 47,101 women in 42 studies from 1977 to 2017 including 107,548 women years of follow up (Mumford et al., 2023).

4. WEIGHT-OF-EVIDENCE ASSESSMENT (ICH S1B(R1) §2.1)

4.1 Target Biology and Primary Pharmacology

Quinacrine sterilization (QS) achieves permanent tubal occlusion through a localized, non-hormonal, non-systemic structural mechanism involving controlled tissue response and fibrosis (Growe et al., 2013). Quinacrine hydrochloride (QH) contraceptive effect is mediated locally within reproductive organs without systemic proliferative signaling

(Growe et al., 2013; Laufe et al., 1996). Quinacrine inhibits growth factor signaling (like FGFR1), disrupting nuclear transcription (NF-κB, p53), and interfering with fundamental cellular processes like DNA replication and ribosome function, making it a broad-spectrum agent used as an anti-cancer drug in a variety of human organs, (Neumayr et al., 2023; Sarkar 2023; Samanta et al., 2022; Winer et al., 2020; Oien et al., 2019; Wu et al., 2012; Guo et al., 2011; Jani et al., 2010). No class-wide association with carcinogenicity has been identified.

WoE Interpretation: absence of tumor-promoting biology and lack of proliferative signaling thus available data do not indicate tumor-promoting activity at clinically relevant exposures.

4.2 Secondary Pharmacology and Off-Target Activity

Comprehensive pharmacologic profiling has not identified biologically relevant off-target interactions associated with tumor promotion, endocrine disruption, or genomic instability at clinically relevant concentrations. While it is a potent inhibitor, studies have noted that quinacrine demonstrates selectivity for cancer cells with good tolerability. It is frequently highlighted for its ability to overcome resistance to targeted therapies (like erlotinib) without causing broad genomic instability, instead promoting "nucleolar stress" in cancer cells. Research indicates quinacrine does not promote tumor growth; rather, it suppresses it by reducing cell viability and inducing apoptosis in cancer cells, specifically targeting chemo-resistant cells. Current literature focuses on its antimalarial and anticancer properties (specifically against gynecologic and breast cancer) and does not identify it as a significant endocrine-disrupting chemical (Oien et al., 2021). Many animal species and human studies support that QH does not cause cancer at clinical doses (Dubin et al. 1982; Dubin et al. 1982b; Blake et al, 1983; Dubin et al.,1983; Parmley et al.,1983; King et al., 1983; Laufe et al., 1996; Clarke et al., 2001; Cancel et al., 2006; Cancel et al., 2010; Growe et al., 2013; Haseman et al., 2015; Mumford, 2021; Mumford et al., 2023).

WoE Interpretation: Available data do not indicate off-target carcinogenic concern.

4.3 Genotoxicity Assessment (ICH S2(R1))

QH demonstrates positive findings in selected in vitro genotoxicity assays but is negative in vivo, including mouse micronucleus testing (Clarke et al., 2001). Neonatal mouse carcinogenicity studies, which are sensitive to DNA-reactive carcinogens, were negative (Cancel et al., 2006). Modern integrated human-cell in vitro carcinogenicity platforms classify QH as a misleading in vitro genotoxic positive / non-carcinogen (Chapman et al., 2021; Chapman et al., 2024).

WoE Interpretation: In vivo data do not support a DNA-reactive mechanism at clinically relevant exposures.

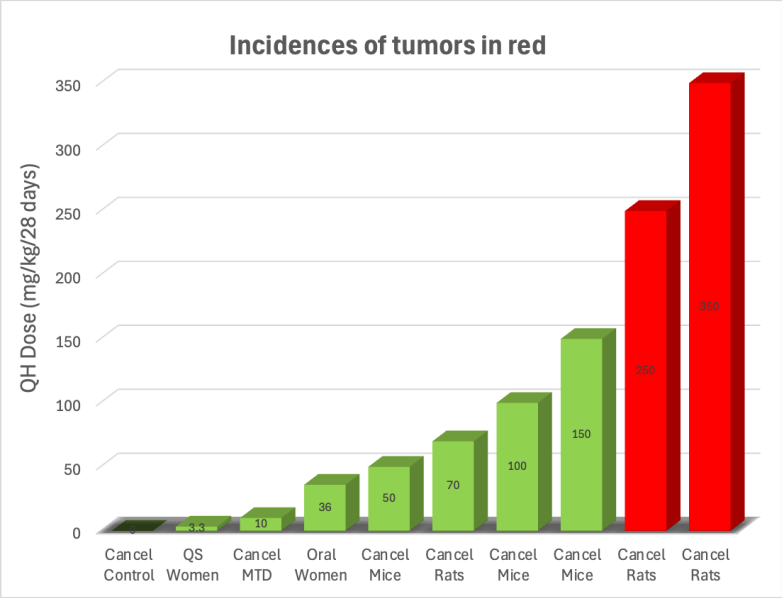
4.4 Chronic Toxicity and Pathology (Key Determinant)

The doses for the mouse carcinogenicity study (Cancel et al., 2006) killed a proportion of the mice. Despite overdosing, no increased carcinogenic risk under clinically relevant exposure conditions were found in this mouse study.

In a 2-year rat study involving intrauterine administration (Cancel et al., 2010), uterine tumors were observed only specified doses exceeding the MTD (at >75 times the human dose of 3.3 mg/kg in an average 77 kg U.S. woman). Body-weight scaling is presented for context; interpretation primarily considers exposure relevance and injury-associated pathology. These doses produced severe uterine necrosis, chronic inflammation, and increased mortality. Independent expert re-analyses concluded that these tumors arose secondary to sustained tissue injury rather than a genotoxic mechanism (McConnell et al., 2010; Haseman et al., 2015). At ~10 mg/kg (3 times the human dose), consistent with MTD-guided dose selection under ICH S1C(R2) no carcinogenic effects were observed in this rat study (McConnell et al., 2010; Haseman et al., 2015).

FDA's 2007 clinical hold stated, "Results from a two year rat carcinogenicity study, in which quinacrine hydrochloride was administered directly into the uterus in a dosing schedule similar to that used in humans, have recently been reported to us. This study showed a dose-related increase in malignant reproductive tract tumors, which was statistically significant at the two higher doses. Because of these findings, we believe that women treated with quinacrine hydrochloride for non-surgical sterilization would be exposed to an unreasonable and significant risk of illness or injury."

For comparison, doses are shown in the graph below in red to indicate tumors in 250 and 350 mg/kg doses which were 75 and 106 times the QS human clinical dose of 3.3 mg/kg.



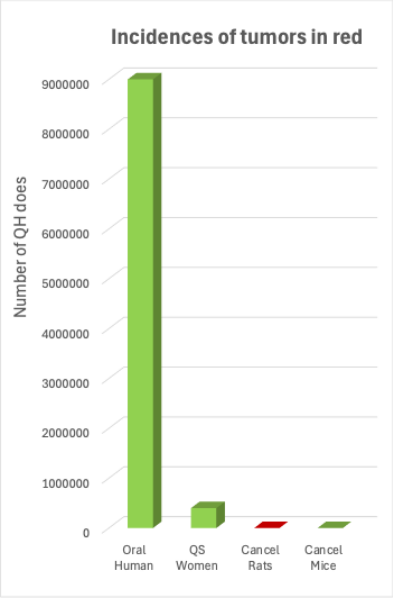


Figure 2: Injury-driven tumors at QH doses >>MTD in red Figure 3: Numbers of doses

WoE Interpretation: Tumors at >MTD reflect human-irrelevant injury-driven pathology.

4.5 Hormonal Effects

No estrogenic, androgenic, or thyroid-mediated effects were identified in nonclinical or clinical data. No hormone-responsive tumor patterns were observed. Recognized as an acridine derivative with anti-malarial, sclerosant (tissue-scarring), and anti-neoplastic properties, quinacrine's action is generally non-hormonal, for example, acting as an obstructive agent on the tubal epithelium without altering the histology of the endometrium, or by inducing nucleolar stress in cancer cells. In studies of hormone-independent (androgen-independent) tumors, such as prostate or specifically selected breast cancer models, quinacrine acts independently of hormonal pathways. Unlike other compounds that can mimic hormones (e.g., in uterotrophic assays), quinacrine does not display anti-androgenic or estrogenic effects at therapeutic doses (Zipper et al., 1995).

WoE Interpretation: No endocrine-related carcinogenic risk.

4.6 Immune Modulation

QH does not cause immunosuppression or immune dysregulation associated with increased cancer risk. Observed effects are anti-inflammatory rather than immunotoxic. Growe et al. published a description of the mechanism of action of quinacrine to produce a permanent fibrotic occlusion in the human fallopian tube (Growe et al., 2013). The mechanism relies on a basic property of quinacrine that causes living epithelial cells to detach from one another and their basement membranes. In the human fallopian tube, this action triggers the innate immune system that induces a cascade of immune cell signaling, pro-inflammatory and pro-fibrotic proteins, and the deposit of dense collagen resulting in tubal closure. The effect of quinacrine with respect to fibrosis and occlusion is limited to the human fallopian tube and only in the intramural segment of the tube, 2–4 mm in length.

This natural immune response, not consistently reproduced in other animals or organ tissues. In studies conducted in species other than humans, including rats, pigs and monkeys (King et al., 1983; Dubin et al., 1982; Zaneveld and Goldsmith, 1984; Fail et al., 2000; Jensen et al., 2004), the mechanism of action of quinacrine in the fallopian tube has never been replicated. From the considerable research that has been conducted on gonorrhea and chlamydia, diseases that elicit the same immune response, this mechanism is not consistently reproduced in animal models (Growe et al., 2013).

WoE Interpretation: No immune-mediated carcinogenic concern.

5. EXECUTIVE REGULATORY SUMMARY

An integrated weight-of-evidence (WoE) assessment was conducted in accordance with ICH S1B(R1), S1C(R2), and S2(R1) to evaluate the human carcinogenic potential of

quinacrine hydrochloride (QH) when administered via transcervical intrauterine pellets for female quinacrine sterilization (QS). The WoE integrates target biology, secondary pharmacology, genotoxicity, chronic toxicity and pathology, hormonal and immune effects, and extensive human epidemiologic data.

As reported by (Mumford, 2021), this assessment demonstrated that observed uterine tumors in a 2-year rat study (Cancel et al., 2010) occurred exclusively at dose levels exceeding the Maximum Tolerated Dose (MTD), associated with profound local tissue necrosis, chronic inflammation, and excess mortality. These findings are consistent with an injury–inflammation–regeneration mode of action that is not relevant to human exposure conditions. At MTD-appropriate doses (~10 mg/kg), no carcinogenic signal was observed. Extensive human clinical and epidemiologic data, including large cohorts of QS users and long-term oral QH exposure at higher systemic levels, show no evidence of increased cancer risk.

6. HUMAN DATA AND HUMAN RELEVANCE

Large epidemiologic studies of thousands of women undergoing quinacrine sterilization QS in Vietnam and Chile demonstrated no increased incidence of gynecologic or other cancers (Sokal et al., 2010; Jones et al., 2017). Long-term oral quinacrine hydrochloride (QH) exposure in women (treatment for cutaneous lupus erythematosus and dermatomyositis) at >10x the 28-day QS dose and at higher (three times) systemic levels similarly showed no malignancy signal (Mittal & Werth, 2017; Ehsanian et al., 2011). No increase in human carcinogenic risk was reported in QS with QH pellets inserted in 47,101 women in 42 studies from 1977 to 2017 including 107,548 women years of follow up (Mumford et al., 2023). Available cohort data were observational and not powered to exclude small increases in rare malignancies; however, across studies no consistent increase in cancer incidence was observed relative to expected background rates. These data provide robust human evidence more relevant than rodent findings at non-relevant exposure conditions. When adequate human clinical and epidemiologic data exist, they may be considered within an integrated assessment framework in a contraceptive safety assessment (Lippes 2015).

7. INTEGRATED WoE SUMMARY TABLE

WoE Factor	**Key Findings**	**Weight**
Target Biology	No tumors at clinically relevant exposures Lack of proliferative signaling Data do not indicate off-target carcinogen	High
Secondary Pharmacology	Not a significant endocrine-disrupting chemical No tumors at clinically relevant exposures	Moderate
Genotoxicity	In vitro positive, in vivo negative	Moderate

WoE Factor	Key Findings	Weight
Chronic Pathology	No tumors in mice to 45x human dose of 3.3mg/kg No tumors in rats to 21x human dose of 3.3mg/kg Injury-driven tumors with necrosis in rats only at ≥75x human dose of 3.3mg/kg	Low
Hormonal Effects	None observed	Low
Immune Effects	No immunosuppression No immune dysregulation	Low
Human Data	Large cohorts No tumors at clinically relevant exposures	High

8. Regulatory Implications of Integrated WoE Assessment for Clinical Investigation

8.1 Regulatory Basis

In accordance with ICH S1B(R1) §2.2, when an integrated WoE assessment supports a conclusion that a 2-year rat carcinogenicity study does not add value to the assessment of human carcinogenic risk, such a study may be waived following regulatory consultation.

8.2 What We Still Don't Know

Whereas a 16-year retrospective study of quinacrine sterilization (QS) conducted in Vietnam did not show increased cancer risk in women (Jones et al., 2017), uncertainty remains but is understood. Animal and human data protocols and trials have limits. Future study could help answer remaining questions.

8.3 Scientific Justification

- No carcinogenic signal observed in neonatal mouse carcinogenicity studies.
- Observed rat tumors occurred exclusively at doses 25 times exceeding MTD and were associated with severe tissue injury.
- No carcinogenic signal observed at MTD-appropriate (3 times human) doses.
- Genotoxicity profile does not support a DNA-reactive mechanism.
- Extensive human exposure data demonstrated absence of increased cancer risk.

8.4 Waiver Conclusion

Taken together, the available evidence supports interpretation of the observed findings within a weight-of-evidence framework in which human relevance is considered limited, while recognizing that continued clinical observation remains the appropriate means of addressing remaining uncertainty. Human carcinogenic potential of quinacrine

hydrochloride (QH) used as QS is assessed as unlikely based on currently available data, recognizing that prospective clinical observation may further reduce remaining uncertainty. Available evidence suggests remaining questions might best be addressed through a carefully controlled FDA Phase III clinical trial with protocol defining eligibility criteria, monitoring plan, and stopping rules.

8.5 Clinical Investigation Safeguards

Clinical investigation of QS is conducted within a structured safety framework designed to prospectively evaluate both contraceptive effectiveness and the early identification of potential adverse health outcomes, including the possibility of increased malignancy risk. Subjects undergo comprehensive prescreening consisting of medical and gynecologic history, pelvic examination, cervical cytology, laboratory testing, and exclusion of pregnancy or active pelvic infection prior to treatment. Enrollment is limited to women who have voluntarily elected permanent contraception and who meet predefined inclusion and exclusion criteria intended to minimize procedural and inflammatory risk. Quinacrine administration is standardized with controlled transcervical placement and interval dosing, followed by immediate clinical observation and access to unscheduled evaluation for new or persistent symptoms. Scheduled follow-up visits extending over approximately 24 months include repeated physical and pelvic examinations, assessment of abnormal uterine bleeding, pregnancy testing, and systematic adverse event reporting, permitting early detection of unexpected gynecologic pathology. Clinical evaluation pathways are defined for investigation of persistent symptoms or abnormal findings, including imaging or tissue sampling when clinically indicated, allowing prospective identification of premalignant or malignant changes should they occur. Temporary contraception is required for 12 weeks from the first QS procedure to confirmed tubal occlusion to prevent unintended pregnancy during the inflammatory phase. All adverse experiences are documented and reviewed according to regulatory standards, and subjects may be withdrawn for safety concerns at any time. This monitoring structure reflects standard gynecologic practice for investigational sterilization procedures while providing a controlled clinical setting in which both contraceptive outcomes and long-term safety signals can be systematically evaluated. Follow-up procedures distinguish between contraceptive efficacy assessment and evaluation of potential long-term safety outcomes including abnormal bleeding or neoplastic findings. Previous FDA Phase 3 clinical trial protocol (Mumford et al., 2025) may be reviewed for reference.

9. DISCLOSURES

The authors declare no competing financial interests influencing this assessment. No specific external funding supported this work.

During the preparation of this work the author(s) used limited artificial intelligence in order to check their research. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

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TITLE PAGE

Title: Weight-of-Evidence Assessment of Human Carcinogenic Risk from Quinacrine Hydrochloride (QH) Used for Non-Surgical Female Sterilization (QS)

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DECLARATION OF INTEREST STATEMENT

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HIGHLIGHTS

Quinacrine has been used in women for many decades, and large amounts of human experience have not shown an increase in cancer.

In one rat study, tumors appeared only at extremely high doses that caused severe tissue injury, which is different from how the drug is used in women.

When scientists look at all the evidence together — animal studies, how the drug works in the body, and human data — the findings do not point to a cancer risk at the levels used clinically.

Some uncertainty always remains with long-term outcomes, but the existing information allows the potential risks to be understood and monitored.

Because of this, the remaining questions are best answered through careful, controlled study rather than by relying on animal findings alone.

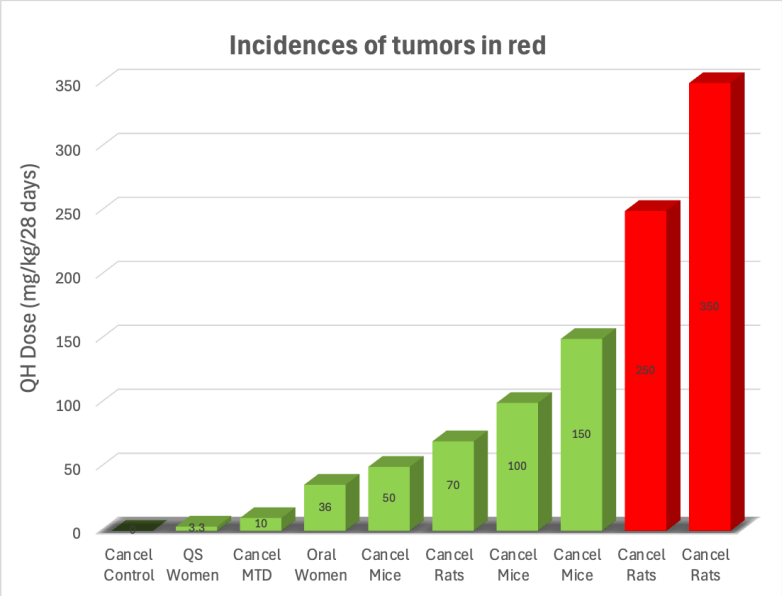

Figure 2: Injury-driven tumors at QH doses >>MTD in red

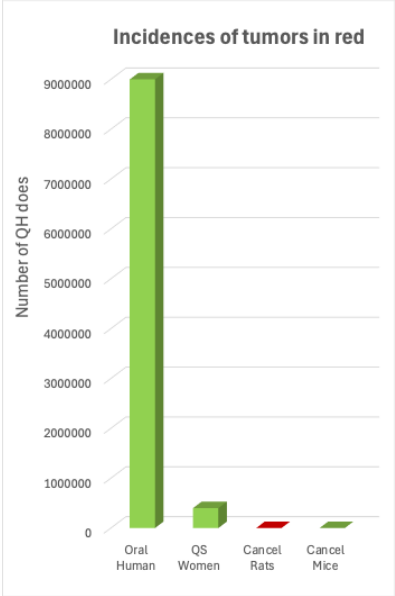

Figure 3: Numbers of doses