

Clomiphene and Its Salts

Clomiphene and its salts are widely prescribed as pharmaceutical agents to treat infertility and induce ovulation in women, and to treat oligospermia (low sperm count) in men. Clomiphene is a selective estrogen receptor modulator.

Clomiphene and its salts passed the human data screen, underwent a preliminary toxicological evaluation, and are being brought to the Carcinogen Identification Committee for consultation. This is a compilation of the relevant studies identified during the preliminary toxicological evaluation.

Epidemiological data

- Cohort Studies
 - Historical prospective cohort study of women treated for infertility in Sweden, 1961-1976: Orgéas *et al.* (2009)
 - *Increased incidence of breast cancer associated with clomiphene*
 - Population-based historical cohort study of women in the Jerusalem Perinatal Study who gave birth in 1974-1976: Calderon-Margalit *et al.* (2009)
 - *Increased risk of uterine cancer, malignant melanoma, and cancer at any site associated with clomiphene*
 - Historical cohort study of women assessed and treated for infertility and infertility-associated disorders in Sweden, 1961-1975: Sanner *et al.* (2009)
 - *Increased risk of borderline ovarian tumors (a subset of epithelial ovarian tumors) associated with clomiphene treatment for ovulatory dysfunction*
 - Historical cohort study of women evaluated for infertility treatment in London, 1963-1999: dos Santos Silva *et al.* (2009)
 - *Increased risk of uterine cancer associated with clomiphene*
 - Historical cohort study of women with infertility problems referred to Danish fertility clinics, 1963-1998: Hannibal *et al.* (2008)
 - *Increased risk of thyroid cancer associated with clomiphene*
 - Retrospective cohort study of U.S. women evaluated for infertility, 1965–1988: Althuis *et al.* (2005)
 - *Increased risk of uterine cancer associated with clomiphene*
- Case-cohort study
 - Ovarian cancer cases in a cohort of women evaluated for infertility in Seattle, 1974-1985: Rossing *et al.* (1994)
 - *Increased risk of ovarian cancer associated with clomiphene*

- Case-control study
 - Population-based study of ovarian cancer in U.S. women: Rossing *et al.* (2004)
 - *No increased risk of ovarian cancer associated with clomiphene*
- Meta-analyses of case-control studies of ovarian cancer
 - Invasive epithelial ovarian cancer: Whittemore *et al.* (1992)
 - *Increased risk associated with use of fertility drugs*
 - Epithelial ovarian tumors of low malignant potential: Harris *et al.* (1992)
 - *Increased risk associated with use of fertility drugs*
- Case Reports
 - Ovarian cancer in users of fertility drugs: Spirtas *et al.* (1993)
 - Ovarian cancer in user of clomiphene: IARC (1979, p. 558)
 - Breast cancer in users of clomiphene: IARC (1979, p. 558)
 - Testicular cancer in users of clomiphene: IARC (1979, p. 558); IARC (1987)
 - Hepatoblastoma in female infant exposed to clomiphene *in utero*: IARC (1987)
 - Liver adenoma in user of clomiphene: IARC (1987)

Animal carcinogenicity data

- Neonatal rat subcutaneous injection study
 - Female Sprague-Dawley rats (single s.c. injection on day 1 of life, observed for 100 days): Clark and McCormack (1977)
 - *Occurrence of hilus-cell tumors of ovary and tumors of uterus*

Other relevant data

- Genotoxicity
 - Rat *in vivo* bone marrow micronuclei assay (*positive*): Duran *et al.* (2006)
 - Review: IARC (1987)
 - Mouse *in vivo* bone marrow micronuclei and chromosomal aberration assays (*negative*)
 - Review: Van Gompel *et al.* (2005, p. 451, 453)
 - *Salmonella* reverse mutation assay (*positive*)
 - *In vitro* chromosome aberration or micronucleus assays (*positive and negative*)
 - GreenScreen (yeast) assay for genotoxicity (*positive*)

- Endocrine system effects
 - Estrogenic and anti-estrogenic activity: IARC (1979)
- Structure activity considerations
 - Structurally similar to another selective estrogen receptor modulator, tamoxifen, which is a Proposition 65 and IARC Group 1 carcinogen.

Reviews

- IARC (1979; 1987)

References¹

Althuis MD, Moghissi KS, Westhoff CL, Scoccia B, Lamb EJ, Lubin JH, Brinton LA (2005). Uterine cancer after use of clomiphene citrate to induce ovulation. *Am J Epidemiol* **161**:607-615.

Calderon-Margalit R, Friedlander Y, Yanetz R, Kleinhaus K, Perrin MC, Manor O, Harlap S, Paltiel O (2009). Cancer risk after exposure to treatments for ovulation induction. *Am J Epidemiol* **169**:365-375.

Clark JH, McCormack S (1977). Clomid or nafoxidine administered to neonatal rats causes reproductive tract abnormalities. *Science* **197**:164-165.

dos Santos Silva I, Wark PA, McCormack VA, Mayer D, Overton C, Little V, Nieto J, Hardiman P, Davies M and MacLean AB (2009). Ovulation-stimulation drugs and cancer risks: a long-term follow-up of a British cohort. *British Journal of Cancer* **100**:1824–1831.

Duran B, Ozdemir I, Demirel Y, Ozdemir O, Cetin A, Guven A (2006). In vivo evaluation of the genotoxic effects of clomiphene citrate on rat reticulocytes: a micronucleus genotoxicity. *Gynecol Obstet Invest* **61**:228-231.

Hannibal CG, Jensen A, Sharif H, Kjaer SK (2008). Risk of thyroid cancer after exposure to fertility drugs: results from a large Danish cohort study. *Hum Reprod* **23**:451-456.

Harris R, Whittemore AS, Itnyre J and the Collaborative Ovarian Cancer Group (1992). Characteristics relating to ovarian cancer risk: Collaborative analysis of 12 US case-control studies. III. Epithelial tumors of low malignant potential in white women. *Am J Epidemiol* **136**:1204-1211.

¹ Excerpts or the complete publication have been provided to members of the Carcinogen Identification Committee, in the order in which they are discussed in this document.

International Agency for Research on Cancer (IARC, 1979). *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*. Volume 21. IARC, Lyon, France.

International Agency for Research on Cancer (IARC, 1987). *IARC Monographs on the evaluation of carcinogenic risks to humans*. Suppl 7, *Overall evaluations of carcinogenicity: An updating of IARC monographs Volumes 1-42*. Lyon, France.

Orgéas CC, Sanner K, Hall P, Conner P, Holte J, Nilsson SJ, Sundfeldt K, Persson I, Chia KS, Wedren S, Dickman PW, Czene K (2009). Breast cancer incidence after hormonal infertility treatment in Sweden: a cohort study. *Am J Obstet Gynecol* **200**:72 e71-77.

Rossing MA, Daling JR, Weiss NS, Moore DE, Self SG (1994). Ovarian tumors in a cohort of infertile women. *N Engl J Med* **331**:771-776.

Rossing MA, Tang M-TC, Flagg EW, Weiss LK, Wicklund KG (2004). A case-control study of ovarian cancer in relation to infertility and the use of ovulation-inducing drugs. *Am J Epidemiol* **160**:1070-1078.

Sanner K, Conner P, Bergfeldt K, Dickman P, Sundfeldt K, Bergh T, Hagenfeldt K, Janson PO, Nilsson S, Persson I (2009). Ovarian epithelial neoplasia after hormonal infertility treatment: long-term follow-up of a historical cohort in Sweden. *Fertil Steril* **91**:1152-1158.

Spirtas R, Kaufman SC, Alexander NJ (1993). Fertility drugs and ovarian cancer: red alert or red herring? *Fertility and Sterility* **59**(2):291-293.

Van Gompel J, Woestenborghs F, Beerens D, Mackie C, Cahill PA, Knight AW, Billinton N, Tweats DJ, Walmsley RM (2005). An assessment of the utility of the yeast GreenScreen assay in pharmaceutical screening. *Mutagenesis* **20**:449-454.

Whittemore AS, Harris R, Itnyre J and the Collaborative Ovarian Cancer Group (1992). Characteristics relating to ovarian cancer risk: Collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. *Am J Epidemiol* **136**:1184-1203.