Annex B: HPT Timeline – Key Events

Bayer statement concerning Landesarchiv documents

During the course of the Review, the Review Team has viewed documents which derive from files of internal documents belonging to Schering AG that, in the late 1970s, were seized by the relevant federal authorities in Germany as part of a review which they conducted relating to hormone pregnancy tests.

These documents have since been stored at the Landesarchiv Berlin. They date principally from a period after sales of Primodos and other HPTs ended in the UK. The documents were subsequently made available to the MHRA for consideration by an Expert Working Group of the UK's Commission on Human Medicines which was established in October 2015 in order to conduct a review to ascertain whether the totality of the available data, on balance, support a casual association between use of an HPT by the mother and adverse pregnancy outcomes.

These documents were not made available by Schering/Bayer and Bayer has drawn to the Review's attention the fact that it has not waived any rights it has in the UK or elsewhere relating to confidentiality and privilege which attach to these documents.

IMMDS Review statement concerning Landesarchiv documents.

The Review sought permission from Bayer to rely on these documents and in this respect, we would draw attention to a statement which the Review will include in its report (above), and on the website and timeline at Bayer's request.

It is important to note, that for legal reasons asserted by Bayer, it has not been possible for the Review to provide the detail of certain documents in the HPT Timeline. This has resulted in a significantly different (and less detailed) timeline initially envisaged by the Review. Additionally, Bayer has asked the Review not to publish or to provide links to the documents in question.

The Independent
MEDICINES & MEDICAL DEVICES
Safety Review

Hormone Pregnancy Tests Timeline – Key Events

July 2020

Disclaimer

The statements made and the opinions expressed in the components of the timeline do not purport to reflect the opinions, views or conclusions of the Independent Medicines and Medical Devices Safety Review's ('IMMDSR). The statements and opinions made do not imply the expression of any opinion whatsoever on the part of the IMMSDR concerning the truthfulness, veracity, accuracy or legal status of any statements or opinions made and published on the IMMDSR website. Nor does the IMMSDR accept any legal liability arising from any statements or opinions so expressed and published.

Annex B: HPT Timeline – Key Events

Key

Evidence Source	Colour
Regulatory/public bodies	
Manufacturers	
Key Studies	
Patient Groups	
Media	
International/devolved administrations	
Significant Events	
Parliamentary Activity	

Timeline

Year	Source	Key Events, opinions
28th February 1942	Zondek et al 1942[1]	**Simplified hormonal treatment of amenorrhea** The first reported use of a combination of estrogens and progestogens to induce bleeding in women suffering from amenorrhea. These findings formed the basis of the use of a combination of estrogen and progestogens as a pregnancy test.
1943	Raynaud (1943)[2]	**Inhibition de l'allongement et de la soudure des paupières des embryons de souris** Reported oestrogen mediated failure of development of the eyelids in mouse embryos (Article in French)
1920s-1940s		**Various papers were published on the roles sex hormones could play in disrupting pregnancy in animal models.** **Smith (1926)[3]** *found that injection of ovarian follicular extracts terminated pregnancy in Rats. The later the in pregnancy the more extract was needed to exert an effect.* **Parkes & Bellerby (1926)[4]** *as for Smith (1926) using mice;* ***Engle & Mermod (1928)[5]*** showed that *'daily implants to anterior pituitary interrupted pregnancy. In the first third of pregnancy implantation was prevented, in the second,*

[1] Zondek, B. (1942) *Simplified hormonal treatment of amenorrhea*. J Am Med Assoc 118(9): 705-707.

[2] Raynaud A. *Inhibition de l'allongement et de la soudure des paupières des embryons de souris.* Comp. Rend. de la Soc. de Biol., 136 (**1943**), pp. 337-338.

[3] Smith, M.G., *On the interruption of pregnancy in the rat by the injection of ovarian follicular extract.* Bull Johns Hopkins Hosp, 1926. **39**(4): p. 203-14.

[4] Parkes, A.S. and C.W. Bellerby, *Studies on the internal secretions of the ovary: II. The effects of injection of the oestrus producing hormone during pregnancy.* The Journal of physiology, 1926. **62**(2): p. 145-155.

[5] Engle, E.T. and C. Mermod, *THE EFFECT OF DAILY TRANSPLANTATION OF THE ANTERIOR LOBE ON THE COURSE OF PREGNANCY IN THE RAT AND MOUSE.* American Journal of Physiology-Legacy Content, 1928. **85**(3): p. 518-526.

		resorption or abortion occurred, but in the last third normal litters were often born.'; **Kelly & Lombard (1931)[6]** oestrin injections can interrupt early guinea pig pregnancy; **Courrier et al (1933)[7]** (In French) comparison between rats, rabbits and mice on levels of follicular extract required to interrupt pregnancy; **Courrier et al (1934)[8]** (in French) rabbit study using crystalized folliculin hormones to trigger abortions; ***Parkes, Dodds & Noble (1938)[9]*** *same effect as in Smith 1926 in rats and rabbits following oral synthetic oestrogens;* **Huggett & Pritchard (1945)[10]** (cited *Smith (1926),* Parkes and Bellerby (1926); Parkes, Dodds & Noble (1938); and Engle & Mermod (1928))
1950	EWG	Amenerone Marketed
1950	Ancel[11]	***La Chimiotératogenèse: Réalisation des monstrousités par des substances chimiques chez les vertébrés*** *(Monograph in French)* Describes the use of sex hormones to generate intersexuality in various vertebrate models, including fish, chicks, amphibia and mammals.
1953	Matthew & Hobson 1953[12]	**Observations on progesterone-oestrogen withdrawal bleeding and the Hogben test in the diagnosis of pregnancy** Study concluded that HPT injections as effective as Hogben test (toad test) (n=104)
1954	Rote Liste (German Pharmacopeia)[13]	Duogynon (Primodos was called Duogynon in many countries outside the UK) The indications for the injectable form are listed as:- *'Sekundäre Amenorrhea, Schwangerschaftsdiagnostik, Abort, Polymenorrhea, Sterilität, Abstillen.'* This translates as

[6] Kelly & Lombard (1931) *The effect of injections of female sex hormone (Oestrin) on conception and pregnancy in the guinea pig.* Surg. Gynec. Obstet.**52**, 713

[7] Courrier et al (1933) *Sur l'avertement folliculinique chez la lapine.* C. R. Soc. Biol. (Paris)**112**, 675.

[8] Courrier R et al (1934) *Etude quantitative de l'avortement folliculinique provoqué, chez la lapine, par l' hormone cristallisée. Réalisation d'un abortement partiele.* C. R. Soc. Biol. (Paris)**116**, 1073

[9] Parkes, A.S., E.C. Dodds, and R.L. Noble, *Interruption of Early Pregnancy by Orally Active Oestrogens.* Br Med J, 1938. **2**(4053): p. 557-9.

[10] Huggett, A.S. and J.J. Pritchard, *Experimental Foetal Death: The Surviving Placenta.* Proceedings of the Royal Society of Medicine, 1945. **38**(6): p. 261-266.

[11] Ancel, P. 1950 *La Chimioteratogenese.* Doin, Paris

[12] Matthew, G. D. and B. M. Hobson (1953) *Observations on progesterone-oestrogen withdrawal bleeding and the Hogben test in the diagnosis of pregnancy*. J Obstet Gynaecol Br Emp **60**(3): 363-367.

[13] https://www.rote-liste.de/

		Seconday amenorrhea, pregnancy diagnosis, abortion/miscarriage, polymenorrhea, sterility, weaning.
3rd March 1956	Dienz & Risse 1956[14]	**Experience with duogynon in amenorrhea and early pregnancy**. (Article in German) 4.6% of pregnant women bleed after Duogynon adminstration.
1956	Matthew 1956[15]	**Simple Clinical Test for the Diagnosis of Early Pregnancy** Study concludes that oral HPT effective and no untoward effects on the pregnancy were noted (n=94).
1958	EWG	Primodos oral marketed as HPT and for secondary amenorrhea
April 1958		Thalidomide first available in UK (prescription only)
April 1958	Nishihara 1958[16]	**Influence of female sex hormones in experimental teratogenesis.** *These data, demonstrate that parenteral estrogen injection has teratogenic effects on developing mice embryos when administered to mothers under the stated experimental conditions. These effects are not so frequent as those demonstrated by Fraser, whose technic of cortisone administration§ has resulted in a 90% incidence of cleft palate formation in our hands. They are definite, however; and they indicate that an additional emphasis is needed on the role of estrogen secretory fluctuations in the pathogenesis of human cleft palates.*
1st June 1958	Wilkins et al.[17]	**Masculinization of the female fetus associated with administration of oral and intramuscular progestins during gestation: non-adrenal female pseudohermaphrodism** Report of 21 cases of females born with partial masculinization of the external genitalia. In 15 of the cases, the mother had been treated because of threatened or habitual abortion with an oral progestin, 17-cthinyltestosterone (anhydrohydroxyprogesterone or ethisterone). In 2 cases the mother had received intramuscular injections of progesterone. In 1 case both

[14] Dienz, H. and E. Risse, *[Experience with duogynon in amenorrhea and early pregnancy].* Medizinische, 1956(9): p. 328-30

[15] Matthew, G. D. (1956) *Simple Clinical Test for the Diagnosis of Early Pregnancy*. British Medical Journal **2**(4999): 979-979.

[16] Nishihara, G., *Influence of female sex hormones in experimental teratogenesis.* Proc Soc Exp Biol Med, 1958. **97**(4): p. 809-12.

[17] Wilkins, L., et al., *Masculinization of the female fetus associated with administration of oral and intramuscular progestins during gestation: non-adrenal female pseudohermaphrodism.* J Clin Endocrinol Metab, 1958. **18**(6): p. 559-85

		intramuscular progesterone and oral methyltcstosterone had been given. In 3 cases no steroids were administered during pregnancy.
30th July 1958	Nalbandov 1958[18]	**Effect of progesterone on ovarian morphology and on embryonal mortality in pregnant rats, pigs, and sheep.** *'Progesterone, under the conditions of this experiment, was neither beneficial nor detrimental to embryonal survival in rats. In pigs, however, even the lower doses of the hormone caused decreased embryonal survival. Limited data suggest that progesterone has an adverse effect on the embryonal survival in sheep. It appears at present that, in pigs, embryos are most susceptible to progesterone damage during the early stages of gestation, while older embryos are significantly more resistant even to higher levels of progesterone.'*
1958	Edwards, J. H.[19]	**Congenital malformations of the central nervous system in Scotland** Paper suggesting a connection between HPTs and non-genital foetal malformations. *'Recently a hormone preparation which disturbs the empty uterus sufficiently to induce menstruation has been widely advertised as a method of diagnosing pregnancy. Although this has not been in use long enough to be relevant to the differences in the years up to 1956, it is the type of insult which is likely to cause foetal malformations, and would often be administered at a stage in pregnancy when it might initiate malformations of the central nervous system.'*
1st November 1959	Grumbach et al 1959[20]	**On the fetal masculinizing action of certain oral progestins** Data are presented on 18 females with congenital masculinization of the external genitalia who were born of mothers treated with certain oral progestins during pregnancy.
5th March 1960	Wilkins et al.[21]	**Masculinization of female fetus due to use of orally given progestins**

[1818] Nalbandov, A.V., *Effect of progesterone on ovarian morphology and on embryonal mortality in pregnant rats, pigs, and sheep.* Ann N Y Acad Sci, 1958. **71**(5): p. 580-7.

[19] Edwards, J. H. (1958) *Congenital Malformations of the Central Nervous System in Scotland*. Br J Prev Soc Med **12**(3): 115-130.

[2020] Grumbach, M. M., et al. (1959) *On the fetal masculinizing action of certain oral progestins*. J Clin Endocrinol Metab **19**: 1369-1380.

[21] Wilkins, L. (1960) *Masculinization of female fetus due to use of orally given progestins.* J Am Med Assoc **172**: 1028-1032.

		Seventy cases of foetal masculinization of female infants associated with oral administration of progestins are presented.
November 1960	Higgins & Sadler[22]	**A two-tablet oral pregnancy test** Study to determine the long-term accuracy of Primodos in diagnosing pregnancy. Four abortions were seen in 43 pregnancies, but authors conclude that abortions could not be definitively attributed to the drug. They conclude that Primodos is a simple, safe and accurate test for pregnancy. Authors outline reasons why laboratory-based urine pregnancy testing was considered inconvenient. *'Although the results of the test may be known in twenty-four to forty-eight hours, there may be several days' delay beyond this before the result reaches the practitioner. In addition, the collection and transmission of the specimen represent a considerable inconvenience to an already busy person.'*
March /April 1961	Edgren & Shipley 1961[23]	**A Quantitative Study of the Termination of Pregnancy in Rats with Estrone**. *'Pregnancy in rats may be terminated by the administration of estrogens to the female. Early stages of pregnancy, during the period of tubal passage, seem most sensitive to this estrogenic effect, although high doses of estrone may be effective as late as the eleventh day postcoitum… In a preliminary study, progesterone given to rats over the first 7 days of pregnancy appeared partially to ameliorate the effects of estrone or estriol, also given over the first 7 days'*
1961		Combined Oral Contraceptive pill launched in UK for married women
December 1961		Thalidomide withdrawn in the UK market (voluntary withdrawal)
25th August 1962	Dubowitz, V.[24]	**Virilization and malformation of the female infant** Case report, drawing attention to a possible association between the administration of Amenerone for 'the diagnosis of pregnancy' and virilisation in a female infant.
1st October 1962	Jackobsen, B.D.[25]	**Hazards of norethindrone therapy during pregnancy** Case reports of foetal masculinisation in cases of recurrent and threatened abortion treated with norethisterone.

[22] Higgins, G.L. and W.R. Sadler, *A two-tablet oral pregnancy test.* Practitioner, 1960. **185**: p. 677-80.
[23] Edgren, R.A. and G.C. Shipley, *A Quantitative Study of the Termination of Pregnancy in Rats with Estrone.* Fertility and Sterility, 1961. **12**(2): p. 178-181.
[24] Dubowitz, V., *Virilisation and malformation of a female infant.* Lancet, 1962. **280**(7252): p. 405-406.
[25] Jacobson, B.D., *Hazards of norethindrone therapy during pregnancy.* Am J Obstet Gynecol, 1962. **84**: p. 962-8.

7th December 1962	*CSD MH 148_42* Pages 4 and 6	In a letter to Dr Heasman (later of CSD) dated 7 December 1962 Dr Carter relates some findings of his study on congenital malformations. No mention is made of a link between hormones and congenital malformations, but he does report that of 15 patients given Amenerone Forte in the first 12 weeks three aborted. In his reply two weeks later Dr Heasman states *'With amenerone forte, I am not in the least surprised because surely this is given to try and prevent abortions.'* This was clarified by Dr Carter by return post on 17 December, where he explains that amenerone forte was used as a pregnancy test, not to prevent threatened abortion.
17th January 1963	*MH 148_42* Page 11	Dr Heasman sent a memo to Dr Cohen on 17 January 1963 stating. *'You will remember that Dr. Carter had some rather flimsy evidence that Amenerone forte was responsible for causing malformations. I attach a press cutting from the Daily Sketch which suggests that Primolut N is also causing malformations… …The evidence given is rather flimsy and it is interesting that Primolut is apparently used to treat threatened abortion and it is perhaps the success of this treatment which allows an already deformed baby to survive.'*
June 1963	CSD[26]	The Committee on Safety of Drugs was formed in June 1963 it began meetings from January 1964. The terms of reference for CSD are below. 1) To invite from the manufacturer or other person developing or proposing to market a drug in the United Kingdom any reports they may think fit on the toxicity tests carried out on it; to consider whether any further tests should be made and whether the drug should be submitted to clinical trials; and to convey their advice to those who submitted the reports 2) To obtain reports of clinical trials of drugs submitted thereto. 3) Taking into account the safety and efficacy of each drug, and the purposes for which it is to be used, to consider whether it may be released for marketing, with or without precautions or restrictions on its use; and to convey their advice to those who submitted reports. 4) To give manufacturers and others concerned any general advice they may think fit on the matters referred to in paragraphs 1-3. 5) To assemble and assess reports about adverse effects of drugs in use and prepare information thereon that may be brought to the notice of doctors and others concerned

[26] *Medical News.* British Medical Journal, 1963. **1**(5344): p. 1554-1556.

		6) To advise the appointing ministers on any of the above matters
Late 1963		Since late 1963 the Chief Medical Officer had requested that the Registrar General was notified of all babies (live and stillborn) born with congenital abnormalities. Returns were sent on form SD.56 which included a codified description of the congenital anomaly as well as patient identifying data.
December 1963	MH 171_64 page 100	Ministry of Health booklet 'Congenital Malformations' was sent out advising *'A good general rule is to give as few drugs as possible to pregnant women, or to women in whom pregnancy is likely.'*
1963-1964	CSD/AR *MH 171_26*	During 1963 and 1964 discussions were held with interested parties over the creation of a Register for Adverse Reactions to Drugs.
1st January 1964	BMJ[27]	**A scheme that required that all congenital abnormalities should be reported to the Registrar General started on 1st January 1964.**
7th March 1964	Wheatley, D.[28]	**Drugs and the Embryo** Letter in the BMJ referencing a prospective and retrospective survey undertaken by the General Practitioner Research Group[29] in which *'Foetal abnormalities occurred in 8.2% of 60 patients given female sex hormones'* Wheatley states that *'the trends for the figures indicate that significance at the 5% level might be expected if the samples were increased in size. Clearly it is of importance to extend the investigation to include larger numbers of patients'*
11th March 1964	British Medical Association CSD/AR *MH 171_26.* Page 112-3	There was some reluctance on the part of the British Medical Association to establish a Register for adverse drug reactions. They were concerned that the CSD should destroy the 'yellow cards' themselves. Minutes of a meeting held on 11 March between representatives of the BMA and the CSD record *'Mr Leigh-Taylor said that he had three worries. The first was that general practitioners were too conscious that they might be liable for the misuse of a drug, and they want a blanket assurance; and secondly coroners might make a habit of asking doctors if they had reported adverse reactions to the Committee. Thirdly solicitors would always wish to see reports if they thought that these might help their client's cases. Destruction of the reports was the only method of removing the doctors' fears. Dr. Ridge indicated that doctors might be more accurate in their*

[27] *Congenital Malformations.* British Medical Journal, 1964. **1**(5375): p. 71-72.
[28] D. Wheatley, Drugs and the Embryo. *Br Med J* **1**, 630-630 (1964).
[29] Practitioner, 1963, **191**, 775

		reports to the Committee than they would be in their own recording, and they could either protect themselves in their own records or even destroy them, however wrong that was.' It was agreed that the content of a yellow card report was similar to the standard of hospital notes that a doctor would make, so would not impact on potential liability.
March 1964	CSD/AR, *MH 171_18.* Page 6 and Smithells 1964[30]	The minutes of the Adverse reactions subcommittee meeting from March 1964 reviewed a pre-publication paper on teratogenic drugs by Dr Smithells from the Prescribers' Journal. Early in the article Dr Smithells writes *'There is no easy road to reassurance. It is very difficult to prove that a drug is teratogenic in the human; thalidomide was not linked with ectromelia for 4 years. It is even more difficult to prove that a drug is not teratogenic in the human. The relationship between teratogenesis in the experimental animal and man is not always very close. Finally, if there are reasonable grounds for suspecting that a drug may be teratogenic, its use in early pregnancy must be stopped. It would be morally indefensible to put the suspicion to the test and the problem must remain unsolved.'* Later in the article there is a specific reference to HPTs. *'Most hormonal preparations cross the placental barrier and may exert their expected effects on the foetal endocrine system. Anti-thyroid drugs, for example, may depress the activity of the foetal thyroid. This may lead to an increased output of thyroid-stimulating hormone by the foetal pituitary gland and thus to the development of a foetal goitre. The effect appears usually to be reversible. Progestational drugs may have a masculinizing effect upon the inborn female, but this also is usually reversible. These effects are not truly teratogenic, but are occasionally serious. No hormonal preparation should be prescribed during pregnancy without a very clear indication.'* *'Most pregnancy test drugs contain a progestational drug and an oestrogen. Experience with thalidomide has shown that a course of only 2 or 3 tablets can be harmful to the embryo, but with the small doses used in the pregnancy test, a hormonal (as opposed to a teratogenic) effect would not be expected to occur. Some unpublished data of the writer suggests that pregnancy test tablets are probably not harmful to the human embryo.'* There is a manuscript of a paper by R.W. Smithells and E.W Chinn entitled 'Pregnancy test drugs and foetal malformations. A prospective study.'[31] This paper carried out a prospective study on prescriptions for Primodos and Amenerone Forte between November 1961 and February

[30] Smithells, R. W. (1964). *Drugs and Foetal Development.* Prescribers' Journal **4**(2): 21-23.

[31] MH 171_39 page 70

		1962. In the 189 pregnancies known to have been exposed to one of these two products in the first 12 weeks of pregnancy there were three congenital abnormalities, one set of identical twins with patent ductus arteriosus (amenerone forte prescribed at 55 days) and a child with a systolic mummer (amenerone prescribed at 40 days). The article concludes *'This study provides no evidence to support the suggestion that pregnancy test drugs may be teratogenic in man. Because these drugs are used so widely (at least in the Liverpool area) there will continue to be incidents in which their administration in early pregnancy is followed by the birth of an abnormal baby. There is at present no evidence to suggest a causal relationship.'* It is unclear if this paper was published, it does not appear in PubMed. The above study is described in Smithells 1965.
May 1964	*CSD/AR MH 171_26.* 1963 Page 147 & 184	The Yellow Card system of adverse reaction reporting was set up. On 4 May 1964 Sir Derek Dunlop wrote to doctors informing them of the start of the Register for Adverse Reactions to Drugs and asking for them to report adverse reactions on pre-paid yellow cards. A reminder letter was sent out on 1 February 1965.
January 1965	Smithells 1965[32]	**The problem of teratogenicity** Smithells concludes that there is no evidence that HPTs are teratogenic (see Smithells 1964, March 1964), but prescribing in pregnancy should be restricted to essential drugs only.
Spring 1966 to early 1967	MH 149_1005; MH 156_633 and MH 159_77	Joint Pricing Committee for England Discussions were held on the provision of pregnancy testing on the NHS. Key events are detailed below.
Early 1966	MH 149_1105 pg 3, 4 & 7	A memo from Mr Rees to Dr Carr and Miss Mozley-Stark dated 23/3 reads *'I feel that we ought to give advance notice to the B.M.A., N.P.U. and A.B.P.I. that we are establishing these immunological tests. Have you any comments on the draft at D5. please.'* The draft letter at D5 to the ABPI, NPU and BMA, advising that *'this type of test* [HPT] *is not very accurate and may be*

[32] ibid

<table>
<tr><td></td><td></td><td>dangerous in that it could possibly precipitate abortion in a not well established pregnancy'

'We are at present in the process of making arrangements for the establishment of centres in hospitals where immunological tests of pregnancy can be made on requests from General Practitioners and these tests are more accurate than hormone tests of the kind described above'

The letter concludes that 'we shall be looking rather more critically at prescriptions for Amenorone etc.'

It is uncertain whether this letter was sent, and if so when.</td></tr>
<tr><td>30th April 1966</td><td>MH171_64 page 289</td><td>In the preceding two years 127 reports of congenital abnormalities following administration of medications were made to CSD. Reports including a hormone are detailed below.

<table>
<tr><th>Hormone</th><th>Total number of reports</th><th>Reports of limb reductions</th></tr>
<tr><td>Ethinyleoestrandiol</td><td>7</td><td>5</td></tr>
<tr><td>Mestranol</td><td>2</td><td>0</td></tr>
<tr><td>Hydroxyprogesterone</td><td>1</td><td>0</td></tr>
<tr><td>Ethisterone</td><td>4</td><td>2</td></tr>
<tr><td>Norethisterone</td><td>7</td><td>3</td></tr>
</table>

Further details of the five cases of limb reductions associated with HPTs are provided below. Amenerone and Amenerone Forte contained Ethinylestradiol and ethisterone. Primodos contained Ethinylestradiol and norethisterone acetate.

<table>
<tr><th>Series No.</th><th>CSD No.</th><th>Age of mother</th><th>Drug taken during 1st trimester</th><th>Period of exposure</th><th>Description of abnormality</th></tr>
<tr><td>5</td><td>00141</td><td>24</td><td>Amenerone
Avomine
Anadin</td><td>4 days at 2nd month during 3rd month</td><td>Hemimelia</td></tr>
<tr><td>8</td><td>01179</td><td>-</td><td>Primodos
Ancoloxin</td><td>2 tabs. At 8 weeks.
First 2 months</td><td>Micromelia</td></tr>
<tr><td>9</td><td>01309</td><td>27</td><td>Amenerone Fort</td><td>3 days at start of pregnancy</td><td>Absent fingers, one hand</td></tr>
<tr><td>10</td><td>01310</td><td>39</td><td>Amenerone Fort</td><td>For 3 days after missing 2 periods</td><td>Absent right femur</td></tr>
<tr><td>32</td><td>06407</td><td>-</td><td>Primodos
Librium</td><td>Pregnancy test at conception</td><td>Missing finger</td></tr>
</table>
</td></tr>
</table>

April 1966	13224 (trans) page 31	**Toxicological and generational experiments using 17α-ethinyl19-nortestosterone acetate in rats** Scoping study to investigate:- - toxicity/teratogenic safety limits; - impact on future fertility/pregnancies; and - the impact of continuous administration on sexual receptivity and conception, birth, rearing ability, etc. In the first two three different dosage groups, 3-, 1- or 0.3 mg, the test substance was administered from the 16th to the 19th day of the first pregnancy. *'For a one-off dose of 30 mg, in almost all animals, irrespective as to when treatment and death of the animals occurred for dissection purposes, the foetuses were regressed or had died and were more or less readily resorbed. There was uterine bleeding.'* The overall report conclusions were. *'Establishing the safety limits* *When comparing the doses, which no longer bring about any undesirable effects in animal experiments, with those applied in the hospital, converting from kg/rat to kg/human, the result was as follows: Daily dose of 17α-ethinyl-19-nortestosterone acetate in women: ~ 4 mg. 80 – 100 times higher doses from day 16 to 19 of pregnancy s.c. administered to pregnant rats, caused no virilisation in the offspring, no inhibited lactation and no delayed birth. These effects only occur at 250 times the clinical dose.* *The one-off s.c. administration of 250 times the clinical dose to rats at various stages of pregnancy only continued to cause partial inhibition of foetal development in individual animals. This effect only becomes clear at 700 – 800 times the clinical dose.* *Given long-term oral intake of approx. 20 times the clinical dose of 17α-ethinyl-19-nortestosterone acetate, readiness to conceive is less and the rearing capacity of the mothers is reduced as a result of inhibited lactation. These effects are associated with the therapeutically desirable effect of the compound and clinical use is also made of these.'*
May 1966	MH 149_1005 pages 16 and 30 +	May 1966 survey of EC10[33] prescriptions 20 tablet packets (for amenorrhea) were ≤3% of prescriptions. HPT tests cost - the NHS c. **£120,000 p.a** (1966).

[33] EC10 refers to the form used for prescriptions

Annex B: HPT Timeline – Key Events

October 1966	MH 149_1105 page 55	Dr J. G. Thomson, Senior Medical Officer at the Ministry of Health sought expert views on the reliability and use of HPTs. In his letter to Dr A. J. N Warrack, the Pathologist in charge of the Group Pathology Laboratory at the City General Hospital, Sheffield, Dr Thomson described HPTs as follows *'I have stated that I should not expect this to be a reliable test, and it is likely that the two does pack, being a test and not a therapy, will not be paid for when prescribed on E.C.10. However, it is desirable to have some authoritative opinion on the reliability of such tests.'*
4th November 1966	MH 149_1105 Pages 54 & 107	4 November 1966 Dr A. J. N Warrack replied to Dr. Thomson stating: *'I have consulted with one or two obstetric colleagues about these [HPTs] on previous occasions and the general opinion is that:-* *(a) The test is unreliable* *(b) It may well be dangerous in that it could possibly precipitate abortion in a not well established pregnancy.* *The latter is very difficult to prove, of course, but this has certainly been suspected in one or two cases here.* *In general, therefore, I would not recommend the use of these materials for pregnancy diagnosis, although perhaps from the Laboratory point of view one is really not qualified to express an opinion.'*
4th November 1966	MH 149_1105 page 56	Letter from Dr Bruce Hobson of the Department of Obstetrics and Gynaecology, University of Edinburgh dated 4 November 1966 to Dr. Thomson describes HPTs as 'not too inaccurate' and goes on to say:- '*My objection is that there are more accurate tests which do not require steroids to be taken by the women. These "withdrawal bleeding" tests should not be done by women who may have difficulty in retaining and early conceptus. It is well known these tests will restore menstruation soon after a missed period. Many of these cases are undoubtedly early abortions. In the series Dr. Matthew and I investigated we had 12 abortions in 83 pregnant women after using Disecron.*'
1967		Combined Oral Contraceptive pill became available to non-married women
11th January 1967	MH 149_1105 page 8	In a memo Dr Carr wrote *'Dr Thomson's minute of 22nd Dec. really answers the specific point of Dr Hedgcock's letter but this is part of a larger problem. The attached papers travelling with*

		B/C26/MAR2/7 concern another aspect. This arises from the marketing of progestogen – oestrogen tablets in packs of two or three for use as a diagnostic tests for pregnancy (e.g. Amenerone forte, Primodos, Norone). Payment for these, when prescribed on E.C.10 for this purpose, have been disallowed by pricing bureaux, at the instance of the Department, because the pharmaceutical service is only required to provide drugs and appliances requisite for treatment or diagnostic reagents on a prescribed list. (See Miss Mozley-Stark's letter of 14th Sept., flagged "B" on folder). There have been several complaints about this, and we have been studying whether these preparations should be added to the list of prescribed reagents.' *'Dr Thomson has obtained expert advice, described in his minute of 4/12/66 in this folder, to the effect that as a test for pregnancy the use of these tablets gives unreliable results and may well be dangerous in that they could precipitate abortion in a not well established pregnancy. You will remember also that some immunological tests for pregnancy. You will remember also that some immunological tests for pregnancy, carried out controlled conditions by experts, have now been developed to an acceptable standard of reliability, and two of the reagents (Pregnostican and Prepuerin) were to be made available on central supply from 1 Jan 67.'*
30th January 1967	MH 149_1105 page 9	Letter from to Dr Shaw to Dr Hedgcock (BMA) *'We have already had reports on several other immunological tests and so far only two have been shown to be reasonably reliable. Hospitals are being asked to make these tests available to general practitioners on request. We do not think that either could suitably be undertaken in general practitioner's surgeries, partly because of the time required and partly because the reagents re unstable and need to be stored at strictly controlled temperatures.'*
1st February 1967	MH 149_1105 page 3	Pregnosticon and Prepuerin[34] were determined to be reliable and accurate by the Subcommittee on Pregnancy Diagnostic Tests. Accordingly, these immunoassays were placed on the Central Supply list from 1 February 1967[35] and arrangements were put in place for these tests to be carried out in hospital pathology labs at the request of GPs.
30th May 1967	CSM, *FD 23_127*	CSD notified of Gal findings in a letter by Dr Kirkman *'I enclose a copy of a letter which my colleagues and I have prepared for submission for publication to 'Nature'. As you*

[34] These were pregnancy tests that could be carried out with a urine sample and used an immunological method rather than live animals (i.e. toads in the Hogben test).

[35] Listed as 1 Jan 1967 in one part of the file 1 Feb in another

		will see our findings, if soundly based, appear to be important in regard to the hormonal pregnancy test itself, in regard to contraceptive medication, and also possibly in regard to the use of hormones for maintenance of pregnancy. Therefore, before despatching this letter we would be grateful for your advice as to whether you think it is proper to draw attention to the matter in this way at the present stage.'
2nd June 1967	CSM, MH 171_39, p6-7	Letter from Dr Inman to Dr Kirkman, regarding the Kirkman-Gal survey study, which Kirkman sent to Inman on 30th May 1967. Kirkman says *'We have picked up about a dozen reports of congenital abnormalities following the use of oestrogen-progestogen mixtures, either for control of menstrual irregularities or conception, or as pregnancy tests… these cases do not constitute evidence of teratogenicity* *Firstly, is there any possibility that the medical or obstetric histories of the women who had pregnancy-tests was different from those of the controls? Your data would be invalidated if, for example, the reason why the survey cases had had pregnancy tests was that they were more than normally worried about a further pregnancy following the birth of a deformed baby. Alternatively had these women some medical illness such as diabetes or hypertension which might make their doctors anxious to detect pregnancy at an early stage.* *The second point is that although you have eliminated the age different as possible factor you have not dealt with the parity of these patients'* Dr Inman goes on to write *'I would be very interesting to see your data on the "drug-history" of these patients.'*
6th June 1967	CSM, MH 171_39, p11	Prof Leslie Witts (chair of the Adverse Reactions sub-committee) replied to a letter sent by Dr Bill Inman, informing him of Dr Kirman's proposed letter to Nature: *'The most useful thing now will be for the facts - or suspicion – to become known to that others can confirm or refute them. The circumstances of the oral pregnancy tests are unique, a big dose of progesterone being given at a time when the embryo is most vulnerable. The difference between Dr. Kirkman's cases and controls is so great that it is unlikely to be explained by the possibilities raised in your letter to him of June 2.'* He suggested writing to Professor Jeffcoate for advice.

Annex B: HPT Timeline – Key Events

13th June 1967	CSM, *MH 171_20, p14*	A letter from Professor Jeffcoate (Professor of Obstetrics and Gynaecology, University of Liverpool) expresses surprise as the finding of an association between HPT use and congenital malformations as there has been long and wide clinical use of hormones and that he suspects *'if Dr Kirkman's statistics are valid, the circumstances calling for the test, rather than the test itself, may be the factors which determine an increased chance of foetal malformation.'*
15th June 1967	CSD/AR MH 171_39, pg 12 see MH171_20 page 9 for the details of the study on Norone	A letter form Dr Inman to Professor Jeffcoate, thanking him for his letter of 13th June and stating. *'I hope to be able to discuss the problem in detail with Dr Kirman and his colleagues earlier in the week.* *You may remember that our Committee agreed to the marketing of Roussel's "Norone" sometime back and I am basing this decision I think on the long, apparently trouble-free history of the use of these pregnancy tests and on the results of a small G.P. trial that the Company had carried out. In the latter there was only one congenital abnormality (anencephaly) among 117 pregnancies followed up. A further 59 pregnancies however were not followed up and I would not think that this could really be classed as a useful contribution to our knowledge about the safety of this procedure.'* The details of the study on Norone appear to be described in MH171_20 page 9.
20th June 1967	CSD/AR MH 171_39, pg 19	A meeting took place between Dr Inman of the CSD and the research team at Carshalton. There are no minutes. Three days afterwards Dr Inman wrote to Isabel Gal stating that he had *'no doubt that you have produced prima facie evidence that these foetal abnormalities may be drug induced. Clearly you should publish your findings, however diffident you may feel about them, in the hope that someone will be sufficiently interested to carry out further work.'* He carried on to state that *'These tests are not essential and it would not be a disaster if your paper had the effect of reducing the frequency of their use.'*, but also outlined two *'major difficulties in the purely scientific evaluation of your data.'* Firstly, the matching of controls and cases. Secondly, the higher rate of congenital abnormalities in the parents and siblings of the cases. Reference is finally made to the recommendation that *'Dr. R. W. Smithells of Alder Hey Children's Hospital at Liverpool, should be contacted with a view t possible prospective or retrospective studies. Dr. Smithells has a foetal malformation register for the Liverpool area and has records which date back many years. As at Queen Mary's the*

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		Liverpool people have plenty of material in the form of children with hydrocephaly who are treated surgically.'
22nd June 1967	Landesarchive 13198 page 10 CSD, FD 23_127 p 2	The CSD discussed the Gal et al 1967 paper. Prof. Jeffcoate is quoted as saying that while these observations *"cannot be dismissed out of hand there is probably nothing in the suggested relationship."* This view is supported by others, *'Dr. Cahals's own view is that while the use of hormonal pregnancy tests at all is questionable have no firm evidence pointing to a true cause-effect relationship between the use of these tests and congenital malformation.'* Dr. Inman said to Schering that the committee was *"not happy"* with the hormonal pregnancy test, however insufficient material was present in order to take any definitive measures. The conclusion was *'So far as the Dunlop Committee are concerned therefore, the position is that they are watching the situation but not propose to take any action at present.'*
23rd June 1967 & 27th June 1967	CSD/AR FD 23_127 page 6 & 5	The MRC were informed of the Gal et al findings by a letter from Derek Richter to Dr Herrald. Dr Richter asked the MRC to fund further investigations and states that he has suggested that Dr Kirkman share these findings with CSD as the association looks *'as if it could be another thalidomide story.'* In his reply dated 27th June Dr Herrald wrote of Dr Kirkman's work *'His recent finding, which is to be communicated to 'Nature', about the possible connection between congenital malformation and the application of hormone pregnancy tests is disturbing and would seem to merit further investigation. I am looking into the question you have raised in this connection and will write to you again on the matter as soon as possible.'*
26th June 1967	CSD/AR MH 171_39 pg 21; 24	Expressing concerns about the quality of the Gal et al paper in a letter to Professor Jeffcoate dated 26 June 1967, Dr Inman writes *'Unfortunately as we suspected, they have selected their cases badly, and on looking at their data it was also apparent that there were rather more congenital abnormalities among parents and siblings on the affected group than the unaffected group.'*
27th June 1967	CSD/AR FD23_127 Page 5	Letter from Dr Herrald to Dr Richter, thanking him for his letter of 23rd June, regarding Dr Kirkman's work on sex hormones during pregnancy and congenital abnormalities, to be communicated in 'Nature'. Herrald states that the findings *'about the possible connection between congenital malformation and the application of hormone pregnancy tests is disturbing and would seem to merit further investigation'*

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27th June 1967	CSD/AR FD 23_127	Sir Charles Harrington memo references Dr. Kirkman's letter of 23rd June. *'On the face of it, this is a disturbing story and would seem to merit further investigation…'*
11th July 1967	CDS/ARM H171/39 P.24	Letter from Dr Inman to Prof Jeffcoate, thanking him for his letter of 7th July. He writes that *'Although I am as unconvinced as you and apparently Dr. Smithells about the validity of this data on the grounds that the selection of cases was wrong, I do not think we can rule out the possibility all together'* *'If we assume that there is no teratogenic effect, Dr. Kirkman's 19 infants with hydrocephalus would have been born to at least 10,000 women who had had the pregnancy test. This is a very large number indeed and I rather doubt whether the test is used all that frequently'* He finishes by suggesting that *'there is a case for further investigation and I hope Dr. Smithells may be able to help us'*
11th July 1976	MH 171_39, p25-26	Dr Inman wrote to Dr Smithells, who held the Liverpool Congenital Abnormalities register. *'Professor Jeffcoate tells me that you already know about this work and like myself you are unconvinced of the validity of the data. I have been to see these workers and came away with the general conclusion that although they had made a prima facie case that was worth investigating further too much reliance should not be placed on their general observations…* *…The Sub-Committee on Adverse Reactions discussed this problem at their meeting last month and agreed with my tentative assessment of the work by Kirkman and his associates. They felt that the case had been made which required investigation and they asked me to write to you in the hope that you may be able to help sought the problem out. I understand from Professor Jeffcoate that you have a very excellent register of abnormal babies and that you might be in a position to carry out prospective studies on this problem.'*
14th July 1967	MH 171_39, p27	Dr Smithells wrote to Dr Inman at CSD, stating he had previously published a prospective study of 189 pregnancies where Amenerone forte or Primodos had been prescribed in the first trimester and no association with congenital malformations was seen. He also said that he had met with Dr Gal and *'I am not at all happy that her hydrocephalic and control groups are really comparable. Professor Jeffcoate also pointed out that even if there is a real increase in the incidence of malformation following the use of these drugs, this could be related to the kind of pregnancy in which they*

		are prescribed (e.g. those with irregular bleeding in the early months). *Certainly in this part of the world pregnancy test drugs are prescribed on a fantastic scale and are quite often prescribed during the second trimester of pregnancy. I think there is a widespread belief amongst the laity that these drugs are abortifacient and I suspect that they are sometimes obtained from G.P.s by giving a misleading history.'*
14th July 1967	CSD/AR FD 23_127	Dr Herrald wrote a memo *'Dr. Cahal's own view is that while the use of hormonal pregnancy tests at all is a questionable procedure, the Committee so far have no firm evidence pointing to a true cause - effect relationship between the use of these tests and congenital malformation. He told me in confidence that one such hormonal product has in fact been investigated and released by the Committee and that no significant difference has been found in the incidence of congenital malformation in a group of mothers given this product and a group of controls.* *Dr. Cahal thinks that Dr. Kirkman's findings are open to criticism statistically, but even more so on the ground that family histories of the mothers in the survey are missing.* *The Committee have consulted Professor Jeffcoate, whose view in general is that while these observations cannot be dismissed out of hand there is probably nothing in the suggested relationship.'*
7th August 1967	Letter from Mrs E Croft, Ministry of Health Reference G/H118/01 dated 7 August 1967 to Secretaries, Regional Health Boards. MH159/78	A letter sent from the Ministry of Health to Regional Hospital Boards and Boards of Governors of teaching hospitals. This letter describes how testing at the Hogben "Toad" test centres had been limited to certain situations *'In practice such requests from general practitioners were usually accepted only on medical or socio-medical grounds.'* The letter goes on *'The Department now recommends that the hospital authorities should arrange for pathology laboratories to accept requests for pregnancy tests on referral form general practitioners and should discuss the introduction of the new arrangements with Local Medical Committees. The requests could be met effectively by using immunological reagents.'* It continued *'Senior Administrative Medical Officers were informed at their meeting on 20 September 1966 that, in order to help hospital authorities to provide this wider service, the Department was placing Pregnosticon and Perpuerin on central supply. These reagents are now available…An amendment to C.S. [Central Supply] List No. 3, giving details of the contracts, was issued on 26th January 1967. This arrangement is not intended to preclude the use of other reagents by pathologists.'*

September 1967		White paper for the Medicines Act
7th October 1967	Gal et al.[36]	**Hormonal Pregnancy Tests and Congenital Malformation** The first statistically significant published report of an association between HPT use and non-genital types of congenital malformations. The paper outlined preliminary findings indicating a statistically significant correlation between HPT use and the neural tube defects meningomyelocele and hydrocephalus: HPT use among 100 mothers of affected children and 100 mothers of healthy babies was compared. This paper provided *prima facie* evidence of an association between HPT use and neural tube malformations. Full findings published in Gal 1972 Advances in Teratology[37].
1967	CSM press release CSD/AR MH 171_67 Page 30	Following the Gal et al 1967 publication, the Committee for the Safety of Medicines gave the following press release *'The Committee have been informed of the results that have been obtained at Carshalton and have sought expert opinion. The consensus of that expert opinion is that there is no scientific evidence to support the view that the hormones used in pregnancy tests can cause congenital malformations. The report was a preliminary one. Further work is required to determine whether the drugs are completely safe. At the moment the committee can find no evidence to support the view that a general warning is necessary.'*
13th October 1967	CSD/AR, *MH 171_39* Page 35	**Extract from a 'Medical News' article.** References the Gal paper then goes on to say *'A Mexican survey had shown a much greater incidence of congenital defects in babies of women in Mexico city who had continued taking oral contraceptives in the early stages of their pregnancy than in those who had not taken such tablets.* *However, the dosage of hormones used in pregnancy test tables is significantly higher than that in contraceptive pills.'*
20th October 1967	CSD/AR, *MH 171_39* Page 32	Dr Carter wrote to CSD on 20 October 1967 stating that he had carried out a small scale experiment as part of his PhD thesis which when combined with the results of the General Practitioner Clinical Trials, seemed to support Dr Gal's

[36] Gal, I., B. Kirman, and J.A.N. Stern, *Hormonal Pregnancy Tests and Congenital Malformation.* Nature, 1967. **216**: p. 83.

[37] Gal, I. *Hormonal imbalance in human reproduction*. In: (Ed) Woolam, D. H. M. Advances in Teratology. P161 - 173. Academic Press. New York/London.

		findings, although Dr Carter describes his study. 86 women given oestrogens and/or androgens in the first 12 weeks of pregnancy. There were 5 malformations, the expected number was 2 and a unclear fraction. 11 abortions were noted, 4½ were expected. Pregnancy wastage was 16, expected was 7 and a fraction (¼?) *For technical reasons tests of statistical significance could not be applied to these figures, which were in any case small'*.
31st October 1967	CSD/AR MH171/39 Page 33	Letter from Dr Inman to Dr Carter, thanking him for a copy of his letter of 20th October. Dr Inman writes that *'this, of course, is a matter of extreme interest to us although we have to admit that at the moment none of the evidence that has been put forward to suggest that pregnancy diagnosis tests may be causally related to congenital malformations amount as yet to convincing evidence of such an effect. Quite clearly such an effect cannot be excluded'*
3rd November 1967	CSD/AR MH 171_39 page 34	Dr Carter wrote to Dr Inman. *'I do not know for sure whether you are aware of the College of GP's Outcome of Pregnancy Survey, a prospective study which is now in course of analysis – this should give a much larger number of women who have received sex hormones in early pregnancy than the figures that I quoted in my letter to Dr. Kirkman from Wheatley's group, and from the series of Dr. Wilson and myself.* *It might be worthwhile, if you are as you say, extremely interested in this matter, having a word in confidence with either Dr. D.L. Crombie or Dr. B.S.C. Slater, who are in charge of this survey.'*
13th November 1967	CSD/AR MH171_39 Page 36	Letter written in confidence, to Dr Crombie, from Dr Inman regarding his study. *'The general pattern of expert opinion casts some doubts about the significance of Dr. Kirkman's findings, but we are nevertheless somewhat concerned about sporadic reports from other sources which has linked congenital abnormalities with progestogens either in the form of oral contraceptives or other preparations used for diagnostic or therapeutic purposes'* He concludes by requesting that Dr Crombie let him know, in confidence, whether his study *'is beginning to show significant results'*

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November 1967	CSD/AR MH 171_39 Page 37	Response to CSD from RCGP, stating that a survey of 10,000 women and their drug prescription during pregnancy had failed to find any positive associations to confirm Dr Gal's findings.
Late 1967	13198 (trans) page 9	Schering UK commissioned expert statistical analysis from Dr Denis Cooke on HPTs and malformation rates. Dr Cooke *'found a strong correlation between use of the hormonal test and the deformity rate between the years 1958 and 1965.'* These findings were independent of Dr Gal's findings. Schering subsequently stated that *'For numerous reasons, however, it would be possible that this was purely incidental.'*
11th December	CSD/AR, *MH 171_39* Page 42	Dr Inman wrote to Dr Gal, in which he writes of his views of the risk/benefit balance of HPTs. *'My personal view about the value of pregnancy tests is identical to yours, I frankly do not think that they are sufficiently useful when compared with other biological methods to justify even the slightest risk of teratogenicity.'*
1967		From 1967 onwards there was a centralised laboratory service that GPs could use to test for pregnancy.
1967	EWG Timeline	Roussel stopped providing free samples.[38] Schering also reduced the number of free samples starting in 1967 and stopping entirely in 1969.
8th January 1968	MH 171_39 p 43	Dr Smithells to Dr Inman *'You wrote to me in July regarding Dr. Gal's publication on a possible relationship between pregnancy test tablets and hydrocephalus. Dr Gal subsequently sent me the draft of her full paper which she had submitted to the B.M.J., but I do not know whether this has been accepted. I have written back to her with one or two queries but have not received a reply. As you know the manufacturers of these tablets are uncertain what action they should take especially as they have nothing to go on but the preliminary letter in Nature. In your letter of July 19th you mention the possibility of further studies, and I am really writing to ask if you have had any further thoughts about this. My own feeling is that, although Dr Gal's paper has not established anything definite, it has raised suspicions which can only be resolved by further studies.'* He concludes by writing that he is *'still willing to help in any way this (he) can'*

[38] For further evidence, see LandesArchiv 13198 page 9 and CSD/AR, *MH 171_39* Page 59

12th January 1968	CSD/AR *MH 171_39, p44*	In a later letter to Dr Smithells, Dr Inman writes about the forthcoming publication of the full results from Gal as part of the Carshalton team: '*I have not myself yet seen a draft of Dr. Gal's paper and I do not know whether it has been submitted by the British Medical Journal. Frankly I would be rather surprised if the Editor accepted it for publication in that journal.'* *'I agree with you entirely that Dr. Gal's paper does not amount to evidence of a definite cause-relationship between the use of these progestogens and foetal abnormalities, but it does raise nasty suspicions which can only be resolved by further work.'* In reference to this further work, Inman writes that *'Personally I doubt if this is the sort of problem that can be carried out by general practitioners and when I first wrote to you I rather hoped you might be in a position to study this problem in a more scientific way.'* He also expresses again his concern over the quality of the Gal et al paper: *'The Carshalton workers drew their affected children and controls from different catchment areas, and this to my mind invalidates their work. I would think it might be quite difficult to carry out a properly controlled study. It seems possible for example that the woman who has a hormonal pregnancy test may not be comparable to other women. She may, for example, be unmarried, she may have had a previously abnormal baby or she may have some disease which might affect the pregnancy and in which early diagnosis of pregnancy was thought essential. There is quite a lot of evidence that some women fondly imagine that the tablets used for pregnancy diagnostic tests may also have an abortifacient action. I have a feeling they may be right, but I know Professor Jeffcoate would disagree with me.'* Looking toward the publication of the Gal paper, Inman writes: *'in view of the unreliability of hormonal pregnancy tests and of doubts about their safety, and of the dubious profitability of these products from the manufacturers point of view, I would not be too surprised if they ceased to promote them when and if the Gal paper is finally published'*
18th January 1968	MH 171_64 page 25	Letter from Dr Ruttle, Medical Officer, CSD to Dr Pooley, Senior Medical Officer, London Borough of Redbridge *'Apart from Thalidomide, we have no direct evidence that any other drugs are teratogenic and we receive reports of*

		congenital malformations, but so far, the incidence is no higher than that to be expected in the population at large. From time to time suspicion is thrown on various groups of drug, especially Meclosine, the use of hormones for pregnancy testing and possible failure in taking of oral contraceptive of pregnancy occurring when the patient firmly asserts that she did, in fact, take the pill as directed. If you come across any instances where you suspect the association of an adverse reaction with the use of any drug we shall be very glad to hear of this and I enclose some or our yellow cards, which you may being a convenient way of doing this.'
6th March 1968	CSD/AR *MH 171_64. Pg 34*	Dr Inman wrote to RCGP to ask them to consult their Register of Pregnancies for any associations between HPT use and neural tube defects.
21st March 1968	CSD/AR*M H 171_64. Pg 35*	RCGP replied to Dr Inman *'Enclosed is a copy of the table giving the results of the analysis of all the pregnancies, with special subdivision by the progesterone, oestrogen mixture, also another table listing the congenital malformations of the babies against the actual drug prescribed, age of mother, etc.'* (The tables described are not with the letter in the file.)
27th April 1968		Free of charge legalised abortion available on the NHS
17th May 1968	CSD/AR *MH 171_39.* Page 48	An extract of 'The Outcome of Pregnancy Study' (unpublished) organised by RCGP Scotland, and led by Norman Dean was sent to CSD. This showed four abnormalities were recorded from 135 women given HPTs (79 were Primodos). A high rate of abortions were noted in the Primodos group. Dr Dean states *'the figure of 10% abortions recorded after Primodos is unlikely to be due to chance.'* He later goes on to say. *'In view of these findings, tentative though they are, it would be my own view that, since there is in any event no very sound medical reason (in my opinion) for the use of such hormonal preparations, Primodos should be withdrawn from use. I would hesitate to offer any opinion regarding any of the other preparations in view of the small numbers.'*
May 1968	Courtney & Valerio 1968	*Teratology in the Macaca mulatta.* *'Retrospective studies of therapeutic agents used at various times during pregnancy in monkeys in the colony have shown that hydroxyprogesterone caproate (Delalutin) and… [lists other non-hormonal agents] …have no apparent effect on the developing monkey fetus.'*

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6th June 1968	LandesArchiv 13198 (trans) pages 9-10	Schering UK in a letter to Schering Germany *'It is our moral duty as a manufacturer to do all we can to ensure the non-hazardousness of the preparations we have on the market. Where a suspicion of this kind has been raised by a researcher, whose integrity and ability can hardly be questioned, the burden of proof must lie with us. It is incumbent upon us to show that the preparation is safe to use, and that it is not the role of outsiders to prove that it is not. Medicolegal, we would get into difficulties, both as a company and as individuals responsible for the development and sale of Primodos, if an association between the anomalies of CNS and our preparation were to be demonstrated. From an ethical point of view, we are not satisfied with what has been done to remove the suspicion which has fallen upon us. Not enough has happened that we can continue to confidently promote the fact that Primodos for pregnant women is available here.'*
11th July 1968	CSD/AR MH171_64 Page 48	Letter from Dr Dean to Sir Derrick Dunlop, explaining he was researching teratogens and requesting that, as the chairman of the CSD, Sir Derek send *'a note of any drugs which have been notified to you as suspicious in this particular context over the past three or four years'* He carries on to explain *'I bring this up now merely because one of our field workers has reported that in connection with one of the abnormalities in our Edinburgh study, your committee was notified of the possibility of a specific drug being implicated'*
16th July 1968	CSD/AR MH171_64 page 49	Dr Inman replied to Dr Dean. *'Studying first the reports we received of abnormalities where the mother had taken antiemetic drugs, such as promethasine and meclonine, there was a surprisingly high proportion of reports of limb deformities, many of them of the "thalidomide-type". I suspect that this was due to selective reporting of such abnormalities and certainly the reported incidence would be much lower than the expected incidence taking into account the widespread use of these drugs in pregnancy.* *Studying the rather small number reports of congenital abnormalities in patients receiving anticonvulsants, I did notice that a surprisingly high proportion of the reports were of congenital deformities of the lip and palate. Clearly if there is anything in this it could well be that the abnormalities associated with epilepsy rather than the drugs used to treat it. Dr. Kuenssberg told me he was not surprised at this finding and quoted some work which had been done in Scotland and which may, in fact, been associated with your field studies. I attempted to set up a small scale investigation to study this problem retrospectively in a plastic surgery unit,*

		but failed to make any progress because of the difficulty of selecting suitable controls. *A third problem was sparked off by a publication in "Nature" from Queen Mary's Hospital for Children, Carshalton. This study which was badly controlled nevertheless raised suspicions that large doses of hormones used in pregnancy diagnosis testing might be producing abnormalities of the central nervous system. We have had a number of reports of congenital spinal deformities and hydrocephalus in the offspring of mothers who had had pregnancy diagnosis tests and similar reports in patients who apparently became pregnancy while using oral contraceptives or while taking steroids for various menstrual disorders. Here again the use of hormones is very widespread and the number of reports is very small. Nevertheless I do not think you could exclude the possibility of a causal relationship completely. Large doses of progesterone are given almost exactly as the time that the neural tube is closing.'*
October 1968		Medicines Act 1968 Royal Ascent
1968	Roussel[39]	A 1968 study comprising interviews with GPs was conducted by Roussel, it looked at all nervous system malformation and HPT use. This study found a slight trend (ES, 95% CI, 1.44 (0.65, 3.20) towards an association between HPT use and overall malformations. This study specifically looked at CNS malformations and found a slight trend (ES, 95% CI, 1.27 (0.28, 5.69) towards an association between HPT use and neural tube defects. However, the Roussel study was very small (n =In the 198 mothers that had received oral HPTs (of which 95 had taken primodos) there were 7 total babies with malformations, and n = 2 2 of them CNS malformations)
1968	British National Formulary (BNF)	The British National Formulary (BNF) in 1968 mentions the risks of teratogenicity in HPTs. *'The following is a list of drugs which if given to the mother may affect the foetus or the breast-feeding infant. The list is not comprehensive. It is wise not to use drugs in the pregnant or breast-feeding mother unless their use is essential.'* Progesterone and gonadotrophins are specifically listed, with the adverse reaction *'Affect genital development of the foetus'.* The BNF is very clear under the Prevention of Adverse Reactions section. *'1. Never use any drug unless there is a good indication. If the patient is pregnant do not use a drug unless the need for it is imperative.'*
1969	See 30th July 1978	Dr. Gal visited Schering in Berlin in 1969. '*At that time, they accepted that the hormonal pregnancy test leads to*

[39] Roussel, *G.P Survey - An Investigation into the Effects of Oral Pregnancy Tests on the Incidence of C.N.S. Malformations.* . Unpublished, 1968

		abortion.' she said, '*However, they could not decide, whether my results, I mean the connection with the malformations, should be accepted or not.'*
January 1969	*CSD/AR MH 171_64.* Pages 231 & 241	The Senior Medical Officer met with Dr Josephine Weatherall of the Registrar General's Office to discuss how the CSD could use the collected reports of babies born with congenital abnormalities (collected since 1963 at the request of the CMO). Over the next few months a study protocol was refined and agreed upon. Initially the intention was that three conditions would be analysed to look for potential drug teratogenicity; cleft palate (antiepileptic drugs); limb reductions (antihistamines); spina bifida (HPTs). Babies with these defects were matched with child of similar age from the same GP practice. The draft letter to part-time medical officers states *'In the course of drug monitoring over the past five years, three possible examples of teratogenicity have been detected:* 1. *Hare-lip and cleft palate in relation to anticonvulsant therapy.* 2. *Spina bifida and hydrocephalus in relation to sex hormones, including oral contraceptives* 3. *Limb deformities in relation to anti-emetics and amphetamine-like substances.* *Of these the first seems quite likely to be a true causal relationship…* *…Suspicion has been aroused by an apparent increase in the incidence of spina bifida where a hormonal pregnancy test was employed. This is not unreasonable because the tests involve a large dose of progestogen and might well be employed at a stage in foetal development when the neural tube is about to close.'* The draft letter to GPs says *'In the initial stages we are limiting the investigation to three types of congenital abnormality; harelip and cleft palate, spina bifida and hydrocephalus and reduction deformities of limbs.* *Although we have very definite reasons for following up these particular groups, we feel that it would be better that you should not know these reasons since this might introduce unconscious bias into your questioning.'* (This study went on to include a wider variety of malformation and was published as Greenberg et al 1975 and Greenberg et al 1977).
1969	Dean et al (unpublished)	'The Outcome of Pregnancy Study' (unpublished) organised by RCGP Scotland, and led by Norman Dean. See 17th May 1968 entry.

8th January 1969	Doll[40] MH171_64 page 214-221	Marc Daniels Lecture *'Recognition of Unwanted Drug Effects'* by Richard Doll at the Royal College of Physicians, London.
Early 1969	13198 (trans) page 11	Dr. Pitchford from Schering asked the RCGP for the Dean et al results. *'He presented the result to Dr. Pitchford at the end of January 1969. It had been found that in the Primodos group (compared to a control group) there was not higher rate of malformations, but a considerably higher at rate of abortions. The RCGP collaborator who had made the evaluation, Dr. Dean, expressed his personal opinion, that these finding justified the registration of Primodos. Dr. XXX presented this explicitly as a personal opinion of Dr. Dean. Dr. Bye, who sent the letter and the report to Dr. Friebel on the 5th of February 1969, said that for the time being it was perhaps wise to act, as if Dr Dean's opinion was justified'*
11 February 1969	13198 (trans) page 11	Dr. Lachnit and Dr. Friebel, Schering Berlin wrote to Schering UK acknowledging receipt of the RCGP survey. They pointed out that it was not determined whether these results were statistically significant, and they felt they were 'by no means alarming' in their opinion, and they in particular did not *'see any basis'* for Dr. Dean's recommendation to withdraw Primodos. They pointed out that no higher rate of malformation in the Primodos group could plausibly be explained by a higher rate of attempted abortions in the women in the Primodos group. They felt Dr Dean's call for recall of Primodos should not be undisputed. They recommended that the RCGP figure should be submitted to Mr Cooke for the purpose of testing their validity, which they were.
17th February 1969	Schering *CSD/AR MH 171_64.* Pages 73 & 74	17 February 1969 Dr Pitchford wrote explaining that rats had proved an unsuitable model and that experiments were being undertaken in baboons. He asked for advice on what investigations Schering might adopt. His letter finishes *'…we have pursued various lines of investigation, but studies in rats presented considerable difficulties, as the Primodos combination administered early in rat pregnancy suppresses FSH and, thereby, interferes with implantation. As the rate neuropore closes by the 11th day of pregnancy, and implantation does not take place until the 7th day, the value of any evidence accumulated during the brief four days with the Primodos combination is, therefore, extremely limited. We are, however, now undertaking a similar study in baboons, but I have not yet had a report on the progress of this work.*

[40] A transcript of this lecture was published on 12 April 1969, see Doll R Recognition of Unwanted Drug Effects. BMJ 1969, 2, 69-76

		In the hope that the Royal College of General Practitioner's study of women's drug history during pregnancy would be more informative, I have kept in touch with Dr. Kuenssberg, and he had now been able to provide me with preliminary data after a hand-sort of their statistics. I am now enclosing a copy of this for your information and would greatly appreciate your comments. You will note that there are three abnormalities in the Primodos group, one of which was a mongol and can, therefore, be discarded, the other being a cleft palate and a congenital dislocation of hip. On preliminary examination, it looks as though the incidence of abnormalities in the Primodos group is lower that that in the total study, but no doubt further statistical analysis will give a more realistic picture. *With regard to the rather high incidence of abortions in the Primodos group, I think it must be borne in mind that women going to their doctor for this type of test often hope that they are not pregnant, and it is not impossible that these women took other steps to terminate their pregnancies.* *My purpose in writing is both to seek your advice on any further line of investigation which we might adopt, and to keep you informed of the fact that my Company is still actively pursuing the question of whether this preparation should be withdrawn from the market.'*
20th February 1969	*CSD/AR MH 171_64.* Page 77	Dr Inman writes that more work needs to be done, he feels that the number of congenital abnormalities in RCGP Study is too small to draw conclusions from. He agrees that Dr. Dean's view that the rate of abortions following HPT use is unlikely to be due to chance, then agrees that it may be that *'women may have interfered with their pregnancy in other ways'* including overdosing on Primodos. He completes his letter *'You say that your company is actively pursuing the question of whether or not Primodos should be withdrawn from the market. Personally my view is that the data you have so far are quite unhelpful in reaching this decision.'*.
5th March 1969	13198 (trans) page 12	Mr Cooke wrote to Dr. Pitchford. In his letter he said numbers of the RCGP study in themselves were 'not conclusive'. But there was a *'trend in the same direction'*, independent of Dr. Gal, which 'is alarming'. On 10 March Dr. Pitchford passed this report on to Dr. Lachnit.
10th March 1969	*CSD/AR MH 171_64.* Page 78-9	Letters from Dr Inman to Dr Laurence and to Professor Lowe, both dated 10 March 1969 stated that the CSD want to utilise any system already in place for the reporting of congenital abnormalities. Dr Inman would like to use their existing study infrastructure to look at two issues; cleft palate and a possible link to antiepileptic drugs and the use of antihistamines/amphetamines and limb deformities. Over the next few months, several letters are then exchanged between Dr Laurence and CSD, Dr Laurence was seeking

		study funding, which CSD do not have. Members of the CSD expressed doubts about the value of the study; the number of individuals being studied was thought too small to provide meaningful results. Funding was eventually secured.
29th April 1969	*CSD/AR MH 171_64.* Page 97	Dr Inman in a letter to Mr Pickard of St. George's hospital *'Our great difficulty is that congenital abnormalities are so rarely reported that we would not, in fact, be able to spot thalidomide should it be re-introduced to the market. The Committee are currently exploring various avenues by which they may prove the chances of early detection of a teratogen. We do not think that the random reporting system will help and we are hoping to develop a system for retrospective enquiry into the drug history of mothers who have borne abnormal children where such births have been notified to the Registrar General.'* This exemplifies the CSD awareness of limitations of the yellow card system and the exploration of new ways to study drugs taken during pregnancy in the context of congenital abnormalities.
30th June 1969	CSD/AR, MH 171_39 Pg. 167	**Safety of Hormone Pregnancy Tests in 'The Medical Letter'[41]** Draft for publication. See entry for August 1969 for reference to Dr Pitchford's analysis of this pre-publication copy of a Medical Letters on Drugs and Therapeutics article paper. The draft mentions preparations used. *Recent studies have raised questions about the safety to the foetus of the hormone pregnancy tests, and of estrogens and progestins when used in pregnancy to treat habitual or threatened abortion'* *'Dr. Carr (Centennial Programme, Dalhousie University faculty of medicine, Halifax, Nova Scotia, 1968) reported that 10 out of 26 (38.8 per cent) spontaneously aborted fetuses of women who became pregnant within six months after discontinuing oral contraceptives showed polyploid configurations (more than two full sets of homologous chromosomes). Only 11 polyploids (4.8 per cent) were found in a series of 227 abortuses from an unselected group which included almost no women who had taken oral contraceptives; the incidence in this unselected group is within the range reported by other investigators for unselected populations. All polyploid fetuses abort.'* *'Medical letter consultants believe that biological and immunologic tests for pregnancy should be used instead of*

[41] Therapeutic Information on Drugs, Med. Lett., 2, 87 (1969)

		hormone tests' The letter goes on to reference the available alternative tests, before concluding that *'recent studies of estrogen and progestin hormones used for diagnosis of pregnancy, or for habitual or threatened abortion indicate an urgent need for further investigation of their safety. Until their safety is established, the use of hormones for such purpose presents unnecessary risk'*
July 1969	CSD AR subcommittee meeting report *CSD/AR MH 171_64.* Page 277	CSD chairman prepares a report for the AR subcommittee meeting, addressing the issue of congenital abnormalities and drug use. Two recommendations are made. Firstly, that contact should be made with the MRC, epidemiological units and with the Directors of special surveys relating to congenital abnormalities (Dr Laurence's study in Cardiff, the RCGP survey in Birmingham and the research by Dr Smithells in Liverpool are specifically mentioned). Secondly that the system of recording the births of children with congenital anomalies to the Registrar General should be examined and improved, and such reports should be regularly communicated to the Adverse Reactions Sub-Committee.
17th July 1969	*CSD/AR MH 171_67. Page 10*	Dr Inman wrote to Dr Gal to inform her that the CSD were finalising the arrangements for the study with the Registrar General and that on the basis of her work they had included HPTs and spina bifida in the study. His letter concludes *'The reason for writing to you is that I wonder whether you have made any progress in the preparation of the major* [text appears to be missing] *which you talked about and on which you based a preliminary communication with 'Nature" in October 1967. I will be very pleased to hear from you.'*
22nd July 1969	LandesArchiv 13198 (trans) page 13	Schering UK wrote to Schering Germany and recommended removing the pregnancy testing indication. See also 17th February 1970 entry.
6th August 1969	*CSD/AR MH 171_64.* Page 122	Dr Inman went to see Dr Gal on 6 August 1969.
7th August 1969	*CSD/AR MH 171_64.* Page 122	In a letter to Dr Kuenssberg, President of RCGP Dr Inman refers to Dr Gal showing him data from the RCGP study *'…which tended to support this hypothesis and also some very disturbing correspondence with the manufacturers relating to teratogenicity studies in animals… I am going to attempt to obtain a complete animal teratogenicity data from the manufacturers of pregnancy diagnosis pills and it will be interesting to compare those with that I have already seen in Dr Gal's office.'*
7th & 8th	*CSD/AR MH*	Dr Inman wrote to Schering requesting teratogenicity data on progestogen and progestogen/estrogen combinations.

Annex B: HPT Timeline – Key Events

August 1969	*171_64.* Page 123	Dr Briggs replied on 8th August to say that the letter had been passed to Dr Pitchford who would get in touch in the near future.
21st August 1969	*CSD/AR MH 171_64.* Page 125	Dr Kuenssberg replied to the letter from Dr Inman dated 7th August 1969, enclosing the same preliminary results from the Dean Study that had first been seen by CSD over a year earlier in May 1968. Dr Kuenssberg states *'79 cases should not produce 3 congenital abnormalities however you look at it, except as part of a chance that the next 921 cases do not produce more than a few additional cases. Even though you cannot back a certainty here, you cannot afford to ignore the warning.'*
29th August 1969	*CSD/AR MH 171_64.* Page 126	In a letter to Dr. Kuenssberg with his view of the RCGP data, dated 29 August 1969, Dr Inman writes. *'Had all 3 of the 79 cases treated with 'Primodos' been spina bifidia, I would have been very much more worried. The main reason I felt that the present data do not throw much light on the Gal hypothesis, was that none of the 3 cases was of spina bifida. Her hypothesis depends, of course, on whether or not the patient was exposed to large doses of progesterone at the time that the neural tube is closing.* *If we assume that the 3 cases were the only abnormalities in these 79 babies, this is not very different form the overall reported incidence of congenital abnormalities. For example, from about 900,000 live births in England and Wales, about 20,000 congenital abnormalities are recorded by the R.G. each year. Two in every 90 births is not very different from 3 in 79. If we consider each of the diagnosis in turn, I would have expected about 1 cleft palate in every 400 births, 1 congenital dislocation in every 600 births and 1 mongol in every 1,200 births. Of course each of these is less frequent than the 1 in 79 that you have recorded, although I doubt if the statistician would regard the difference as significant.'*
August 1969	Roussel[42] CSD/AR, *MH 171_39* pages 167-169 and page 207-212	Dr Inman wrote to the HPT manufacturers asking for their laboratory testing results relating to these products. In response Dr Young at Roussel sent two papers, the Roussel survey[43] and preliminary results of the RCGP study[44]. Schering replied with animal test results, and Dr Pitchford's analysis of a pre-publication copy of a Medical Letters on Drugs and Therapeutics article paper dated August 1969.

[42] Roussel, *G.P Survey - An Investigation into the Effects of Oral Pregnancy Tests on the Incidence of C.N.S. Malformations.* . Unpublished, 1968.
[43] Roussel, *G.P Survey - An Investigation into the Effects of Oral Pregnancy Tests on the Incidence of C.N.S. Malformations.* . Unpublished, 1968.
[44]

		The CSD papers contain a pre-publication copy Safety of Hormone Pregnancy Tests dated 30 June 1969. This paper referenced the Gal et al 1967 paper, and did not contain any new research relating to hormone pregnancy tests and the association with congenital malformations. The animal test results were testing ANOVLAR (therapeutic dose: 4 mg norethisterone acetate + 0.05 mg ethinyloestradiol/70kg/day) on mice and rabbits. They found *'neither a dose 10 times nor 20 times (rabbits) or 100 times (mice) the therapeutic dose induces gross pathological malformations of the F_1 generation. As expected, the high dosages merely increase the resorption rate in both species of animal.'* This analysis of the Medical Letter draft paper was *'designed to present evidence other than that quoted in the Medical Letter which suggests that the conclusions drawn by Medical Letter can be disputed and may be entirely erroneous.'*. Dr Pitchford states the following about Gal et al 1967 *The two groups appear to be unmatched as the treated group contains twice as many mothers over 35 years as the control group; it is well known that older women are more likely to produce babies with congenital malformations.* *The usage of hormonal by tests by only 4% of the control group appears to be unrepresentative of the population as a whole. Sales figures between 1956 and 1966 show a total number of units sold to be 800,000 and births over the same period were 2,000,000. If pregnancy tests had been used in all pregnant women who continued to term, this would represent 40% usage; even assuming that a high proportion were applied in non-pregnant women or those who did not continue to term, it would seem doubtful if this would reduce the figure to the 4% level stated by Gal.* *Several of the women in Gal's treated group were unmarried mothers who had obtained their supplies of hormonal pregnancy tests illegally and taken much more than the prescribed dose. The reluctance of such women to admit to the self-administration of abortifacient drugs might have considerable bearing on their exposure to teratogens.* *The abnormalities described by Gal are due to defective fusion of the neural folds which occurs during the fourth week of gestation in the human. Her paper does not give details of the time at which hormonal pregnancy tests were applied in every case, but the average interval between*

		conception and the test is 5.6 weeks, i.e. too late in pregnancy to cause faults in fusion of the neural folds. *According to our statisticians, many other factors (not mentioned by either Gal or Medical Letter) can affect the validity of this type of retrospective study, viz:-* - *The time which has elapsed since the drug was taken.* - *The knowledge of the drug hypothesis on the part of the mother with the malformed child.* - *The difference in level of authority between the interviewer and respondent.* - *The interviewer's knowledge of the drug hypothesis.* - *The standardisation of interviewing technique.* - *The degree of emotional significance of the enquiry for the respondent. If several of these disturbing factors coincide, then considerable bias may appear in results.* *Evidence from other sources. Confidential information supplied by the Royal College of General Practitioners on the drug history of over 15,000 pregnant women failed to show any statistical significant increase of congenital abnormalities in children born to women who had received hormone pregnancy tests.*
3rd September 1969	CSD/AR MH171_39 page 58	In a letter to Dr. Inman, Dr. Young (Roussel) writes of information regarding Amenorone and Amenorone Forte in relation to neurological malformation of children whose mothers took the product. *'This information includes first a standard teratological study in rat and rabbit carried out by Arthur D. Little Research Institute in Musselburgh. As can be expected, this study was somewhat difficult to carry out in view of undeniable interference with ovum implantation in these animals which high doses of hormones inevitably induce. Nevertheless the results which we of course discussed at great length with Dr. Lister of A.D.L. seemed satisfactory in the circumstances.'* Reference is made to a GP study of 20 GP practices, covering 1,750 pregnancies, covering all oral pregnancy tests. Reference is also made to the RCGP study of 9,822 pregnancies. *'One common feature which immediately emerges is the somewhat higher incidence of abortion noted in the pregnancy test treated groups. This did not surprise us and stems, we believe, from the fact that this group is one which can be considered to be at risk in the sense that an early*

<table>
<tr><td></td><td></td><td>pregnancy test is often taken because of a desire to be sure of known pregnancy and there is of course no control at any other moment which may be taken within this group. Our results of course do not indicate whether the termination of pregnancy was due to natural causes, the pregnancy test itself or anything else. Nevertheless, the incidence of these abortions is still relatively low.'

Dr. Young concludes by stating 'that we ceased to promote Amenorone and Amenorone Forte in the United Kingdom several years ago and that we have now removed pregnancy test as an inducation. We have even requested MIMS to delete "Pregnancy test" and to merely give "Treatment of amenorrhoea" as the indication for these products'</td></tr>
<tr><td>7th November 1969</td><td>CSD/AR MH171_39 page 61</td><td>In a letter to Dr. Young (Roussel) Dr Inman writes ‘I shall shortly try and find time to read the two studies that were carried out by general practitioners. From what you say, however, these did not really produce any concrete results and it is somewhat difficult to summon up enough enthusiasm to place a high priority on this when so much other and possibly more important work is pressing.’</td></tr>
<tr><td>Late 1969</td><td>Schering/Roussel LandesArchiv 13198 page 9 and CSD/AR, MH 171_39 Page 59 and Annex 3 of EWG Report</td><td>Schering agreed in late 1969 that the distribution of free samples of HPTs would stop, the active advertising of Primodos as a pregnancy test would cease and the literature would be withdrawn.
In a letter from Similar action was taken by Roussel to Dr Inman dated 3 September 1969 it states that for ‘I am sure you will want to know that we ceased to promote Amenerone Forte and Amenerone Forte in the United Kingdom several years ago and that we have now removed pregnancy test as an indication.’. It seems that this position was adopted.
<table>
<tr><td></td><td>1966</td><td>1967</td><td>1968</td><td>Up to June 1969</td></tr>
<tr><td>Samples given out</td><td>25,539</td><td>2,379</td><td>150</td><td>36</td></tr>
</table>
</td></tr>
<tr><td>17th February 1970</td><td>Bayer written evidence</td><td>Dr Ruttle of the MacGregor committee wrote to Schering suggesting the deletion of the pregnancy testing indication. In this letter Dr. Ruttle writes. ‘The Committee would be prepared to place the product in A.3 if the promotional indication as a “pregnancy test” were withdrawn and I would suggest that the most appropriate and, acceptable to the Committee, promotion be “symptomatic treatment of amenorrhea to produce withdrawal bleeding”.</td></tr>
</table>

Annex B: HPT Timeline – Key Events

February 1970	MacGregor Committee	The MacGregor Committee published the 8th Edition of the PropList, a booklet that was sent out free of charge at intervals to prescribers. They did not send notifications about individual products (such as Dear Doctor letters) to prescribers. Amongst the HPTs, neither Primodos nor Pregornot are listed in the 8th edition. Those that were listed are: Amenerone Amenerone Forte Menstrogen Orasecron Norlestrin Norlutin-A Secrodyl
9th March 1970	Bayer evidence to IMMDS	Maxine Staniford responded to the MacGregor Committee's request to remove the pregnancy testing indication for HPTs, on behalf of Schering *'we agree to the deletion of "pregnancy test" from the indications, and to the promotional statement "the symptomatic treatment of amenorrhea not due to pregnancy, by producing withdrawal bleeding".*
27th April 1970	13227 Page 114	Schering report Protocol 1441 'ZK. No. 5.422(1) ZK No. 4.944 (II); I – Norethisterone acetate + II – 500 I + 1 II - Testing for embryotoxic effects in rats.' This report carried out experiments using the same ratio of I and II as was in Primodos. Impregnated female rats were administered daily from 6th to 15th day during pregnancy with; 0.0, 0.5 mg I plus 0.001 mg II / kg; or 5.0 mg I plus 0.01 mg II/kg. The summary noted *'Following application of 5.0 mg I plus 0.01 II / kg of the substances, the only substance-related effect amongst the mother animals was a reduced increase in body weight (Table 1). After the end of treatment, the increase in body weight was more pronounced.* *The aplasia of the tail found after application of 0.5 mg I plus 0.001 mg II/kg (Tab. 2) is known to us in the form of spontaneous malformation in untreated animals of the strain of rat used by us.* *No connection can be ruled out with certainty between the two abnormalities (subcutaneous oedema throughout the body, anophthalmia on both sides and malformation of the brain) found in group 3 (5.0 mg I plus 0.01 mg II / kg) and the application of the substance.'*
April 1970	Bayer evidence to IMMDS	The MacGregor Committee acknowledged the suggestions from Schering (removing the pregnancy test indication and altering promotional statements) and confirmed that Primodos would be placed in category A.3.

		The change in indication was agreed early in the year and the packaging and package inserts (datasheets) were subsequently amended. New package inserts were available by November 1970.
June 1970	MH 171/67 page 50	In June 1970 preliminary results from what would go on to become the Greenberg papers showed eight of the 87 babies with abnormalities had been exposed to hormones compared to two of the controls.
June 1970	MacGregor Committee	The MacGregor Committee published the Addition to the 8th Edition of the PropList. Amongst the HPTs, neither Primodos nor Pregornot are listed in the 8th edition. Those that were listed are: Amenerone Amenerone Forte Menstrogen Orasecron Norlestrin Norlutin-A Secrodyl
June 1970	CSD/AR *MH 171_65* Page 10	CSD Adverse Reactions Subcommittee received an update on the progress of the CSD/Registrar General's Office study. This covered 87 births with abnormalities born between March and May 1969 and with a matched control for each affected child (total 174 babies). The progress report states *'The numbers of cases studies are too small to test the various hypotheses for which the groups of abnormalities were selected in the first place.'* It goes on to discuss progestogens in more detail *'Eight of the proband* [affected children] *were positive against only two of the controls, but the excess was not concentrated in spina bifida.'*
August 1970	MIMS[45]	Primodos indication changed from '*secondary amenorrhea, early diagnosis of pregnancy*' to '*amenorrhea not due to pregnancy*'
October 1970	Crombie et al.[46]	**Teratogenic Drugs – R.C.G.P Survey** This paper studied approximately 10,000 women and had been discussed between RCGP and CSD the previous year. The published results display the observed figures with the expected numbers in brackets and state *'hormones an excess 30 (23.1) over expected numbers for a congenital abnormality outcome, but the only significant difference is observed with hormones after the ninth week – 12 (6.3). The*

[45] Monthly Index of Medical Specialties.

[46] Crombie, D.L., et al., *Teratogenic drugs--R.C.G.P. survey.* Br Med J, 1970. **4**(5728): p. 178-9.

		excess of hormone prescription in stillbirth outcomes 18 (8.3) is highly significant, becoming evident after the ninth week of pregnancy 8 (2.2), although the expected and observed numbers are very small for this period.' The paper goes on to state *'The effect of drugs on congenital abnormality outcome must be relatively insignificant and indirect since the total excess of prescription in those with a congenital abnormality outcome compared with all those who reach term is 6%. This excess is evenly distributed throughout the first 22 weeks of pregnancy, and no clustering of excess prescriptions is found in the first nine weeks. Any relationship between excess drug consumption and congenital abnormality outcome is indirect and possibly more directly related to the morbid condition for which the drugs were given.'*
November 1970	Gidley et al. 1970[47]	**Teratogenic and other effects produced in mice by norethynodrel and its 3-hydroxymetabolites.** *'Cranial retardation was produced in the offspring of CFl mice that were treated with norethynodrel [17u-ethynyl-estr-5(lO)-en-3-on-17p-ol] or its metabolites [17u-ethynyl-estr-5(10)-ene-3a,17p-diol and the corresponding 3&17p-diol] on days 8-10 of gestation. The most active agent was the 3p,17p-diol. Incomplete development of the parietal bones was observed in 64.1% of fetuses examined from mothers treated with 0.6 mg/kg of the 3p,17/5'-diol. Five percent of all fetuses in this treatment group had exencephaly. An anomaly resembling cryptorchidism occurred when the diols were administered on gestation days 11-13.'*
2nd January 1971	*Bretherton 1971[48]*	**Letter to Medical Journal of Australia.** Abstract: The onus for the fairly widespread use of hormone pregnancy preparations as pregnancy tests falls on the method of detailing used by drug companies. The detailing states that if the cause of a secondary amenorrhea is not pregnancy, then a menstrual period will be "triggered off"; however it also infers that if the cause is pregnancy, no ill effect will result. How could the drug company have possibly investigated the intrauterine contents of a pregnant woman to substantiate harmlessness? Practitioners who have used hormone pregnancy tests have experienced that a proportion of patients report that some bleeding per vaginam has resulted – "a stain", "some spotting", "a loss for a day or 2 but not as much as a period." In recent yearbooks, investigators have reported a higher percentages of

[47] Gidley, J.T., et al., *Teratogenic and other effects produced in mice by norethynodrel and its 3-hydroxymetabolites.* Teratology, 1970. **3**(4): p. 339-344.

[48] Bretherton, R.C., *The indiscriminate use of hormone pregnancy tests.* Med J Aust, 1971. **1**(1): p. 48.

		congenital abnormalities when there has been bleeding per vaginam during pregnancy, irrespective of the amount of blood loss. I obtained a consensus of opinion from practitioners who had experience in the therapeutic termination of pregnancy. They had all formed the impression that they had found a higher percentage of associated black intrauterine blood clots in cases who had previously been administered hormone pregnancy tests. Apart from the haemorrhagic detachment of the ovum from the uterine wall, teratogenic effects should also be considered; because of these, drug companies have advised that similar preparations such as anovulatory tablets be ceased if pregnancy is suspected. I would like to establish these points: 1) that no unnecessary drugs be prescribed to women with wanted pregnancies; 2) that in particular no drugs designed to trigger off uterine bleeding be prescribed to women with wanted pregnancies (if diagnostic tests are needed then harmless urine pregnancy tests should be used); 3) that reputable companies be enticed to cease detailing hormonal preparations as pregnancy tests.
3rd February 1971	13227 Page 134	Schering report Protocol 1443, dated 3 February 1971, was entitled 'ZK. No. 5.422(1) ZK No. 4.944 (II); I – Norethisterone acetate + II – 500 I + 1 II -Testing for embryotoxic effects in rabbits.' This report carried out experiments using the same ratio of I and II as was in Primodos. Impregnated female rabbits were administered daily from 6th to 18th day with; 0.0; 0.5 mg I plus 0.001 mg II / kg; or 5.0 mg I + 0.01 mg II/kg. The summary noted *'During application of 5.0 mg I plus 0.01 mg II / kg of the substances, a significant ($p < 0.0027$, Table 3) reduction in body weight increase amongst the mother animals was observed. On the 28th day p.c. no living foetuses were found in these mother animals but only resorptions without macroscopically detectable foetal residues. This finding shows that this dose was highly embryotoxic and resulted in the early death of the foetuses (resorptions without macroscopically detectable foetal residues)'* *'0.5 mg I plus 0.001 mg II/kg were tolerated without symptoms. The nature and frequency of occasional abnormalities that occurred after this dose (departure from normal ossification of the cranium) are known to us in the form of spontaneous malformations in untreated control animals of the strain of rabbit used by us Following the application of 0.1 and 1.0 mg/kg, no substance-induced changes set in. After 10.0 mg/kg, a significant increase ($P < 0.01$) in the rate of foetuses with skeletal abnormalities (predominantly delayed ossification) was discovered.'*

Annex B: HPT Timeline – Key Events

23rd February 1971	Bayer Evidence	Schering applied for a product licence of right for Primodos. The only recommended clinical use was listed as secondary amenorrhoea. The packaging leaflet section reads: '*Primodos is intended for the symptomatic treatment of secondary amenorrhoea of short duration not due to pregnancy, by the production of a withdrawal bleeding.'.* This application was granted, PLR No 0053/5027
1st March 1971	13226 page 52	ZK. No. 5,356 (I) ZK. No. 4,902 (II) (50 I + 3 II) I - progesterone + II - oestradiol benzoate Testing the effect on implantation in rats. Protocol No. 2121 *'From day 1 to day 6 p.c., 10 inseminated female rats were administered 10.0 mg / kg 1 + 0.6 mg / kg of II dissolved in castor oil + benzyl benzoate (6 + 4) s.c. The effect of the substances on implantation and on early embryonic development was assessed by examining dams and foetuses.* *After administration of 10.0 mg / kg 1 + 0.6 mg / kg of II, no implantation could be observed in any of the treated dams. In addition, no corpus luteum could be found in any of these animals. Consequently the substances administered to the dams led to the death of the embryos in the earliest stages of their development and / or prevented implantation altogether (see Table 1). According to this finding, the increase in body weight of the dams from day 0 to 13 was greatly reduced. However, a direct effect of the oestradiol benzoate on the increase in body weight of the treated dams, especially during the administration period, cannot be ruled out (see Table 1).'*
15th April 1971	Herbst et al.[49]	**Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women**
May 1971	*BN 116_12 at page 3*	The issue of congenital abnormalities was raised at the Committee for the Safety of Drugs Adverse Reactions subcommittee. The CSD/RGO study is still suspended at this point. The sub-committee was presented with paper (AR) (71) 17 Monitoring of Congenital Abnormalities. This paper discusses the pilot phase: *'This exercise demonstrated that a retrospective screening technique was practicable and also that the quality of most general practitioners' records was much higher than anticipated. The procedure was inexpensive and the analysis required very little effort on the part of the Headquarters medical staff. 500 to 1,000 similar investigations each would be well within the capabilities of the medical officers currently available for field work and the Committee may feel that this would*

[49] Herbst, A.L., H. Ulfelder, and D.C. Poskanzer, *Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women.* N Engl J Med, 1971. **284**(15): p. 878-81.

		provide a useful screening procedure for the detection of teratogens. In a sense it could be regarded as an extension of the early warning system and it is even possible that, once a potential hazard had been identified, the same technique might be employed for further "in depth" studies of a specific problem.'
1st September 1971		Effective date of the Medicines Act. This is the date from which the provisions of the Act were in force.
15th September 1971	MH 171_65 page 14 and *CSM/AR BN 116_14*	At the September meeting of the CSD Adverse Reactions Sub-committee the attention of the sub-committee was drawn to reports from the CSD Adverse Reactions Register of congenital abnormalities following in utero exposure to Oestrogen/Progesterone Mixtures. Follow up and further analysis of these reports was undertaken in preparation for the next subcommittee meeting.
15th October 1971	Laurence[50]	**Hormonal Pregnancy Tests and Neural Tube Malformations** A study focussing on neural tube malformations and potential links with HPT use. The study compared HPT use among 271 mothers of affected children and 323 mothers of healthy babies in three UK locations, found no statistically significant link, (ES = 1.26, CI 0.71, 2.22). Dr Laurence had collated his series results from Cardiff with series from Exeter and from London. The case and control selection used by Gal was commented upon by Laurence.
27th October 1971	CSM/AR 171_65 page 2	Dr Crombie, the lead author on the R.C.G.P paper sent the data on congenital abnormalities to Dr. Michael Linnett of CSD on 27 October 1971. In the letter he states *'I enclose as much information as we have at the moment on the relationship (really so far as we are concerned the non-relationship) of steroids in any form to malformed outcomes. The numbers are of course small but they suggest that if there is any relationship it must be a very weak one. The relationship between large doses of oestrogenic and progestergens is probably much stronger but I enclose a little bit of information about these as well.'*
November 1971	*CSM/AR BN 116_14.* Page 16 and Page 7	Item 5 on the agenda of the November meeting on the CSD Adverse Reactions was *'Congenital Abnormalities linked with the Use of Oestrogen/Progesterone Mixtures. (Paper CSM/AR/71/31 herewith).'*

[50] Laurence, M., et al., *Hormonal Pregnancy Tests and Neural Tube Malformations.* Nature, 1971. **233**: p. 495

CSM/AR/71/31 was a paper prepared by Dr Inman entitled Reports of Congenital Abnormalities linked with the use of Oestrogen-Progestogen Mixtures. In it he writes about reports to the CSD Adverse reactions register. Between 1965 to September 1971 there were 30 reports of congenital abnormalities following in utero exposure to oestrogen/progestogen mixtures, 11 of which were following HPT use: *'Dr Gal and colleagues (1967) reported a possible association between the use of hormonal pregnancy tests and the occurrence of spina bifida. Among the abnormalities reported to the Committee, only one of eleven was a case of spina bifida, and thus the reports to the Committee add no support to Dr. Gal's hypothesis.'*

Item 5 reads: *'Dr Inman reported that the conclusions drawn from an attempt to evaluate reports of congenitally abnormal infants who had been exposed to oestrogen/progesterone mixtures in utero were largely negative. The incidence of these abnormalities in infants so exposed was not abnormally high and those abnormalities which had occurred did not fall into any particular pattern. This evidence did not prove conclusively that there was no connection between congenital abnormalities and the administration of oestrogen/progesterone mixtures to pregnant women. Nevertheless having regard to the limited capacity of the professional secretariat to make special studies the Committee agree that this particular subject could now be set aside.*
The question of still-births was raised in the discussion. Dr Inman said that reports of still-births resulting from the administration of ovarian and pituitary hormones to pregnant women had however never been asked for and it was consequently more difficult still to draw conclusions about this as a possible reaction.'

Ref	Pregnancy test	Approximate time of test	Nature of abnormality	Notes
01141	Amenerone	6th week	Hemimelia, heart	1
01179	Primodos	8th week	Micromelia	2
01309	Amenerone	4th week	Absent fingers, one hand	
06023	Primodos	6th week	Fused labia	
06407	Primodos	During first trimester	4 missing fingers	
06461	Amenerone	? at 8th week	Complete absence of eyes	
07648	Primodos	6th week	S.B. multiple abnormalities	3
11240	Primodos	6th week	Heart	
13209	Amenerone	In 1st trimester	Hare-lip & cleft palate	
14543	Amenerone	6th week	Intestinal atresia	

<table>
<tr><td></td><td></td><td>
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<tr><td>24271</td><td>Primodos</td><td>“early pregnancy”</td><td>Anencephaly. Spina bifida</td><td>4</td></tr>
</table>
Notes.
1 Aspirin and Avomine during first 2 months.
2. Ancoloxin (possibly) at end of 2nd month.
3. Dramamine during 2nd month,
4 Ancoloxin during first trimester</td></tr>
<tr><td>1971</td><td>British National Formulary (BNF)</td><td>By 1971 the BNF list of drugs that were known or suspected teratogens had increased. Progestogens were still linked to virilization, no other malformation was listed. The <u>Genital System: Female Hormones</u> section contained a subsection entitled Combinations of Oestrogens and Progestogens, which ended ‘Combinations with a higher dose of progestogen, e.g. Primodos, should no longer be used in the early diagnosis of pregnancy as results are unreliable. They have been superseded by urine tests.’</td></tr>
<tr><td>1971</td><td>13195 pg 75</td><td>Recall of Primodos/Duogynon in Finland</td></tr>
<tr><td>19th January 1972</td><td>BN116_15</td><td>Drugs Taken During Pregnancy and Congenital Malformations

Presented by Prof. Lowe of the Welsh National School to the Committee for the Safety of Medicines on 19th January 1972 CSM/AR/72/4. The paper reviewed the available data and did not mention HPTs as a potential teratogen.</td></tr>
<tr><td>April 1972</td><td>Brotherton & Craft 1972[51]</td><td>A clinical and pathologic survey of 91 cases of spontaneous abortion

7.6% spontaneous abortion following the use of hormonal pregnancy tests</td></tr>
<tr><td>1972</td><td>Gal, I[52]</td><td>Hormonal Imbalance in Human Reproduction, in Advances in Teratology

The complete results of Gal’s HPT study were published in Advances in Teratology.

Writing of the possibility of HPTs being used as an abortifacient, Gal wrote:
‘Probably because of their menorrhagic property, the tablets are frequently used to induce abortion. Similar trends were noticed amongst our study cases, who were taking the pregnancy test tablets. In all but one of the 19 cases, the</td></tr>
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[51] Brotherton, J. and I.L. Craft, *A clinical and pathologic survey of 91 cases of spontaneous abortion.* Fertil Steril, 1972. **23**(4): p. 289-94

[52] Gal, I., *Hormonal Imbalance in Human Reproduction*, in *Advances in Teratology*. 1972.

		pregnancy was unwanted (these included 2 illegitimacies) and, of the 4 control cases, one was a contraceptive failure, and 3 were illegitimate pregnancies. Thorough investigations did not reveal any other attempts to terminate the pregnancy in the above cases.' This paper indicates that overdosing also occurred in the UK. Dr Gal states *'All the 23 mothers who took pregnancy test tablets received them without any prescription (supplied from medical samples – all confirmed) and two of them obtained a second dose from the chemist.'*
November 1972	Gal, I[53]	Gal published another letter in Nature. This letter drew on the research described in her 1967 letter. In her 1972 letter she writes *'The hormonal pregnancy test is used frequently because it is a simple diagnostic procedure and, according to the manufacturers' (Scherings) earlier description, it is safe because the hormones do not affect the course of pregnancy. However, Scherings no longer recommend 'Primodos' for diagnosis of pregnancy themselves.'*
24th November 1972	Laurence, K.M.[54]	**Reply to Gal** In the letter immediately following Gal's 1972 letter, Dr Lawrence points out three elements that raise doubt of the Gal findings. Firstly, the choice of controls by Gal. Interestingly Laurence does refer to her Advances in Teratology paper, pointing out that the *'self-same controls'* used in the HPT study were used in the Vitamin A study, where they produced a highly significant result, which all but disappeared when the controls were matched to the hospital where the affected baby was born. Secondly, the fact that his own study from three different locations had failed to replicate her findings. Thirdly, that there was thirty years of epidemiological data which did not support such an aetiology for neural tube defects. He concludes. *'It is therefore unlikely that either hormone pregnancy tests or Vitamin A deficiency play a significant part in the genesis of central nervous system malformations.'*
28th December 1972	13226 (trans) page 136	**Study 773. Testing of ZK. 4.944 (aethinyloestradiol) for embryotoxic effects on rabbits – preliminary tests.** A preliminary study to determine the appropriate dosage range for systematic testing of ZK. 4.944 for embryotoxicity in rabbits. *7 inseminated female rabbits, at 6 – 18 days p.c., were administered with a daily dose of either 0.0 or 0.1 mg/kg bw. of the test substance via a gastric feeding tube. The effect of*

[53] Gal, I., *Risks and benefits of the use of hormonal pregnancy test tablets.* Nature, 1972. **240**(5378): p. 241-2

[54] Laurence, K.M., *Reply to Gal.* Nature, 1972. **240**: p. 242.

		the substance administered on embryonic development was evaluated on the basis of examinations on the mother animals, and the fetuses. *After administration of 0.1mg/kg bw. of aethinyloestradiol, evidence of embryotoxic effects could be seen in all gestating test animals. However, the implantation conditions of the control mother animals, and the stereomicroscopic adspection of the fetuses of the control animals showed normal results.* *Only around half (26) of the 50 implanted fetuses from the mother animals administered with 0.1 mg/kg bw. of aethinyloestradiol were living fetuses on the 20th day p.c.. However, all of these fetuses showed clear signs of retardation when compared with fetuses from control animals. Anomalies cannot, however, be identified in these fetuses on macroscopic and/or stereomicroscopic examination.* *The remainder of the implanted fetuses from the mother animals administered with 0.1 mg/kg bw. of aethinyloestradiol consisted of resorptions with fetal remains (20), resorptions with no fetal remains (3), and one dead fetus*
30th January 1973	Nora & Nora[55]	**Birth Defects and Oral Contraceptives** Reported two statistically significant findings. Firstly, case studies on the use of progestogen-oestrogen mixes and VACTEL/DiGeorge Syndrome. Secondly a study linking hormone exposure and cardiac malformations. In the first element 12 babies were studied: 10 infants were affected by VACTEL (vertebral, anal, cardiac, tracheal, oesophageal, limb) and two were cases of DiGeorge Syndrome. Eight of these patients had been given hormones either as an HPT or mistakenly without realising that pregnancy existed. A statistically significant different is stated, but it is not clear what is being analysed. The numbers in the second study linking cardiac defects and hormone exposure are clearer. *'A retrospective study of 224 patients with congenital heart disease disclosed that 20 patients received progestogen-oestrogen at the vulnerable period of cardiogenesis compared with 4 of 262 controls ($p < 0.001$).'* Their studies combined women who were given HPTs and who took the contraceptive pill early in pregnancy, from this letter it was impossible to know who took HPTs. They conclude the paper *'Until these more definitive data are available it would be prudent to emphasise the need to document the absence of pregnancy before undertaking oral contraception and to reconsider the risk-benefit ratio of pregnancy testing with hormonal agents.'*

[55] Nora, J. and A. Nora, *BIRTH DEFECTS AND ORAL CONTRACEPTIVES.* The Lancet, 1973. **301**(7809): p. 941-942.

17th March 1973	Levy et al.[56]	**Hormone Treatment During Pregnancy and Congenital Heart Defects** A study on HPT use and cardiac anomalies. Levy et al 1973 looked specifically at transposition of the great vessels (TGV). They carried out a case control study on 76 mothers whose child had a transposition of the great vessels. These were matched with children who had a known chromosomal abnormality. Of the 76 mothers, ten had been given some form of hormone in early pregnancy (one of whom was given a hormone pregnancy test and six of whom given sex hormones for threatened abortion). When the paper was published the one woman who had received an HPT was grouped together with the six women who had been given hormones for threatened abortion. None of the mothers in the control group were given hormones during pregnancy. A statistically significant difference between the groups of p = 0.007 was reported. These numbers give an Odds Ratio of just over 16.51 and a 95% confidence interval of 0.93 to 294.46. The paper concludes *'Congenital heart defects are thought to be multifactorial in origin. Hormonal treatment during pregnancy may be a predisposing factor. We suggest that the effects of hormones on the developing fetus, especially oestrogens and progestational agents, should be further investigated.'* The highly statistically significant results in the Levy paper included women who were given hormones for threatened abortion. The association for the one woman who had received an HPT was not statistically significant (p = 0.50), with an effect size of 3.04 and confidence intervals of 0.12 to 75.81 (EWG Annex 27)[57].
21st March 1973 and 16th May 1973	CSM/AR BN116_17 page 9	The matter of Congenital abnormalities was raised at the CSM Adverse Reactions subcommittee meeting in March, and further discussed at their meeting in May 1973. The minutes from the latter meeting state at 3.8: *'Congenital Abnormality Study (Minute 4.2 of 73/2) Dr Inman tabled details of the first analysis of the results of the study. He said he was indebted to Dr Greenberg and Dr Lindsay, two of the "part-time medical officers", for their help in preparing the analysis. The results showed some potentially quite striking findings.* *The Chairman thought they were sufficiently important to warrant extension of the study to obtain results from larger*

[56] Levy, E., A. Cohen, and F.C. Fraser, *HORMONE TREATMENT DURING PREGNANCY AND CONGENITAL HEART DEFECTS.* The Lancet, 1973. **301**(7803): p. 611.

[57] Statistics summarised and presented as part of the EWG report. Expert Working Group on Hormone Pregnancy Test – Annexes to the report, Annex 27, p. 13, available at: https://mhra-gov.filecamp.com/s/wZS1hD90RgZwlbpX/fo/m9rnGIuUCRo6txXH/fi/mkoz8lu3PYKnc59C

		numbers. Professor Finney supported this view. He thought the results could be statistically significant; even if they were not sufficiently impressive to justify further intensive follow-ups of these cases.'
6th April 1973	Sever LE.[58]	**Hormonal pregnancy tests and spina bifida** A re-examination of the Gal 1972 data. The author concludes that since cases were meningomycele, exposure to a teratogenic agent needed to have taken place before closure of the neural tube at day 28 (week 4) of gestation. Gal states that the average time from conception to HPT was 5.6 weeks (39 days), from which Sever infers that a proportion of cases must have been exposed after the critical period of organogenesis.
17th April 1973	LandesArchive files 13226 page 112	These indicate that Schering had tested a compound, ZK 4.944 (17α-ethynyl-oestra-1,3,5(10)-triene-3,17-diol also known as Mestranol) as an emergency contraceptive.[59] Each Primodos tablet contained a total of 0.02 mg of ethinylestradiol and 10 mg of norethisterone acetate. The report on study ZK 4.944 on rats found a dose-dependent embryo-lethal effect at doses of 0.1 mg/kg and 0.3 mg/kg and could not rule out a teratogenic effect. At doses of 0.03 mg/kg no embryolethal or teratogenic effects were detected. The question of embryo-lethal and teratogenic effects of ZK 4.944 were not addressed any further as it was stated that ZK 4.944 was intended to be used for the emergency post-coital prevention of pregnancy.
May 1973	MH 171_67 page 52	Note Dr Inman to Dr Reid 'Monitoring of Congenital Abnormalities – Some New Developments' He reports on two groups; children with cleft palates and their matched controls; children with other abnormalities and their controls. *'Because of the shortage of medical staff, the trial has only been going at about half speed nevertheless I have already accumulated data on more than 130 abnormal babies together with comparable controls.*' *'In both groups there is an apparent excess of use of hormonal pregnancy tests. This supports the suspicion that we already had when we designed the study, though our original suspicions were based on an alleged increase in the incidence of spina bifida and hydrocephalus in babies exposed to large doses of hormones during the first or second month of pregnancy.*

[58] Sever, L.E., *Hormonal Pregnancy Tests and Spina Bifida.* Nature, 1973. **242**: p. 410.

[59] Mestranol is a pro-drug which converts to ethinylestradiol (one of the components of Primodos) in the body.

		One other finding of interest is in the lower part of the first table. It would appear that the mothers of more control babies had received "other drugs" than the mothers of babies with abnormalities. A preliminary analysis of this situation, which I have not tabulated separately, suggests that there may be a deficit of use of iron and folic acid during early pregnancy in the mothers of abnormal babies.'
16th June 1973	Kaufman [60]	**Birth defects and oral contraceptives** Case report of a patient with VACTERL syndrome, who had been exposed to DES and progesterone in the first trimester. Did not relate to HPTs specifically.
4th July 1973	Janerich et al.[61]	**Hormones and limb-reduction deformities** Study reporting results from an ongoing study of limb reductions and oral contraception practices of the mothers. 76 children affected by limb reductions were compared with 76 controls, exposure to hormones in utero was compared. Among the affected children four had been exposed to in utero hormones due to pill failure compared to just one pill failure in the control group. All of the affected children in the exposed group had a non-identical twin who was not affected, this was noted in the paper as given an unusually high rate of twinning. This letter did not mention hormone pregnancy tests. This letter appears to be preliminary results which were published in full in their 1974 publication.
4th August 1973	Oakley et al.[62]	**Hormonal pregnancy tests and congenital malformations** Study looking at HPT use and several different malformation types. Women who had given birth to a child with a congenital malformation or chromosomal abnormality were surveyed. These included various types of neural tube defects; cleft lip and cleft palate; various digestive system and abdominal wall defects; limb reductions; and multiple malformations. Children with chromosomal abnormalities were used as controls. Their survey included a question on whether their pregnancy had been diagnosed using an HPT. Of the 433 women who answered the HPT question, 46 (10.6%) had received such a test in the first trimester. Oakley et al reported an association between HPT use and neural tube defects, which did not reach statistical

[60] Kaufman, R.L., *Birth defects and oral contraceptives.* Lancet, 1973. **1**(7816): p. 1396.
[61] Janerich, D.T., J.M. Piper, and D.M. Glebatis, *Hormones and limb-reduction deformities.* Lancet, 1973. **2**(7820): p. 96-7
[62] Oakley, G.P., Jr., J.W. Flynt, Jr., and A. Falek, *Hormonal pregnancy tests and congenital malformations.* Lancet, 1973. **2**(7823): p. 256-7

		significance. This study could be further broken down into conditions which had occurred after HPT use, spina bifida which was statistically significant and anencephaly which was not. In their article Oakley et al state: *'Gal et al suggested that such tests cause neural-tube defects. Laurence et al however, found no difference in history of in-utero exposure to the tests between 271 cases of anencephaly and spina bifida and 3232 normal controls. The findings in our large group of neural-tube defects support the latter findings and leave little reason, now, to think that hormonal pregnancy tests cause neural-tube malformations.'* Later in the article, they write *'These data show no definite evidence for the teratogenicity of hormonal pregnancy tests. One should not, however, conclude that our study proves that the test are not teratogenic. To show that the tests do not cause defects is difficult and requires studies different from the one we did. Because of questions recently raised about the safety of the tests and in the absence of appropriate studies convincingly demonstrating the safety of the tests, physicians should be careful in the use of the agents"*
27th August 1973	13226 (trans) pg 156	Schering report ZK No. 4944 Aethinyloestradiol 'Investigating embryotoxic effects on rabbits' *'Each of 13, 14 or 15 inseminated female rabbits at 6 to 18 days p.c., were administered 0.01, 0.03 or 0.1mg/kg bw of the test substance p.o. via gastric feeding tube as a microcrystal suspension. Fourteen control animals received a solvent substance during the same time period, and in equal volumes. The effect of the substance administered on embryonic development was evaluated on the basis of examinations on the mothers and the fetuses.* *After concluding the trial on the animals, and after evaluation of the fetal material, the results of the trial could be compiled as following:* *1.The quantity of substance of 0.01mg/kg bw. could be seen to be slightly embryotoxic, as 21.9% of all implanted embryos (9.3% in the control group) died, and on the day when resection was carried out, these were found as resorptions without fetal remains in the majority. Of the living fetus material that could be extracted, however, evidence for teratogenic effects for this quantity of test substance administered could not be found.* *2. The administration of 0.03mg/kg bw. of the test substance has a clear embryotoxic effect. Around 1/3 (33.6%) of all implanted embryos died due to administration of the substance. On resection day, these were found in the main as resorptions without fetal remains. The examination of extracted fetuses showed that no teratogenic effect could be observed even after administration of 0.03mg/kg bw. of the substance.*

		3. The administration of 0.1mg/kg bw. of the substance has extremely severe embryotoxic effects. 53.2% of all implanted embryos died and on resection day were found in the main as resorptions without fetal remains. Evidence for teratogenic effects for the quantity of substance of 0.1mg/kg bw. could not be found.'
10th October 1973	FDA Federal Register	FDA give notice over Medroxyprogesterone acetate; norethindrone; norethindrone acetate; progesterone; dydrogesterone; and hydroxyprogesterone. It states *'In addition, data have become available which suggest a possible association of prenatal hormonal treatment of mothers with congenital heart defects in the offspring. The Food and Drug Administration reviewed available material and has presented the problem to its Obstetrics and Gynecology Advisory Committee. On the basis of these questions of safety raised by inferential evidence supporting the existence of an association between the administration of progestins during early pregnancy and the occurrence of congenital malformations. The potential risk of teratogenic effects is considered high enough to warrant removal of pregnancy-related indications from the labelling of progestins currently marketed for systemic use. Those indications, some of which were evaluated as effective, and others, as probably or possibly effective for the drugs listed above, are:* *1. Presumptive test for pregnancy;* *2. Treatment of threatened and habitual abortion; and* *3. Treatment of any abnormalities of pregnancy including pregnancy complicating diabetes.'*
1974	13195 pg 75	Recall of Primodos/Duogynon in Korea
1974	Robertson-Rintoul[63]	**Letter: Oral contraception: potential hazards of hormone therapy during pregnancy** Robertson-Rintoul published a letter describing five Australian case studies where either HPTs or oral contraceptives were used during early pregnancy. Primodos was used in two cases, in one the infant had a congenital heart lesion and the second baby had an unspecified skeletal defect. The two cases of pill failures where the developing embryo was exposed to Minovlar resulted in a congenital heart lesion and exomphalos. Exomphalos is a weakness of the baby's abdominal wall where the umbilical cord joins it. This weakness allows the abdominal contents, mainly the bowel and the liver to protrude outside the

[63] Robertson-Rintoul, J., *Letter: Oral contraception: potential hazards of hormone therapy during pregnancy.* Lancet, 1974. **2**(7879): p. 515-6.

		abdominal cavity where they are contained in a loose sac that surrounds the umbilical cord. A fifth child was exposed to hormones in unspecified utero and was described as normal.
8th June 1974	Mulvihill et al 1974[64]	**Letter: Congenital heart defects and prenatal sex hormones** In a letter in the Lancet they describe how they retrospectively examined medical records. The affected group consisted of 88 children with conotruncal defects[65] under the age of five who were seen at the Children's Cardiac Centre, John Hopkins Hospital between January 1968 to April 1973. The affected group included children with the following conotruncal defects: 63 transposition of the great vessels (TGV), 19 single ventricle and 6 corrected transpositions. Two control groups were selected from the children seen at the Cardiac Centre, children with ventricular septal defect and children with normal hearts (usually referred for a functional murmur). Each group consisted of 30 female children and 58 male children. There were 4 affected children (all TGV) who had been exposed to sex hormones in the first trimester, compared to 3 exposed children in each of the control groups. The authors conclude *'These results, obtained retrospectively, fail to support the suggested association between transposition complexes and prenatal exposure to sex hormone. Rather, they point to the need for further studies of different design.'*
15th June 1974	David and O'Callaghan[66]	**Letter: Birth defects and oral hormone preparations** In a letter to the Lancet they described their retrospective audit of patients with oesophagael atresia (live births and stillbirths) born in Devon Somerset, Bristol and Gloucestershire between 1956-1972. This was then compared to the sales of HPTs and oral contraceptives. Their hypothesis was *'If exogenous sex hormones were a major or exclusive cause of the VACTEL association, we would expect to find (a) few cases before the widespread introduction of oral hormone preparations, (b) a steady increase in cases in parallel with the increasing use of oral contraceptives, and (c) a decrease in cases after the cessation of promotion of pregnancy-test tablets in 1969'* . They reported that there was no linear trend and that their

[64] Mulvihill, J.J., C.G. Mulvihill, and C.A. Neill, *Letter: Congenital heart defects and prenatal sex hormones.* Lancet, 1974. **1**(7867): p. 1168

[65] congenital cardiac outflow tract anomalies

[66] David, T.J. and S.E. O' Callaghan, *BIRTH DEFECTS AND ORAL HORMONE PREPARATIONS.* The Lancet, 1974. **303**(7868): p. 1236.

		data did not support the suggestion that oral contraceptives or oral hormone pregnancy-test tablets cause oesophageal atresia alone or as part of the VACTEL association
3rd October 1974	Nora & Nora[67]	**Can the Pill Cause Birth Defects?** Editorial in which the authors describe the potential link between progestogen/estrogen and a constellation of developmental anomalies known as VACTERL. They appraise retrospective studies as a means to better understand this link before concluding that it is prudent to discontinue the use of hormonal pregnancy tests. They add that is also prudent to emphasise the need to demonstrate the absence of pregnancy before oral-contraceptive therapy is initiated.
3rd October 1974	Janerich et al[68]	**Oral contraceptives and congenital limb-reduction defects** This paper compared the drug histories of 108 children with limb reductions and 108 normal controls. Hormone exposure for these groups was compared, this included HPTs, pregnancies that occurred while taking oral contraceptives and cases where hormones were used as a supportive measure to prevent threatened abortion. Retrospective telephone interviews were carried out. The paper reported that 15 of the mothers of malformed children had received hormones compared to just 4 of the control mothers, this gave highly significant difference in hormone use between cases and controls. (p = 0.02). All of affected children who had been exposed to hormones were male, which let the authors to suggest a sex-specific effect of the developing fetus. When the three mothers who were exposed to HPTs were analysed the result is not statistically significant, with an effect estimate of 3.06 and confidence intervals of 0.24 to 161.94. (EWG Annex 27)[69]
20th November 1974	CSM/AR BN116_19 Page 17 and MH 171_6 pg 1	The CSM Adverse reactions sub-committee met and discussed the Maternal Drug Histories study. It was decided that this would be raised at the CSM meeting a week later. Papers were prepared on this topic by Dr Inman, CSM/AR/74/48(A) and CSM/AR/74/48(B).

[67] Nora, J.J. and A.H. Nora, *Can the Pill Cause Birth Defects?* New England Journal of Medicine, 1974. **291**(14): p. 731-732.

[68] Janerich, D.T., J.M. Piper, and D.M. Glebatis, *Oral Contraceptives and Congenital Limb-Reduction Defects.* New England Journal of Medicine, 1974. **291**(14): p. 697-700

[69] Expert Working Group on Hormone Pregnancy Test – Annexes to the report, Annex 27, available at: https://mhra-gov.filecamp.com/s/wZS1hD90RgZwlbpX/fo/m9rnGIuUCRo6txXH/fi/mkoz8lu3PYKnc59C

		Paper A is a synopsis and paper B is the preliminary analysis. He concludes paper A *'If this finding is confirmed the actual number of babies who may have been affected by the hormonal pregnancy test could be quite large. The control data suggests that about 5% of fetuses are exposed to the test. This would be equivalent to about 40,000 exposures per annum. If the test is associated with a two- or threefold increase in the risk of an abnormality, the removal of the test might effect a substantial reduction in the number of abnormal babies born in the United Kingdom. Since alternative pregnancy tests are available and other published evidence supports the same hypothesis the Committee may wish to consider whether or not the manufacturers of hormonal pregnancy tests should be put in the picture at this stage of the study. Most of the products on the market are used for other purposes both by pregnant and non-pregnant women, and if the Committee agree that action should be considered, it could take the form of a discrete withdrawal of one indication for the use of these drugs rather than a recommendation that the product licences should be withdrawn absolutely.'* The second paper, paper B outlines the results from the study. 136 affected babies were studies and 149 controls were matched. 23 affected babies had been exposed to a hormone pregnancy test, compared to 9 controls. This gives a statistically significant difference. The paper describes the affected children who had been exposed to HPTs *'This group included two mongols one of whose patients had normal karyotypes. In the other the mother had an XXX chromosome content. The third patient was a male child who allegedly had a bilateral inguinal herniae at birth but who one week later was found to be entirely normal. If these three children are removed the difference between the cases and controls remains significant at the 5% level. Eleven of the 23 babies (48%) had anencephaly, spina bifida or hydrocephalus, often in addition to other abnormalities and this proportion was identical to the proportion in babies with these abnormalities in the whole group of 149 patients.'*
28th November 1974	CSM BN116_5 Page 5	The minutes from the CSM meeting record that Recommendations from the Adverse Reactions Sub-Committee were made. The first of the recommendations related to the Maternal drug histories in babies with congenital abnormality. The relevant minutes read *'A study into the maternal drug history of babies with congenital abnormality had been in progress since 1968. On the basis of the information which had been assessed to date it appeared that hormonal pregnancy tests might carry a*

		teratogenic hazard. For this reason an interim report had been prepared by the Secretariat. The Sub Committee considered that the preliminary results of the study should be completed in the shortest possible time, and if the interim fears proved valid, the results should be published. They did not feel, however, that the publication of the preliminary findings was justified, although they thought that an approach might be made to the manufacturers, of whom there were only a small number, with a view to inviting them to consider voluntarily deleting this indication for these products. The Committee endorsed the views of the Sub-Committee as regards completion of the study but considered that in view of the possibility of leakage of information, combined with the advice that the study ought to be completed within six months, no approach should be made to the manufacturers at this stage.' See entry below (Schering memo 22nd January 1975) which documents contact from Dr Inman (CSD) with Dr Esche of Schering regarding malformation concerns.
30th November 1974	BMJ Editorial[70]	**Synthetic Sex Hormones and Infants** The evidence on hormone exposure and congenital malformations was reviewed. The focus is mainly on oral contraceptives, but the authors do state. *'However, in each instance where sex steroids are used the risk-benefit ratio should be critically assessed. As others have stressed, there is little justification for the continued use of withdrawal-type pregnancy tests when alternative methods are available.'*
11th January 1975	Brogan, W.F.[71]	**Letter: Cleft lip and palate and pregnancy tests** A retrospective case study of 222 cases of cleft lip/palate, designed to investigate maternal histories during the first trimester and parental histories prior to conception. 10% received oral or parenteral HPTs between the 5th-8th week of gestation.
15th January 1975	CSM/AR BN116_19 Page 17	The position adopted by the main Committee was discussed by the Adverse Reactions sub-committee at their January meeting. The minutes note at 3.5(i) *'Members were advised that the Main Committee had endorsed the Sub-Committee's view as regards completion of the study but had considered that in view of the possibility of leakage of information, combined with the advice that the study ought to be completed within six months, no approach should be made to the manufacturers of hormonal pregnancy tests at this stage.'* It is clear that there was a difference of opinion

[70] *Editorial: Synthetic sex hormones and infants.* Br Med J, 1974. **4**(5943): p. 485-6

[71] Brogan, W.F., *Letter: Cleft lip and palate and pregnancy tests.* Med J Aust, 1975. **1**(2): p. 44.

		between the main CSM and the Adverse Reactions Sub-Committee as later in the minutes at 4.6 it is noted *'The Sub-Committee were advised of the progress made in this study, which it was hoped would be completed by May. Members expressed concern that the Main Committee had decided not to approach the manufacturers of hormonal pregnancy kits at this stage (Minute 3.5 refers), and were concerned that criticism could be levelled against the Committee if they failed to give early warning of an apparent hazard merely to enable a study to be prepared for publication.* *They therefore endorsed the recommendation made at the last meeting that an early approach should be made to these manufacturers in order than they might be forewarned in case they wished to take any actions.'* Note: We are aware of other highly relevant information in the LandesArchiv related to conversations between Dr Inman and Schering at this time, which we cannot refer to due to legal privilege. Another issued raised at this meeting was the effectiveness of warning letters sent by manufacturers and by the Committee. Minute 5 Practolol – effectiveness of warning letters (CSM/AR/75/3) notes *'The results of a small survey that had been carried out by the Secretariat were presented. The survey had attempted to check the validity of the claim by ICI Limited that their two letters on adverse reactions to practolol had reached at least 80% of doctors.* *Members noted that the results indicated that only about half of the ICI letters had reached practitioners and the apparent preference of the profession in favour of receiving information about adverse reactions from the Committee.* *It was suggested that a similar survey should be carried out following the issue of another Adverse Reactions leaflet, although the proposed practolol leaflet should not be selected since wide publicity has already been given to the practolol problem.'*
January 1975	13222 Page 29	Contact was made with Schering and was recorded in a Schering memo from 22 January. *'After a phone conversation with Mr Dr Esche, Mr Behrmann would like to inform you that: In addition to the news from Australia:* *Dr Esche has informed us that Dr Pitchford from England has heard from Mr Inman of the Committee on Drug Safety, that hormonal combinations for pregnancy diagnosis are considered to lead to an increased rate of malformations. The quote is thought to be 5:1 in favour of non-applications of these preparations. Thus, DUOGYNON will not be used for pregnancy testing in England any longer. DUOGYNON Ampoules are not available in England.'*

22 January 1975	13198 page 15 (translation)	Memorandum from Amon with a Summary of Primodos (dated 23/09/1975) *On the 22nd of January 1975, Dr. Pitchford wrote a confidential letter to H. Dr. Meiler and informed him that he had been called by Dr. Inman. Over the last five years, drug monitoring in pregnant women had shown, that those who had taken a hormonal test are at a relative risk of 5:1 to have miscarried child. The investigation has not yet been completed, but it is to be expected that a corresponding publication will be published within the next six months. In order to avoid unnecessary attention, the unofficial way had been chosen and the concerned manufacturers had already been informed so that they could already take action to prevent medicolegal problems.'*
30th January 1975	Nora & Nora[72]	**A syndrome of multiple congenital anomalies associated with teratogenic exposure.** A paper on VACTERL anomalies (vertebra, Anal, Cardiac, Tracheoesophagael, Renal and Limb) and exposure to hormones in utero. 19 VACTERL patients were matched against two control groups, the first group had chromosomal abnormalities other than Down Syndrome, the second group had functional heart murmurs. In the affected group 13 out of 19 had been exposed to hormones in utero (9 to HPTs). This was statistically significantly different from two hormone exposures out of 15 in the chromosomal abnormalities group ($p < 0.025$) and three hormone exposures in 30 in the controls with functional murmurs ($p<0.005$). The two index cases were excluded from the statistical analysis. One index case had a history of recurrent abortion, so would have been excluded on that basis, but it is not clear why the other index case was excluded. The VACTREL frequency Nora and Nora observed was also found to be statistically significantly different to the Denver and Atlanta populations (both $p < 0.001$). when calculated the effect size was statistically significant at13.5 with confidence intervals of 2.28 to 94.33.
January-March 1975	FDA Drug Bulletin	**Warning On Use Of Sex Hormones In Pregnancy** The FDA provided a warning that *'estrogenic and progestational hormones should not be used in early pregnancy for any purpose. Such use of these sex hormones may seriously damage the fetus (congenital anomalies, including heart and limb reduction defects)'*

[72] Nora, A.H. and J.J. Nora, *A syndrome of multiple congenital anomalies associated with teratogenic exposure.* Archives of Environmental Health, 1975. **30**(1): p. 17-21

		'FDA and its Ob-Gyn Advisory Committee have concluded that the potential risk of teratogenicity also precludes use of those as diagnostic test for pregnancy' The bulletin continues: *'Other satisfactory tests are available. Moreover, if pregnancy is suspected in a patient receiving oral contraceptives, these should be discontinued immediately. Obviously, every effort should be made to assure that a woman is not pregnant before prescribing sex hormones for any purpose.'* The above requirements for the patient labelling were set out in the Federal Register of 29 September 1976 (41 FR 43117)
11th February 1975	Federal Register, Vol. 40, No. 29 Page 6383	**Combination Drug Containing Norethindrone Acetate and Ethinyl Estradiol – Notice of Withdrawal of Approval of New Drug Application** Notice of withdrawal of approval for Gestest tablets, containing norethindrone acetate and ethinyl estradiol, following evaluation of reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group. The Commissioner of Food and Drugs *'concluded that, although the drug is effective as a presumptive test for pregnancy, there is a lack of proof of safety for that use in view of the potential danger in the presence of pregnancy and the availability of a number of very accurate chemical tests to detect pregnancy. The holder of the new drug application has waived Its opportunity for a hearing, and no other interested person has requested a hearing. Therefore, approval of the new drug application is now being withdrawn'*
11th February 1975	WHO	WHO Inter-Governmental Drug Information Circulars on the subject of hormonal pregnancy tests No .144 (11 Feb 1975)
27th February 1975	CSM BN116_6 page 12-13	The main CSM committee met *'Professor Cranston reported that the Sub-Committee on Adverse Reactions had felt some concern that no action had been taken on the interim report on their study into the maternal drug history of babies with congenital abnormality. The report had demonstrated that hormonal pregnancy tests may carry teratogenic hazards and he felt that an interim warning on the basis of the preliminary findings should be given to the profession with a leaflet in the Adverse Reactions series if the final report justified it.* *In the light of this and of the further information in the paper, the Committee agreed that a letter should be send to one of*

		the medical journals. The text should be approved by the Sub Committee on Adverse Reactions and copies should be sent to members so that they could comment.'
1st March 1975	Jaffe et al[73]	**Letter: Incidence of congenital limb-reduction deformities** A letter in the Lancet. This describes a case series of limb reductions seen at Northwick Park Hospital between 1972 to 1975. Of the seven babies described two had been exposed to hormones in pregnancy, one repeated testing with an HPT, the other to support threatened miscarriage. Both of these children were girls which the authors point out casts doubt on Janerich's sex specific theory.
3rd March 1975	13222 Page 48	Dr Pitchford of Schering Chemicals Ltd wrote to Dr Esche of Schering AG stating the following. *'According to the letter from Dr Inman, Committee of Safety of Medicines, it is only a matter of time until a publication appears that claims a relationship between malformations and hormonal pregnancy tests. If this happens, many publications with similar content will follow.* *Mr Pitchford did already voice concerns regarding PRIMODOS Oral (DUOGYNON Oral) in a letter to Mr Friebel in 1969.* *The decision of the sales department to only comply with requirements from the Authority is not approved by Dr Pitchford. He has pointed out that there will be a publication in autumn in which oral pregnancy tests will be condemned. Therefore, the Committee of Safety of Medicines has decided to warn the producers in advance and to recommend to name 'pregnancy' as a contraindication for oral pregnancy tests. Dr Pitchford has asked if the decision of the sales department means that we want to wait until the publication appears and we then will be forced to draw consequences, or if we prefer to follow already the recommendations of the Committee of Safety of Medicines. As far as England is concerned, he would recommend the latter.'* Note: We are aware of other highly relevant information in the LandesArchiv see statement on page 1.
19th March 1975	CSM & CSM/AR BN116_19 page 10.	A draft (dated 17 March 1975) of the Greenberg et al 1975 letter was circulated to the Adverse Reactions subcommittee for approval. At their meeting the Adverse Reactions Sub-Committee discussed the letter and submitted it to the Main

[73] Jaffe, P., et al., *Letter: Incidence of congenital limb-reduction deformities.* Lancet, 1975. **1**(7905): p. 526-7

		CSM. It was subsequently approved for publication by the Main CSM
22nd March 1975	Harlap et al[74]	**Letter: Birth defects and oestrogens and progesterones in pregnancy** This letter reported the Jerusalem Perinatal Study, a prospective survey of mothers undertaken between 1966-1968. 11,468 babies were born to women who had been interviewed. Harlap et al reported that 432 babies (3.8%) were born after definite or probably administration of oestrogens or progesterones. 47 had one of more major or minor malformation – a rate of 108.8 per 1000, compared with 77.6 per 1000 babies with no history of exposure to hormones ($p<0.02$). Of these, 21 of the babies who were born after definite or probable hormone exposure had one or more major congenital abnormality – a rate of 48.6 per 1000, compared with 38.6 per 1000 births for the non-exposed babies. This gave a risk of major malformations that was about 26% higher in the group exposed or probably exposed to hormones and an increase of 33% for minor malformations. The effect estimate and confidence intervals for the 21 babies show a trend towards an association between hormone use and all major congenital malformations, but are not statistically significant. The effect estimate is 1.26 and CI of 0.82 to 1.92. However, these figures are not specific for HPTs, when HPTs are specifically referred to the article acknowledges a potential confounding factor *'9 mothers who had taken the pill or had had hormonal pregnancy tests produced babies without malformations, all of whom survived the first year of life. The mothers of 29 babies had taken drugs to induce abortion, and it is assumed that in the majority of cases these also were hormonal pregnancy tests, since there is a popular supposition amongst Jerusalem women, exploited by gynaecologists, that such tests are abortifacient.'*
6th April 1975	WHO	WHO Inter-Governmental Drug Information Circulars on the subject of hormonal pregnancy tests No. 150
10th April 1975	*13227* (trans) page 1	Schering received a report on ZK No. 4.94 (17α-ethinyl-estra-1.3.5 (10) – triene-3.17-diol or ethinylestradiol) entitled 'Test for embryotoxic effect in rabbits'. Skeletal malformations were seen in all groups, including controls. The authors wrote that the rate of malformations in the treatment groups did not deviate from the norm. The report summary stated *'From the 6th to 18th day p.c., 12 or 14*

[74] Harlap, S., R. Prywes, and A.M. Davies, *Letter: Birth defects and oestrogens and progesterones in pregnancy.* Lancet, 1975. **1**(7908): p. 682-3

		inseminated female rabbits were administered the substance in the form of a microcrystalline suspension at doses of 0.001; 0.003 or 0.01 mg/kg body weight via a tube, p.o. During this same period, 12 control animals were given the same volumes of carrier fluid. The effect of the substance applied on embryonic development was assessed on the basis of tests conducted on the mother animals and foetuses. *On completion of the animal experiments and following evaluation of the foetuses, the test results can be summarised as follows:* *Following application of 0.001, 0.003 or 0.01 mg/kg body weight of the substance to the mother animals, no findings were obtained, either from the latter or from the foetuses that deviated from the norm and were attributable to administration of the substance. In particular, no embryotoxic effect of the substance quantities could be detected.'*
26th April 1975	Greenberg et al[75]	**Letter: Hormonal pregnancy tests and congenital malformations** Greenberg et al published a letter in BMJ containing preliminary results from the CSM/OPCS study (the Registrar General's Office had been renamed to the Office of Populations Censuses and Surveys). This letter reported on the births of malformed children in England and Wales between 1971 and 1972 notified to the OPCS. *'At present we can make only a preliminary report of our findings in relation to maternal exposure to withdrawal-type hormonal pregnancy tests consisting of a short course of treatment with a mixture of a progestogen and an oestrogen. Pregnancy is usually confirmed if bleeding does not occur after the test.* *The findings are shown in the table. A total of 23 mothers of abnormal babies had been exposed during the first trimester of pregnancy to drugs containing hormones compared with only eight of the control mothers. One of the 23 had also taken an oral contraceptive and tablets of norethisterone. The use of iron and folic acid and of other drugs in the first three months of pregnancy was approximately the same in the case and control groups.'* The letter ends *'This evidence supports the recommendation given in your article that '"There is little justification for the continued use of withdrawal-type pregnancy tests when alternative methods are available."'*

[75] Greenberg, G., et al., *Letter: Hormonal pregnancy tests and congenital malformations.* Br Med J, 1975. **2**(5964): p. 191-2.

21st May 1975	*CSM/AR BN116_19* page 4.	The publication of the Greenberg et al letter was noted in the minutes of the Adverse Reactions subcommittee meeting. Also discussed at this meeting were Recommendations for the Main Committee. These included Hormonal Pregnancy tests. The minutes of the Adverse Reactions Sub-Committee meeting of 21 May 1975 note the following under Any Other Business at 13.1 *'Dr Harris explained that a number of other drug regulatory authorities including FDA, Ireland and Australia had issued papers on the hazards which may be associated with hormonal pregnancy tests and an article had been published in "Nature" in 1967 and the Chairman of the Main Committee had been approached by a representative of the Sunday Times who wanted to know what action the Committee on Safety of Medicines had taken in this matter. Sir Eric was concerned about possible legal implications in that if there were an association known to the Committee then there may be a legal obligation to warn physician as soon as possible. The Department's legal advisor thought that this was a matter which could cause difficulty in the future.* *Sir Eric's view was that the Committee was reluctant to publish a warning before full information was available, but the action of the other drug regulatory authorities may put them into the position of having to do so.* *The Sub-Committee agreed to the suggestion that a leaflet in the Adverse Reactions Series should be published, but emphasized that it should be made clear that the Committee were unable to give a final decision and that the leaflet should avoid telling prescribers what to do.* *The Committee agreed to a draft leaflet.'*
25th May 1975	*Sunday Times*[76]	A Sunday Times article by the campaigning journalist Oliver Gillie on appeared under the headline 'These drugs can deform babies but mothers are not warned'.
29th May 1975	*CSM Bn116_6*	The CSM meeting minutes record at 13.1 *'The Sub-Committee were aware that a number of other drug regulatory authorities had issued papers drawing attention to the hazards which may be associated with hormonal pregnancy tests; that an article had been published in "Nature" in 1967 on the same subject and that a representative of the Sunday Times was enquiring what action the Committee on Safety of Medicines were taking in the matter. There was a suggestion that the Committee may have a legal obligation to advise the medical profession of hazards as soon as they knew about them. The preliminary results of the Committee's case-control study had been*

[76] Gillie, O., *These Drugs Can Deform Babies but Mothers Are Not Warned*, in *The Sunday Times*. 25 May 1976.

		published in the BMJ of 26 April. Although they would have preferred to wait for the completion of the study, they felt that it was necessary, in view of the action by other drug regulatory authorities and of the public's concern, to issue a statement without delay. They recommended therefore that a leaflet in the Adverse Reactions Series be issued, and has prepared a draft for this purpose. The Committee agree to this course of action (see Item 14 below).' Item 14 of these minutes reads as follows *'Since the meeting of the Sub-Committee on Adverse Reactions an article had been published in the Sunday Times, which drew attention to the possibility of congenital deformities appearing in the children of mothers who had had pregnancy diagnosed by this method. This had stimulated a considerable amount of press interest and in the light of this a further revision of the draft warning notice had been prepared in consultation with the Chairman. A copy of this was put before the Committee for its approval, an issue of a letter along these lines was agreed. The Committee also advised the Health Departments that measures should be taken to ensure that this indication is no longer included in licences for such products and to require the insertion in all promotional literature of a warning about this possible hazard in pregnancy.'*
5th June 1975	CSM[77]	CSM publish 'Hormonal Pregnancy Tests: A possible association with congenital abnormalities' The press release states *'The Committee of Safety of Medicines have sent to all doctors in the United Kingdom a letter informing them of a possible association between hormonal pregnancy tests and an increased incidence of congenital abnormalities. They recommend that, in view of the possible hazard, doctors should not normally prescribe certain hormonal preparations for pregnancy tests.'* It goes on to state *'The Committee have already published an early warning letter in the British Medical Journal. As further evidence accumulated they felt it right that all doctors should be made aware, at this state, of the Committee's provisional conclusions, particularly as other means of diagnosing pregnancy are available. They emphasise that these are preliminary conclusions. The outcome of the study will be made known when it is completed later this year.'* The letter reiterates the above points and goes on to state *'As the data began to accumulate it was felt advisable to inform the companies known to be concerned and it was ascertained either that they had ceased to promote the products for this use, or that the product had been removed from the market. With this*

[77] CSM Adverse Reaction Series No 13

		further evidence of this possible hazard, the Committee have advised the Health Departments that measures should be taken to ensure that this indication is not included in licences for such products and to require the insertion in all promotional literature of a warning about this possible hazard in pregnancy.'
5th June 1975 – July 1975	*Bayer evidence*	Dr Bye the Medical Director of Schering Chemicals limited wrote to the editor of the Monthly Index of Medical Specialties (MIMS) asking for the following addition to the Primodos entry *'Contraindication – Pregnancy'*. A chain for correspondence followed, and in which the editor at MIMS stated that in view of the indication to specifically exclude pregnancy the addition of the contraindication was unnecessary. Schering pushed back and in a letter of 26 June 1975 Dr Pitchford writes *'You may not be aware of the recent events concerning products like Primodos, which were formerly used for pregnancy testing, but which we have for several years not recommended for that purpose. The Committee on Safety of Medicines has recently started that because there is a suspicion that they can cause foetal abnormalities, such products should not be used as pregnancy tests, and because it is well known that very many doctors are continuing to do so we feel that we should take all reasonable steps to deter them. We agree that the contraindication in pregnancy is implicit in the stated uses of Primodos, but since such an implicit statement in our own literature previously has failed to stop the use of Primodos as a pregnancy test, it seems that it should be made explicit in MIMS as elsewhere.'* The conclusion of these discussions was that the indication that appeared in MIMS would be *'Secondary Amenorrhea of short duration, where pregnancy has been excluded.'*
30th June 1975	*MH 171_67page 28*	Dr Gal wrote to Sir Eric Scowen. She outlines her previous research, and the fact that she has not been able to obtain funding, despite asking CSM for help, and is *'practically without a post and have no opportunity to pursue my research interest.'* She concludes *'As the Committee of Safety of Medicine, jointly with the Office of Population Census, are conducting large scale studies into the problem to which I have drawn their attention, and is still of my interest (Greenberg et al, BMJ. ii. 19. 1975, Adverse reaction Series 13 1975), I would like to ask you whether there would be any chance of utilising my experience in the above field.'*
30th June 1975	*MH 171_67* page 29	Dr Gal wrote to Dr Inman raising several issues. Firstly '*I am somewhat surprised that the Committee, instead of recognising my contribution to the problem in their preliminary warning (Greenberg et al, BMJ. ii, 19.1975) and*

		in the warning notice (Adverse reaction Series No.13, 1975) stated in the official press communique that the preliminary findings have emerged from a wider study which is being undertaken by the Committee to detect any relationship between congenital abnormalities and the use of drugs during pregnancy (Information from the DHSS Press Officer).' Dr Gal then outlines the letters from CDS stating she had a prima facie case, that her work should be published to raise awareness in the profession and the further supportive correspondence and meetings with Dr Inman. Her letter goes on *'Considering all the above, you may understand my disappointment that I learn from your article in the BMJ that the Committee on Safety of Medicines itself is conducting a study into this problem, and their preliminary finding substantiated my original suggestion. Although it is a well known fact that in medical and industrial circles my name is closely associated with the hormonal pregnancy test, I first learned from the BBC that a warning notice had been issued when they wanted to interview me in connection with this matter.* *It is even more disheartening that the Department of Health turned down the request to support my fundamental human studies into the teratological safety of exogenous sex hormone preparations, in 1972, which was then interrupted in its well advanced stage. In addition, the Committee on Safety of Medicine itself declined to give moral support for my research which otherwise could have enabled Dr Kuenssberg to allocate a grant from the Royal College of General Practitioners Research Fund in 1973. Apparently at the time the Members of the Committee were already well aware of the importance of the problem which I had intended to pursue further (Greenberg et al, BMJ. ii, 19.1975).'*
8th July 1975.	*MH 171_67* Page 33/34	Dr Inman replied to Dr Gal. His letter starts. *'Thank you very much for your letter of 30th June. I have had you on my conscience for some time, I believe you did attempt to contact me on the telephone a while ago. I had intended to write rather than telephone because I am becoming increasingly deaf and find it particularly difficult to hear female voices on the telephone.'* He goes on to state *'The Committee does not normally give any bibliography in its brief pamphlets. Of course, when we come to write up this study in detail, we will give due recognition to your most important discovery of 1967.'* The letter then states that Dr Gal's work was not cited as the CSM study had not found a relationship between HPTs and spina bifida, and continues *'Although the Committee did not regard your original results as proving the case I can assure you that your findings were extremely valuable to me when launching a case-control study.'* The letter goes on *'Our study has aimed at obtaining*

		the whole maternal drug-history (with the exception of non-prescribed medicines) and, when we started, no one suspected that hormonal pregnancy tests would show us so early in the study. We have been informed that none of the manufacturers was promoting these mixtures as pregnancy tests and only comparatively recently discovered that some doctors were persisting in using them. Because of this we published a preliminary communication, although our scientific instincts were against this. The Committee felt that we had a duty to publish this warning even though the case was not proven.'.
14th July 1975	*MH 171_ 67* page 35-36	In her reply Dr Gal discusses Dr Inman's letter of 8 July. *'There is a considerable difference between discovery and confirmation or refutation of other workers' findings. Therefore I feel my contribution to the concept of the teratological effect of hormonal pregnancy tests deserves a different recognition from the authors referred to in the BMJ leading article. As my priority concerning the observation has been reiterated in your last letter, it is hard to understand the Committee's mis-leading statement on this matter. In my opinion the presentation of the Committee's past involvements with the Companies concerned also deserves criticism.'* The letter continues that she has always reported on congenital abnormalities rather than just on spina bifida. She then writes *'The statement in your present letter, "although the Committee did not regard your original results as proving the case" differs considerably from the sentiment expressed in your earlier letter of 23rd June 1967: "First of all I have no doubts that you have produced prima facie evidence that these fetal abnormalities may be drug induced".'* She then discusses the appropriate matching of controls and the differing approaches taken in Dr Gal's and the CSD's study. The penultimate paragraph of this letter reads *'The recognition of my contribution to science by the Authorities would not be such an issue if it would not be accompanied by many other problems. It seems it would be just about time that the DHSS officially recognized the clinical significance of my discovery. Could you advise me regarding this matter, or perhaps you would like to act on my behalf?'*
22nd July 1975		WHO Inter-Governmental Drug Information Circulars on the subject of hormonal pregnancy tests No 155 (22 July 1975)
4th August 1975	*MH 171_ 67* Page 39	Dr Gal wrote to Sir Eric Scowen, [*this seems to be in response to an earlier letter that is not in the National Archives file*], in which Sir Eric wrote *'After consultation with a number of outside experts, they felt you had not provided any proof for your hypothesis'* Dr Gal disputes this on several grounds, including *'The only significance of these*

		"expert opinions" is now that they have affected the Committee's judgment; hence the importance of my findings is only now appreciated after 8 years delay.' She writes *'By down playing the significance of the original observation (as attempted in yours and in Dr. Inman's letters, and as stated in the official press communique and in the article in the "Sunday Times" on 8th June) the Committee's responsibility is not averted from allowing the 8 years use of an un-necessary diagnostic test table, whose serious irreversible adverse effects were well known to them. It is also of interest that the warning on the hormonal pregnancy test was introduced earlier in the United States, Australia and Ireland than here, despite the fact that the concept originated in this country, and the Committee was in the favourable position of having first-hand knowledge of it in 1967. Although the Committee's own study confirmed my observation (BMJ. 28 Apr.1975), active steps were only taken on 5th June, due to pressure of the public press ("Sunday Times" 25 May).* *I believe it is unfortunate that a Committee, which was originally set up because of the thalidomide tragedy, did not respond more readily to a report concerning another teratogen.'*
5th August 1975	*MH 171_67* Page 45.	Dr Gal wrote to Professor Reid expressing her dissatisfaction with the Committee on the Safety of Medicine's handling of the hormone pregnancy test issue.
7th August 1975	*MH 171_67* page 44	Dr Reid writes to Dr Inman stating that he is unclear what Dr Gal is seeking, that it may be any or all of: greater attention should have been paid to her 1967 publication; official recognition in the Greenberg et al 1975; that she should have been given research funding by the Department; that she wants to be involved in further work.
15th August 1975	MH 171/67 *Page 50-51*	Dr Inman prepared an internal document entitled 'Background to and Summary of Files relating to Dr. Isabel Gal, Hormonal Pregnancy Tests and Congenital Abnormalities' This document refers to concern first being raised by V. H. Edwards (1958, B.J. Prev. Soc. Med. 12, 3) who remarked that HPTs provided the *'type of insult which is likely to cause foetal malformations and would often be administered at a stage of pregnancy when it might initiate malformations of the central nervous system'* He references the Smithells 1964 paper before detailing *'the Gal episdode'*. He details various pertinent correspondence, as well as the Gal 1967 paper and correspondence with Gal since then.

		Dr Inman details his pilot study based on OPCS notifications of *'abnormal babies'* and matched controls. *'Eight of the 87 abnormal babies had been exposed to progestogens (mostly hormonal pregnancy tests) compared with 2 controls'* He carries on to write that *'at this stage there was a suggestion that Dr. Gal might be correct but the matter was by no means settled'*
19th August 1975	*MH 171_ 67* page 46-8	Dr Inman prepared a memo to Prof. Reid about HPT issue. '*As you have suggested it is not easy to understand all the grounds for Dr. Gal's complaints. Clearly she feels aggrieved that nobody has come forward to support her continued work on the biochemical aspects of teratology, and she feels that the Committee has brushed aside the results of her study on hormonal pregnancy tests. I do not understand her allegation that the Committee failed to respect confidences; the draft of her publication was shown only to Committee members prior to publication and her results were not leaked. Dr. Gal was not the first worker to investigate the teratogenicity of these tests. We gave careful consideration to her work and I personally went to a lot of trouble on her behalf (I note that the file contains 14 letters addressed to her from myself and I met with her on three separate occasions for prolonged discussions).* *The Department would be vulnerable if Dr. Gal launched an attack on the Committee by drawing attention to the eight years that elapsed from the time she published her observations to the time we were in a position to publish a preliminary communication based on our own work. She is aware that the pilot stage of our study commenced in 1969 and it must be obvious to her, from the small number of cases assembled in our preliminary communication, that progress has been extremely slow. It may not have escaped her notice that, if the relative risk suggested by our publication turned out to be true, a large number of congenitally abnormal babies have been born as a result of hormonal pregnancy tests carried out after publication of her paper.* *I would certainly be happy to see Dr. Gal and I may be the person most likely to succeed in placating her, although I can make no promise on this score.'* Dr Inman also attached a summary entitled <u>Hormonal Pregnancy Tests & Congenital Abnormalities: Dr Isabel Gal</u> in which he wrote a brief history of events including, a description of the CDS/OPCS study *'Various difficulties precluded the enlargement of the study until 1972. In May 1973 I minuted you on our progress at that time (copy attached). You will note that there was still an apparent*

		excess of use of hormonal pregnancy tests by the mothers of affected babies and that we also had some suspicion that the benzodiazepine tranquilizers might be teratogenic.'
27th August 1975	*MH 171_67* Page 43	Sir Eric Scowen wrote to Dr Gal *'I would, however, like to comment on one important statement made in your letter, namely that the Committee's own study has confirmed your observation regarding the possible relationship between foetal damage and the use of hormonal pregnancy tests. I would like to emphasize that the Committee do not regard their findings as being firm and that when additional cases are analysed it is still possible that the final result will differ from the preliminary ones. Even if the preliminary results are confirmed by later studies, it may still be impossible to be sure if the circumstances of these tests, rather than the tests themselves, are responsible.'*
4th September 1975	*MH 171_67*	Professor Reid replied to Dr Gal's letter of 5 August 1975 suggesting she met with Dr Inman to resolve this matter. Dr Inman also wrote to Dr Gal and a meeting was arranged for Tuesday 7 October 1975. [78]
September 1975	Birmingham study[79]	**Morbidity and Drugs in Pregnancy: The Influence of Illness and Drugs on the Aetiology of Congenital Malformations** RCGP Birmingham study. This was released in September 1975 and consisted of women who were pregnant in 1964. The abstract states that *'In a prospective study involving 9,000 pregnant women, no cause-and-effect relationships have been established between morbidity recorded or drugs taken during early pregnancy and subsequent congenital malformations… …It is also very unlikely that any drug in common use in 1964 had even a minor influence on congenital malformations recognizable in the first six weeks of life.'* Sex hormones, including HPTs, are classed in the 'non-corticosteroid hormones' category. There is no specific discussion of HPTs or sex hormones in this paper, just the general statements mentioned earlier.
4th October 1975	*MH 171_67* page 70	Dr Gal replied to Sir Eric Scowen raising several points. Firstly in relation to the Commission's view that findings were not firm *'While I fully appreciate the scientific value of such analysis, I am reluctant to accept that the result of a*

[78] The dates on this appear slightly confused, the 7th October 1975 fell on a Tuesday, one letter refers to Tuesday 6th, a memo refers to the meeting as on 9th October.

[79] The Birmingham Research Unit of the Royal College of General, P., *Morbidity and drugs in pregnancy: The influence of illness and drugs on the aetiology of congenital malformations.* The Journal of the Royal College of General Practitioners, 1975. **25**(158): p. 631-645.

		statistical analysis can provide "hard-evidence" in human teratology. In the available evidences the statistics have served already useful pointers to the clinical importance of the problem.' She goes on to state that she has discussed the potential reasons for conflicting studies with Dr Inman, and that in her view independent studies revealing similar trends are more important than whether or not statistical significance is reached and she recalls a lecture given by Sir Eric to the British Association. Her letter then focusses on the value of her biological research that lack of funding has hampered *'The problem of cause and effect relationship between the test and congenital malformations has been thoroughly discussed with Dr. Inman in 1967 when Professor Jeffcoate raised this question in his comments on the hormonal pregnancy test. You may note from my publications that the data were analysed accordingly. In spite of this, I believe the conventional methods used in epidemiological type of studies are not quite appropriate for the investigation of a problem of such complexity. It seems that fundamental biological investigations would help to understand more about the problem than repetition of similar types of epidemiological studies. Realising this, I have conducted a preliminary fundamental study into the teratological effect of exogenous sex hormone preparations. Unfortunately all my efforts have failed to gain further financial support for this very important project, since 1972 (including my request to the MRC and to the DHSS).'* Her letter then continues *'The final outcome of your study (whether affirmative or otherwise will not alter the general principal regarding the use of drugs in early pregnancy. Drugs used for in-vivo pregnancy testing are good illustrative examples for Dr Austin Flint's words of "Don't use a drug if you don't have to", which you recalled in the above lecture. Therefore, it is not understandable why your Committee did not ban the use of hormonal pregnancy tests at the time when their attention was originally called to its adverse effect. While the members of the Committee were searching for their own evidence (although meanwhile, in the ensuing eight years, many additional evidences were available), women were exposed to this unnecessary harm. At the recent European Teratological Society Meeting (Freudenstadt, Sept. 1975) I have not only experienced international recognition of the problem, but also observed the surprise of many scientists on your Committee's attitude and their delay in taking action concerning this matter.'* She then goes on to ask for the three WHO Inter-Governmental Drug Information Circulars.
7th Octob	*MH 171_67*	Dr Inman met with Dr Gal.

er 1975[80]		
13th October	*MH 171_67* Page 73	Dr Inman wrote to Dr Gal. He references their previous meeting, describes the difficulties he sees in attempting to get research funding for a project that involves the deliberate exposure of the human foetus in utero to various drugs, and advises her to omit that part of her proposal. The letter continues *'The question of your future work is, I believe, quite a separate issue from your feelings about the apparent failure of various people to recognize your work and this in turn is a separate matter from the question of the 8-year gap between your publication and ours. The answer to the latter, is, quite simply, that the facilities for a more rapid assessment of the problem simply were not available.'* He concludes *'I think the most significant outcome of our meeting earlier last week was that we succeeded in parting as friends and colleagues. I am very sympathetic to your difficulties and I think you are now more sympathetic to mine. I will certainly help in any way I can, but I am sure you appreciate the difficulties and that you will not expect too much from any efforts I may make on your behalf.'*
15th October 1975	MH 171_67 page 74	In a memo of this meeting for Dr. Harris, Sir Richard Doll and Sir Eric Scowen, Dr Inman writes *'I spent an exhausting three hours with Dr. Isabel Gal on Tuesday, 9th October and probably my only significant achievement was to part company on reasonably friendly terms. Much of the time was spent trying to disentangle a sizable collection of bones of contention.'* He describes how Dr Gal believes her work as a teratologist has not been recognized and how from 1967 onwards *'…since other published evidence also tended to support her hypothesis, she believes that the Committee and the Department should have been more sympathetic in supporting her application to continue her work and she blames the Committee and the Department for the fact that her application to the Medical Research Council was turned down.'* He then discusses the ethical issues raised in her research proposal, which suggested exposing women who were booked in for abortion to various drugs and then examining the aborted fetuses to look for teratogenicity. He continues *'she feels she has strong grounds for attacking the Committee about the eight-year gap between her paper and the appearance of the preliminary communication in the British Medical Journal based on the Committee's study. She feels she should have been given an opportunity to discuss our results with her before publication, and that the letter in the BMJ should*

[80] The dates on this appear slightly confused, the 7th October 1975 fell on a Tuesday, one letter refers to Tuesday 6th, a memo refers to the meeting as on 9th October.

		have acknowledged her personally as the discoverer of the teratogenic potential of hormonal pregnancy tests, that the Committee probably would not have initiated the study had she not first drawn attention to the hazard and that a large number of abnormal babies may have been born during the eight years that have elapsed. Most of these criticisms had been answered in early correspondence with her, but of course we are defenceless in the matter of the eight-year delay. *I think, though I am not certain, that I convinced her that it would be a tactical mistake on her part to use this major criticism as a means of putting pressure on the Committee or the Department to add support to any further grant application. I also advised her in her own interests, and have since confirmed this in writing to her, that in my view it would be inadvisable to pursue the idea of conducting direct toxicity studies on the human foetus and I did undertake, with some reluctance, to help her to the extent of passing her revised application to the appropriate people if she sent it to me.* *Isabel Gal is an intelligent, dedicated but rather sad little person. I dealt with her sympathetically to the best of my ability, but I do not believe that we have heard the last of this matter.'*
November 1975	MH 171_67	A series of correspondence between Dr Gal and Dr Inman on her research proposal that she was about to submit to DHSS. Dr Inman offers advice and details what he feels would be improvements.
1st December 1975	MH 171_67 page 100	Dr Inman wrote to Dr Kay at RCGP on Dr Gal's behalf. He included her research proposal and wrote *'It occurred to me that there might be a considerable overlap between the kind of work you are doing and the sort of project she has in mind. I have been trying to help her to write a proposal for transmission to the DHSS and I enclose a copy of her first effort in confidence. As you can see it is obviously far too ambitious and comprehensive, and also somewhat disorganized. On another piece of paper you will find my suggestions as to how her programme might be rearranged in a more logical order depending upon the facilities available.* *Apart from putting her in touch with various people there is little more I can do to help her. I advised her that she should get in touch with you initially as the person most likely to be in a position to offer advice.'*
1975	13195 pg 75	Recall of Primodos/Duogynon in Japan, Sri-Lanka, Sweden, New Zealand

January 1976

Kullander and Kallen [81]

A prospective study of drugs and pregnancy

Kullander and Kallen published a prospective study of 6,376 pregnancies. They looked specifically at Primodos use, and studied the outcomes of 156 women given Primodos in the second month of gestation. They found the outcomes detailed in the table below. In the paragraph on Primodos they write. *'It is obvious that the group of induced abortions containing unwanted pregnancies, shows a high incidence of Primodos usage (χ^2 = 12.9 at 1d.f. p<0.01). In the group of future miscarriages, a slightly increased incidence is also seen – this agrees with the high frequency of unwanted pregnancies in this group, probably hiding a number of induced abortions (cf. 9).'* Later in the article they write about the Primodos cohort *'…the number of infants with major malformations in general was not increased in this group. The figures do not exclude a teratogenic effect of such hormone preparations but they give no support to it.'* In a section about the effect of gestagens they write *'A weak correlation can be found between the use of sex steroids and the birth of malformed infants without any cause-and-effect existing. Gestagens were, in the present study, prescribed more offed if bleeding had occurred early during the present pregnancy, or if previous reproductive failure had occurred, than if no such complicating factor existed. Both of these problems are associated with the birth of more malformed infants than normal.'*

Pregnancy outcome	No. of women	Number using Primodos	% using Primodos
Miscarriage	448	15	3.3
Induced abortion	154	13	8.4
Total Live Births	**5753**	**128**	**2.2**
Normal infant	4910	107	2.2
Dead infant	92	1	-
Major abnormality	194	4	2.1
Minor abnormality	551	16	2.9

[81] Kullander, S. and B. Kallen, *A prospective study of drugs and pregnancy.1. Psychopharmaca 3. Hormones.* Acta Obstet Gynecol Scand, 1976. **55**(3): p. 221-4

		Kullander & Kallen 1976 Summaries of pregnancies where Primodos was used in the second month of amenorrhea as a pregnancy diagnosis test
14th January 1976	*BN 116_21* page 28	At the CSM Adverse Reactions Sub-Committee meeting the Maternal Drug histories study was discussed. *'For the benefit of new members, the Chairman explained that this study had been commenced about seven years ago and much material had been collected. Preliminary analysis had produced certain suspisions but the Sub-Committee had decided that it would be unwise to draw definite conclusions until all the data were examined. The Sub-Committee had therefore resisted making any preliminary reports except those concerning the hormonal pregnancy tests where their preliminary results appeared to confirm published work.'* *'Difficulties were still being experienced in obtaining certain data from OPCS computer and consequently it had not been possible to prepare a paper for the meeting. However, although progress was slow, it was thought that it may be possible to prepare a paper for the next meeting. During the discussion members' attention was drawn to a recent article by Professor Illingworth which warned that many preparations including aspirin and iron could prove to be dangerous when taken in pregnancy. The Secretariat were asked to include with their paper copies of this article and copies of other recent relevant articles.'*
1st March 1976	*BN 116_21* page 20	At the CSM Adverse Reactions Sub-Committee meeting the Maternal Drug histories study was discussed at minute 9. *'Dr Inman in introducing the paper stated that the distribution of abnormalities in the study did not represent the distribution in the general population of abnormal births. Some minor abnormalities had been excluded and there might possibly have been some slight geographical bias. He added that the results of the study, so far, showed there were four classes of drugs for which use by cases exceeded use by controls to an important extent: these were hormonal pregnancy tests, benzodiazepines, antibiotics and barbiturates. Discussion centred on the methods of selection of the cases and control babies; the possible sources of bias in the selection, and the doubtful accuracy of the general practitioners' record. Doubts were voiced about patients' compliance in taking the drugs prescribed. The possible importance of use of over the counter drugs, for which no information had been collected, was also discussed.'* *'The Sub-Committee agreed that the study was important and that the paper should be published. Professor Finney*

		undertook to assist the authors when preparing the work for publication.' *'Suggestions included basing a future study on ante-clinics. Reference was also made to the work the Royal College of General Practitioners had done in developing a monitoring system of drugs used in pregnancy and to a paper prepared for the Sub-Committee by Professor Lowe, both of which provided useful information about this particular aspect of monitoring. It was agreed that Professor Vere and Dr Meade should help in drawing up plans on which further studies could be based.'*
1st March 1976	13193 (German) p41	Licence to import Duogynon withdrawn in Australia as the Australian Drug Evaluation Committee was of the opinion that the products were still being used as a pregnancy test; withdrawn at a wholesaler level requested 16 December 1976 for the same reason. An unsuccessful appeal was made by Schering in 1977.
12th July 1976	LandesArchiv *13227* Page 72	Schering report 2300 entitled 'ZK. No. 5.422;Testing for embryotoxic effects on rabbits following intragastral administration from the 6th – 18th day post coitum.' This report assumed a human daily dose of approx. 0.08 mg/kg in humans based on the use of the ANOVLAR® oral contraceptive pill. These experiments tested 0.1, 1.0 and 10.0 mg/kg approximately 1-, 10- and 100 times the human dose. The summary noted *'After 0.1 mg/kg, a slight (29%) and after 1.0 mg/kg a large (71%) increase in the resorption rate occurred. After 10.0 mg/kg a resorption rate of 100% was observed.'* The final conclusions stated *'In rabbits, ZK.5.422 results in increasing, dose-dependent embryo-lethal effects from 0.1 mg/kg upwards. . . After the only partially embryo-lethal doses (0.1 and 1.0 mg/kg) there were no indications that the substance had any teratogenic effect.'*
22nd July 1976		The Congenital Disabilities (Civil Liability) Act 1976 became effective on 22 July 1976. This Act created a clear legal mechanism for a child born disabled due to negligent treatment of the mother during pregnancy to bring a civil action for damages. It was prospective and did not apply to children would had been born before this date.
14th August 1976	Hellstrom et al 1976[82]	**Prenatal sex-hormone exposure and congenital limb-reduction defects** In a letter in the Lancet Hellstrom reported a Swedish study on limb reductions and in utero sex hormone exposure.

[82] Hellström, B., et al., *PRENATAL SEX-HORMONE EXPOSURE AND CONGENITAL LIMB-REDUCTION DEFECTS.* The Lancet, 1976. **308**(7981): p. 372-373.

		They carried out a retrospective analysis of 32 children with limb reductions and compared them to 30 children with spina bifida as a control group. In the limb reduction group three boys had an HPT, four children (three girls, one boy) had been given hormones to support a pregnancy. In the spina bifida group one boy had been exposed to an HPT. They concluded *'This study is too small to be conclusive but the figures point in the same direction as those of Janerich et al. Further studies are urgently needed, the suspicion that hormonal pregnancy tests can be teratogenic makes it prudent to discontinue the use of these tests. This decision has been made by the medical authorities in Sweden.'*
23rd August 1976	13227 Page 50	Schering report 2330 entitled 'ZK. No. 5.422; norethisterone acetate -Testing for embryotoxic effects on rats following intragastral administration from the 6th – 15th day post coitum.' This report assumed a human daily dose of approx. 0.08 mg/kg in humans based on the use of the ANOVLAR® oral contraceptive pill. These experiments tested 0.1, 1.0 and 10.0 mg/kg approximately 1-, 10- and 100 times the human dose. The summary noted *'Following the application of 0.1 and 1.0 mg/kg, no substance-induced changes set in. After 10.0 mg/kg, a significant increase ($P < 0.01$) in the rate of foetuses with skeletal abnormalities (predominantly delayed ossification) was discovered.'* The final conclusions stated *'There are no embryotoxic effects on rats following i.g. application of 0.1 and 1.0 mg/kg ZK. 5.422. The maximum dose (10.0 mg/kg) at which slight toxic effects could not be ruled out from amongst the mother animals (depressed growth), resulted in retarded but not teratogenic or lethal effects in the foetus.'*
29th September 1976	Federal Register 29 September 1976 (41 FR 43117)	The requirements detailed in the March/April 1975 FDA Bulleting for the patient labelling were set out in the Federal Register of 29 September 1976 (41 FR 43117)
17th November 1976	BN116_21 Page 5.	The Maternal Drug histories study was discussed at the CSM Adverse Reactions Sub-Committee meeting. Minute 8 reads *'Dr Greenberg presented her paper to the Sub-Committee. She said that the data now available confirmed the association previously reported with hormonal pregnancy tests. It was now proposed to submit an article to the BMJ. The Secretariat also wished to continue the study in order to clear up outstanding problems and in particular to look at the benzodiazepines.'*

11th December 1976	Dillon S.[83]	**Congenital malformations and hormones in pregnancy** A letter to the BMJ describing case series of 13 infants exposed to various hormones in utero, there is no control group. Of those exposed to HPTs there are two cases: a case of spina bifida/hydrocephalus exposed in the 6th week of pregnancy and a case of transposition of the great vessels exposed in the 4th week of pregnancy. In the letter Dillon states *'Continuation of the contraceptive pill into pregnancy will satisfy the requirement that fetal damage must occur at the time of organogenesis, but in the case of pregnancy diagnosis hormones and progestogens as used above the critical period of fetal vulnerability could well be past. It might be that in the group of progestogen-treated mothers in which there was a high fetal salvage rate defective infants had survived who would otherwise have been aborted.'*
1976	13195 pg 75	Recall of Primodos/Duogynon in Portugal, Rhodesia, import stop in Australia
13th January 1977	Heinonen et al 1976[84]	**Cardiovascular birth defects and antenatal exposure to female sex hormones** Heinonen et al published a study on congenital heart defects and exogenous sex hormone exposure in pregnancy in NEJM. They carried out a survey on 50,282 pregnancies and found 1,042 women had been given female hormones during the first four months of pregnancy. They carried out a survey on 50,282 pregnancies and found 1,042 women had been given female hormones during the first four months of pregnancy. Of these 1.042 women 19 had given birth to a child with cardiovascular defects, a rate of 18.2 per 1,000. This compared to a rate of 7.8 per 1,000 in the women who were not exposed to hormones. They reported *'After the data were controlled for a wide variety of potentially confounding factors by multivariate methods, the association between in utero exposure to female hormones and cardiovascular birth defects was statistically significant ($p < 0.05$).'* All hormones were grouped in this analysis, analysis of the nine affected women who were exposed to HPTs gives a statistically significant effect estimate of 2.10 with confidence intervals of 1.37 to 5.06. (EWG Annex 27)

[83] Dillon S., *Congenital malformations and hormones in pregnancy.* British Medical Journal, 1976. **2**(6049): p. 1446-1446.

[84] Heinonen, O.P., et al., *Cardiovascular birth defects and antenatal exposure to female sex hormones.* N Engl J Med, 1977. **296**(2): p. 67-70

26th February 1977	Goujard and Rumeau-Rouquette 1976[85]	**First-trimester exposure to progestogen/oestrogen and congenital malformations** In a letter to the Lancet Goujard and Rumeau-Rouqette reported the results of a prospective survey carried out in Paris. This survey of 12,764 women was conducted in Paris from 1963 to 1969. They found no significant difference in overall malformation rates, and no statistically significant differences in rates of congenital heart defects (n=5, OR=1.05; 95%-CI 0.42-2.66)or skeletal abnormalities (n=5, OR=1.07; 95%-CI 0.38-3.01). They did find a higher rate of microcephaly in the exposed group, significant at 1% (n=4, OR=5.62; 95%-CI 1.59-19.89). They wrote *'The figures for the global rate of malformed infants are drawn from substantial series, but the numbers of individual malformations are small. The significance of microcephaly in the exposed group is not easy to interpret.'* The letter concludes *'Our data show no definitive evidence for the teratogenicity of hormonal pregnancy tests, and our impression is that any risk of malformation is small. Nevertheless, it would be better to discontinue the use of pregnancy testing with hormonal agents.'*
23rd April 1977	Janerich et al[86]	**Congenital heart disease and prenatal exposure to exogenous sex hormones** A study looking at 104 infants with congenital heart disease matched with normal controls. Of 18 exposures in cases 10 had HPTs. Three control children were exposed to sex hormones, of these two were exposed to HPTs. No effect of concomitant prescribed drugs or infectious agents was seen. HPT most strongly associated with most severe forms of CHD which tend to cause early death. Results support the hypothesis that sex hormone exposure during pregnancy may cause congenital heart disease – more strongly associated with multiple malformations than single heart lesions. *'we can predict that no more than 19 additional cases of CHD would be produced by a similar level of hormone use during pregnancy among a population of 100 000 births. If hormone-related cases of CHD tend to be more severe, and so the infant dies early, the actual burden of hormone-*

[85] Goujard, J. and C. Rumeau-Rouquette, *First-trimester exposure to progestagen/oestrogen and congenital malformations.* Lancet, 1977. **1**(8009): p. 482-3

[86] Janerich, D.T., et al., *Congenital heart disease and prenatal exposure to exogenous sex hormones.* Br Med J, 1977. **1**(6068): p. 1058-60

		caused CHD among surviving infants is probably small, although not negligible.' Using the same study procedures for matched case-control studies of other birth defects including anencephaly (66 pairs), spina bifida (135), Down's syndrome (103), hypospadias (99) no increase in the number of patients exposed to hormones was identified.
27th May 1977	13201 Page 63	Dr Detering sent a memo relating to the Sunday Times article. *'We refer to the attached notification addressed to the PR office from 10/05/1977 regarding the mentioned case which was published in The Sunday Times on 8 May 1977. This case was the motivation for a discussion between Mr. Dr. Wiseman from SLC and the two signatories on 25 May 1977.* *The result was that, regarding the case at hand, no further action or response was performed.* *SCL continued to work on the synopsis that was originally developed by Dr. Pitchford on the development of Primodos since its introduction on the market. Based on this paper, the virilisation has never been of importance in England. The deletion of the indication for pregnancy tests was indeed based on the first publication from Gal in Nature in 1967, where a relationship between hormonal pregnancy tests and a deficient closure of the neural canal was suspected.* *The change of the indication was conducted without creating a public stir; no explicit warning or public comment for the change of indication was made by SCL (in accordance with Dr. Inman from the English health authority) because it was based on weak scientific evidence. (It was suspected that sexual steroids – as they are used for the hormonal pregnancy test – could cause malformations of any kind. The only malformation for which we saw a real risk – with improper use – was the risk of virilisation of the female foetus through gestagens that are derived from the nortestosteron.'*
28th May 1977	Gal 1977[87]	**Hormonal pregnancy tests and congenital malformations** A letter to the BMJ highlighting the articles which have supported her 1967 observation that there was an association between hormones and congenital malformations (Janerich et al 1974; Levy et al 1973; Nora & Nora 1973; Harlap et al 1975; Greenberg etl al 1975). *'The large variety of malformations reported by the above workers seems to be a clear indication that the teratogenic effect of hormonal pregnancy tests and other exogenous sex hormones is not specific but rather depends on the state of*

[87] Gal, I., *Hormonal pregnancy tests and congenital malformations.* Br Med J, 1977. **1**(6073): p. 1411

		fetal development at which the insult occurs – probably in a similar mode of action to that of many other powerful teratogens.'
22nd July 1977	FDA 22 July 1977 Federal Register (42 FR 37646) professional labelling and (42 FR 37643) patient labelling.	FDA notice with labelling requirements for progestational drugs other than contraceptives including a box warning against use in the first four months of pregnancy. Reports during the past several years have indicated that the use of sex hormones during early pregnancy may seriously damage the offspring. Several reports suggest an association between intrauterine exposure to sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects.' The final regulation was published in the Federal Register on 13 October 1978 (43 FR 47178) and was codified at 21 CFR 310.516)
July – September 1977	WHO[88]	**Drug Information Bulletin:** Reviews the literature on hormones and malformations and the actions taken in various counties including the US.
September 1977	Bayer evidence Attachment 1	An application was made by Schering to renew a batch of Product Licences of Right, including the PLR for Primodos.
27th September 1977	Bayer evidence Attachment 1	A renewal of the Primodos PLR was granted.
1st October 1977	Greenberg et al 1977[89]	**Maternal drug histories and congenital abnormalities** The full results were published in the British Medical Journal. They reported the drug histories for 836 mothers who had given birth to a baby with a congenital malformation. Each affected mother was paired with a control woman from the same GP practice who gave birth to a normal baby within three months of the birth of the affected baby. They analysed neural tube defects, oral clefts, limb malformations and other abnormalities. Medicines containing 331 different active ingredients had been prescribed to the mothers during the first trimester, they reported that for four groups of drugs-hormonal pregnancy tests (HPT), benzodiazepines, antibiotics, and barbiturates-there was a notable difference between case and control usage. They also found that the affected mothers had a higher rate of family history of congenital abnormalities, which they investigated *'A*

[88] WHO July – September 1977 Drug Information Bulletin PDT/DI/77.3

[89] Greenberg, G., et al., *Maternal drug histories and congenital abnormalities.* Br Med J, 1977. **2**(6091): p. 853-6

		separate analysis, excluding mothers with a personal or family history of abnormality, shows that this cannot account for the effect associated with HPT, but could account for differences associated with other drug groups (table V). Nine of the 93 mothers of abnormal babies who had used HPT had a personal or family history of congenital malformations. None of the 55 control mothers had such a history. The difference between case and control use of HPT remains significant when these nine mothers of affected babies are excluded (χ^2 9.42; P <0 01; McNemar's test).' They concluded *'The excess use of HPT by case mothers found by us was not great and the association with malformations nonspecific; alternative risk-free methods of pregnancy diagnosis are, however, available and the use of HPTs is unnecessary.'*
late September/ early October	BN116_24 page 5	Dr Wiseman of Schering reports that he became aware of the prescription data for Primodos for June 1967 to June 1977.
14th October 1977	BN116_24 Pg 6	Dr Wiseman wrote to GPs and gynaecologists. His letter reads *'It has been suggested in recent press articles that Primodos is still being used as a hormone pregnancy test. We would remind you than in 1975 the Committee on Safety of Medicines wrote to all doctors informing them that a theoretical association existed between hormonal tests and the possibility of congenital malformations, and that because reliable and non-hormonal methods of diagnosing pregnancy were available, Primodos and other similar products should not be used as a pregnancy test.* *The use of Primodos as a hormonal pregnancy test has not been recommended by this Company for many years. Moreover, since 1975 this Company has specifically contraindicated the use of Primodos in pregnancy. The indication for Primodos is for the symptomatic treatment of secondary amenorrhoea of short duration, not due to pregnancy.* *Enclosed is a data sheet for your further information.'*
21st October 1977		An article was published in General Practitioner highlighting the fact that the hormonal pregnancy testing was still being used by some GPs
25th October 1977	BN116_24 Page 5	Dr Greenberg of CSM phoned Dr Wiseman of Schering enquiring about prescription data in the General Practitioner article. In response, later that day Dr Wiseman wrote to Dr Griffin, the Principal Medical Officer at CSM. *'The total prescriptions for Primodos from July '76 to June '77 were*

		55,000; it appears that 9.3% of these prescriptions being used as pregnancy tests, but it should be borne in mind that these are sample data based on only seven prescriptions for the year. It should also be noted, however, that the sales of Primodos have been falling for many years and thus the total prescriptions for the second 6 months of this period are smaller than the first 6 months. Moreover, in view of the recent adverse publicity given to Primodos I would expect the sales to fall even further. My own letters to GPs and gynaecologists (copy enclosed together with the data sheet) should halt the further prescribing of Primodos as an hormonal pregnancy test.'
27th October 1977	BN116_9 page 12.	The Committee of Safety of Medicines meeting minutes discuss hormone pregnancy tests in 'Any Other Business' item 20.3 to 20.6 *'The Chairman said a recent article in the General Practitioner had suggested that Primodos was still being prescribed for pregnancy tests. In addition there had been further suggestion to this effect in the media, including a recent television programme. He also drew attention to the letter which Schering Chemicals Ltd had sent to doctors on 14 October, and to a further letter from the Company which suggested 9.3% of total prescriptions for Primodos from July 1976 to June 1977 had been for use in pregnancy testing. In these circumstances he considered that it would be advisable for the Committee to send a further waning leaflet to doctors, reminding them of the possible hazards and drawing attention to the recent published article by Greenberg et al.* *It was accepted that, while the quantitative assumptions about usage made in the General Practitioner article were questionable, any prescribing of Primodos or similar products for pregnancy testing was unacceptable. Some members stated that such prescribing had been drawn to their attention recently.'* *'The question of whether the Committee's warning leaflet should be used for such reminders or whether they should be reserved for new dangers was raised. After it had been pointed out that the alternative was to advise the licensing authority to take action under Section 62 of the Medicines Act, it was accepted that there was not objection in principle to the use of the leaflets in the manner suggested where an issue of such potential danger was involved.* *The Committee agreed that a new waning leaflet should be sent as soon as possible, the wording of which was to be decided by the Secretariat, in consultation with the Chairman.'*

17th November 1977	CSM issued Leaflet 16 in the Adverse Reaction Series	CSM issued Leaflet 16 in the Adverse Reaction Series entitled "HORMONAL PREGNANCY TESTS AND CONGENITAL ABNORMALITIES: A further statement" to all doctors, hospital principal pharmacists and retail pharmacists. It reads *'In June 1975 the Committee on Safety of Medicines published a warning about a possible association between Hormonal Pregnancy Tests and Congenital abnormalities (Adverse Reactions Series No. 13) The publication was based on preliminary evidence: further results have now been published (Greenberg, et al British Medical Journal 1977, 2, 853-856) and the association is confirmed.* *The Committee therefore reiterate their view, expressed in their earlier warning (which is attached) that hormonal tests for pregnancy should not be used.* *Alternative methods are available which are free from this risk.* *Most of the preparations referred to in the earlier leaflet were removed from the market. The data sheets for those which remain for other indications state clearly that pregnancy is a contraindication for their use.'*
14th December 1977	13201 Page 31	Dr Granitza sent a memo describing a meeting with Dr Pitchford.
21st/ 22nd December 1977	13201 Page 29, 13201 (German) page 295	Dr Granitza sent a memos describing a meeting between Schering representative and their lawyers, Mr Dodds-Smith and Mr Clothier QC. See also Bayer's written evidence to the IMMDS Review in response to question 24.
1978	Nora and Nora 1978[90]	**Maternal exposure to exogenous progestogen/estrogen as a potential cause of birth defects.** Abstract reads *'The literature is reviewed on the possible causal relationship between birth defects and maternal exposure to exogenous sex hormones at the vulnerable period of embryogenesis. Five separate personal studies (3 case-control and 2 cohort) are also reviewed to illustrate methodological problems in reaching confident conclusions about etiology. Although prospective data are not sufficient to provide definite answers, the probability is growing that exogenous sex hormones produce birth defects in genetically-predisposed individuals. Prudence dictates that exposure to progestogen/estrogen during early pregnancy be minimized through elimination of uses with unfavourable*

[90] Nora, A.H. and J.J. Nora, *Maternal exposure to exogenous progestogen/estrogen as a potential cause of birth defects.* Adv Plan Parent, 1978. **12**(3): p. 156-69.

		risk:benefit ratios, such as hormonal pregnancy tests and threatened abortion.'
1st January 1978	German Federal Health Authority	From 01/01/1978 Federal Health Authority in Germany Review of the files on the potential link between HPTs and congenital malformation.
25th January 1978	Bayer evidence Attachment 5	Dr Wiseman of Schering wrote to the DHSS. His letter states '*Owing to the falling demand for our products… Primodos (PLR 0053/5027) (x 2 and x 20 tablets)… we have decided to discontinue marketing the preparations give above. Except in the case of Primolut Depot, where packs of 3 and 20 will remain, these represent deletions from our product range. We are writing to request that our Product licences of Right should be terminated for those products or presentations given above.'*
8th February 1978	IMMDS public call for Evidence	Jack Ashley (the Labour M.P. for Stoke on Trent), invited parents of children who were thought to have been damaged by an HPT to a meeting at the House of Commons. He had been influential in helping to gain compensation for those families who had suffered from the effects of thalidomide.
9th February 1978	Wolff U 1978.[91]	Article on potential reform of the abortion law in Germany mentioned Duogynon (Primodos) *"the use of Duogynon tablets and "syringes" should definitely be a matter of the past! Unfortunately, these kinds of practices, which are hardly acceptable, are reported in the counselling centres [where women had to seek advice before a legal abortion could be performed] quite often."*
February 1978		As a consequence of the meeting with Mr Ashley MP the Association for Children Damaged by Hormone Pregnancy Tests was set up and chaired by Val Williams. The aims of the ACDHPT were fourfold. To have HPTs removed from the market; To advise, support and assist parents of children who may have been affected by the use of an hormone pregnancy test; To bring to the attention of the public and the authorities the plight of parents and children so affected; To raise money to finance a legal bid for compensation for these children.
1978	13195 pg 75	Sales of Primodos ceased in England
17th February 1978	13198 page 227 (German)	Dr Wiseman's report of a meeting with Prof XXX.

[91] U. Wolff, *Ist die "Reform des § 218 gescheitert?* Deutsches Ärzteblatt, 1978. **6**(9): p. 317-20.

28th February / 3rd March / 6th March 1978	Hansard	28th February: Request from Mr Ashley for an inquiry. Mr Moyle gives an overview of the previous studies, including that the CSD study in 1977 confirmed an association between hormonal pregnancy tests and nonspecific congenital abnormalities. It states that pregnancy testing was removed from indications in 1975, and that warnings were sent to doctors that year and in 1977, and that Primodos has been removed from the market since. It also notes that only one of the products included in the warning remains on the market, for other gynaecological uses. The answer continues: "*It has not been proved that any of the drugs used as hormonal pregnancy tests in fact caused foetal damage. The study showed only a statistically significant difference between the number of malformed babies born to mothers who have taken the drugs when compared with controls.*" It briefly discusses the issues with making wider calculations, or undertaking further study. It concludes: "*I have looked carefully into this matter, and I am advised it is not possible for further scientific inquiry to produce any meaningful results.*" 2nd March: A number of questions from Mr Ashley, including about claims that pregnant women are still using the hormone pregnancy test. Mr Moyle responded that Primodos has not been promoted for pregnancy testing since 1969. The Department of Health/CSM have not discussed matters of compensation with the Company. The manufacturers advised the licensing authority in January 1978 that they had decided to discontinue marketing Primodos for commercial reasons. Prescribing is a matter of clinical judgement, and the CSM seeks to provide doctors with relevant facts, in this case, two articles in the BMJ, two warning leaflets. In addition, manufacturers have written to doctors to remind them of the same point. 6th March: Further exchanges refer to the feasibility of further studies or estimates of those affected. Mr Moyle states: "*I do not believe that a further attempt to establish a cause and effect relationship between hormone pregnancy tests and congenital abnormalities would be practicable.*" Note: We are aware of other highly relevant information in the LandesArchiv related to conversations between Dr Inman and Schering at this time, which we cannot refer to due to legal privilege.
17th March 1978	LandesArchiv 13192 (German) p125	Company circular, providing updates on the current situation around Duogynon and Primodos states "For reasons of company politics – namely to avoid a repetition of such dubious claims for damages in other countries -, the Spartenleitung Pharma took a decision on 14/2/1978 to

		withdraw the recommendation of the use of all forms of DUOGYNON as a pregnancy test everywhere in the world and to advise that the existence of a pregnancy must be excluded before the preparations are prescribed." Texts of packing slips were immediately amended and packs available to Schering AG and foreign subsidiaries were repacked. Physicians were informed (although the circular does not say how this was carried out). It also provides an update on the "Permanent Commission for Steroid Toxicology" of the German Society for Endocrinology. The statement was shortly to appear in the Deutsches Ärzteblatt, but a summary of the main content is provided. It has not been possible to draw conclusions from the animal studies to the situation in man. The epidemiological studies left many questions unanswered. The Commission points out that the presence of pregnancy has been regarded as a contraindication for oral administration of hormonal preparation since 1974, and that parenteral administration is unnecessary as alternative laboratory tests are available. "*The Commission considers the teratogenic risk – if one exists at all – to be minimal.*" The circular states it will now contact German physicians to inform them that the use of parenteral forms of administration of DUOGYNON as a pregnancy test is also to be discontinued.[92] The circular emphasises that "*although there is no necessity from a scientific point of view to regard the use of Duogynon for the diagnosis of pregnancy as a contraindication, for political reasons we urgently advise against the use of Duogynon for the diagnosis of pregnancy..*"
March /April 1978	13918 (german) page 294	Correspondence between Schering and LWT. *'Dr Isabel Gal published the results of her research on the possible association of hormonal pregnancy tests and congenital malformations in October 1967 and yet PRIMODOS continued to be the recommended as a pregnancy test in the UK until July 1970.* *The gal study was reviewed by the company. We immediately established direct contact with both Dr. Gal and what was then the committee on safety of medicine.* *Other independent experts subsequently expressed doubts about the validity of her conclusions.* *According to our opinion, even up to date no substantive (handwritten correction to substantial) evidence is available to support the hypothesis of a causal relationship between*

[92] Landesarchiv file 12223 page 23 of the original or page 16 of the translation

		the application of hormonal pregnancy tests and any other type of malformation observed in humans.'
7th & 8th April 1978	13198 page 64	On 7-8 April 1978 a Symposium was held in Bermuda. A Schering Circular reports that: "*In the informal atmosphere of the Castle Harbor Hotel, there was a good chance to co-operate with Dr. Inman, co-author of the Greenberg-Inman study, in which an increased risk of malformations after administering female sexual steroids to pregnancy diagnosis was suspected. The study had led to considerable publicity in England especially in October.* *Dr. Inman spontaneously told me that he was "unhappy" because of the consequences that had resulted from the publication of the work. He had never said that a clear causal relationship exists between two hormonal pregnancy tests and malformations. It was simply an association….* *For him the liability claims, which now result from the suspicion, were completely unexpected, also the political consequences. He was primarily concerned with the questions of Mr. Ashley in the lower house.'* *"He reported that the questions to be answered by him on the desk piled up, it was probably more than 200. He made it clear that he wanted to quit his service with the authorities and go to the university.* *It is particularly important that he has destroyed all the material on which his investigation is based, or made it unrecognizable, which makes it impossible to trace the individual cases taken into the investigation. I understood Dr. Inman that he did this to prevent individual claims from using this material. It is clear that Dr. Inman expects to be interviewed as a witness or ala expert by the court in our dispute…'"* *'"He conceded that the inclusion of a larger proportion of very young and older women in the case group alone could explain the weak risk of miscarriage which he had calculated. He also gives other bias possibilities. He further contends that it may well be a pseudo association and that a large hormone exposure observed in the case group has nothing to do with the malformations, but that this association is due to a previously unidentified third factor."'*
10th April 1978		10 April 1978 Jack Ashley MP asked the Secretary of State for Social services *'(1) if he will list in the Official Report all the drugs which have been prescribed for hormone pregnancy tests in the last 10 years, together with the names of their manufacturers;(2) which of the drugs used in hormone pregnancy tests have been withdrawn from the market; when they were withdrawn; and what official reason*

was given for their withdrawal;(3) what consultations he has had with the Committee on Safety of Medicines about the use of hormone pregnancy test drugs; what advice he was given by the committee; and what action he took in the light of that advice;(4) if he has had discussions with foreign Governments on foreign manufactures about the use of hormone pregnancy test drugs both in Great Britain and abroad; and, if so, with whom he held these discussions;(5) if, in the light of facts disclosed in his letters to the hon. Member for Stoke-on-Trent, South, he will now hold an inquiry into the manufacture, testing and prescribing of hormone pregnancy test drugs'

In reply Sir Roland Moyle stated *National Health Service prescription forms do not indicate the reason for the prescription, nor are they retained for more than about six months. I list below all drugs which, as far as is known, have been used or recommended for hormonal pregnancy testing in the last 10 years, together with the names of the licence holders and, where appropriate, the date and reason given for withdrawal.'* These are reproduced below.
'In 1975 the United Kingdom Health Ministers acting as the licensing authority were advised by the Committee on Safety of Medicines that measures should be taken to ensure that indications for pregnancy testing were no longer included in the licences for such products and to require the insertion in all promotional literature of a warning about the possible hazard in pregnancy. The licensing authority accepted and acted upon the committee's advice. Adverse reaction warnings were issued by the committee to all doctors. The Committee on Safety of Medicines has exchanged information on the use of hormonal pregnancy tests with the World Health Organisation and with other drug regulatory authorities. I have looked carefully into this matter and I do not think that an inquiry would be helpful.

Name	*Licence Holder*	*Date product withdrawn from UK market*	*Reason given for withdrawal*
Amenerone	Roussel Labs Ltd	May 1977	Discontinued for commercial reasons
Amenerone Forte	Roussel Labs Ltd.	May 1977`	Discontinued for commercial reasons
Disecron	British Schering Ltd. (never licensed	March 1969	Discontinued for commercial reasons

	under the Medicines Act)		
Menstrogen	Organon Laboratories	March 1975	Discontinued for commercial reasons
Norlutin A	Parke-Davis and Company Ltd.	1975	Discontinued for commercial reasons
Norone	Roussel Labs Ltd (never licensed under the Medicines Act)	January 1969	Discontinued for commercial reasons
Orasecron	Nicholas Laboratories Ltd.	June 1975	Discontinued for commercial reasons
Paralut	Wallace Manufacture Chemists	Prior to 1971	Discontinued for commercial reasons
Pregornot	Marshall's Pharamceuticals Ltd	Not known	Not known
Secrodyl	Duncan Flockhart and Company Ltd.	February 1975	Discontinued for commercial reasons
Primodos	Parke-Davis and Company Ltd.*	January 1978	Discontinued for commercial reasons
Norlestrin	Parke-Davis and Company Ltd.	Remains available for various gynaecological uses including	

		<table><tr><td></td><td></td><td>contraception</td><td></td></tr><tr><td colspan="4">Notes: (1) Not all the products carried indications for pregnancy testing. (2) Some indications for pregnancy testing were removed at a date earlier than withdrawal of the product.</td></tr></table>
10th April 1978	13201 (german)262	Letter and notes from SCL to Amon
23rd April 1978	Sunday Times[93]	A piece by Oliver Gillie in the Sunday Times focussed on Schering's actions after the 1967 Gal paper.
23rd May 1978	13200 (translated) 183	Meeting of PRIMODOS working group on the 23rd May 1978 (unsorted)
24th May 1978	13200 (German) Page 166	Dr Granitza sent a memo relating the worldwide withdrawal of Primodos.
26th May 1978		26 May 1978 the matter was again raised in the House of Commons by Jack Ashley MP. In this debate he again called for a public inquiry. He asked the Secretary of State whether he accepted that studies show that hormonal pregnancy testing often causes abnormalities in babies In his reply Sir Roland Moyle stated *'Until today my answer to that question might have been "Yes". However, today I have been able to get some evidence of testing in this field by the German Research Association. This study was planned in 1963 in response to the thalidomide tragedy in which my hon. Friend played such an outstanding part. It is the most comprehensive investigation ever conducted. It covered nearly 15,000 women, and nearly 8,000 of the tests on those women have been evaluated in the preliminary report.* *The results of the study do not provide evidence that hormonal pregnancy tests were harmful. The study shows that many other factors can influence the outcome of pregnancy. For example, women with abnormal babies had had, according to the study, more previous miscarriages, had had more abnormal children and had suffered more frequently from chronic diseases of various kinds. Cigarette smoking was shown to have an unfavourable effect.* *Of the 7,870 women covered in the preliminary report, 337 had used hormonal pregnancy test drugs. In a group of this size it would be expected that there would be 5·4 major*

[93] Gillie O. *Drug company ignored deformity risk for 10 years* Sunday Times, 23 April 1978. page 6.

		abnormalities in the births to these women. In fact, it turned out that there were six. There would have been expected to be 74·8 minor abnormalities in babies born to a group of women of this number. In fact, there were 76. Therefore, it is difficult to connect that piece of evidence with the case that hormonal pregnancy testing damages the foetus.
May 1978	13198 page 63	Internal memo from Dr Wiseman to Dr Detering *'On 26th May the Minister of Health answered Jack Ashley's questions on Primodos in the House of Commons. He referred to Deutsche Forschungs-Gemeinschaft report. Part of his answer read as follows: 'of the 7870 women covered in the preliminary report, 337 had used hormonal pregnancy test drugs. in a group of this size it would be expected that there would be 5.4 major abnormalities in the births to these women. In fact, it turned out that there were six. There would have been expected to be 74.8 minor abnormalities in babies born to a group of women of this number. In fact, there were 76'. I can find no reference to these figures, or any table from which these figures can be calculated, in the DFG booklet. I presume therefore that Inman, who was sent a copy of our translation a few weeks ago, contacted the co-ordinator of the study to obtain the necessary figures on HPTs. would be grateful if you could also obtain all pertinent HPT data from this study for us as soon as possible.'*
5th June 1978	13200 page 166 (German)	Schering Management discussion with Mr Clothier.
6th June 1978	Written evidence to the Review	A meeting was held between Sir Roland Moyle and representatives of the Association. Association members reported that at this meeting Sir Roland agreed to reconsider a public inquiry if the Association could produce new evidence.
7th June 1978	13198 page 182 (German)	Note from Dr Wiseman to Ian Dodds-Smith re. a telephone call with Dr Bill Inman " *Dr Detering had felt diffident about contacting the organisation of the DFG study in order to determine where Moyle, the Minister of Health, had derived the figures which were quoted in the House of Commons. It seemed prudent therefore to find out this information by telephoning Dr. Inman. Bill Inman told me that he had obtained the figures in a private letter from Dr Koller, who was responsible for the data in the DFG study. He went on to tell me that he had advised the Minister that the studies, apart from his own which was in a sort of middle ground, fell into one of two categories: there were either case-control studies (with all the difficulties of matching etc.), which were usually small, sometimes anecdotal, and some of these showed an*

		association between HPTs and malformations; or they were large prospective studies, sometimes involving thousands of patients, and the four major ones of these all showed no association. (He quoted the Boston study of Heinonen, the French study, the DFG report, and the RCGP study). He also mentioned another reference which was quoted in the Hansard report which referred to Cyril Clark's study on the influence of maternal history on pregnancy-outcome. *From comments and hints that Bill Inman made e.g. arguments with his co-authors about the validity of their findings, I gathered that he wished to disclaim responsibility for the study published in the BMJ in October 1977. He repeatedly emphasised that the association was a very weak one and that there were many other confounding or unidentified factors which could account for this discrepancy.* *I had the feeling that he now very much regrets publication of this paper."*
16th June 1978	13218 page 17	Schering AG files note *'Prof. Haller informs that no significant difference resulted in his research results regarding the malformation rate at women with and without hormonal pregnancy tests: 3879 women without hormonal pregnancy test showed 96 malformations, corresponding with 2.47 %. 789 women with hormonal pregnancy test during early pregnancy showed 22 malformations, corresponding with 2.66 %.'*
16th June 1978	LWTV the 'London Programme'	Press interest in HPTs had been gathering, with a London Weekend Television programme airing on Sunday 16th June 1978.This programme highlighted the actions and knowledge of CSD/CSM and Schering and the eight year delay between Dr Gal's findings in 1967 and the warning in 1975.
19th June 1978	13193 page 62	Reference to the belief that Primodos may act as an abortifacient. Attachment to SL-minutes 246 / TOP *'Our Korean interlocutors told us that in this case, hormonal pregnancy diagnosis is practically irrelevant. Women who desire to have children primarily go to the doctor, who uses an extracorporeal test. These women do everything to keep their child from harm. Women who do not wish to keep their pregnancy (mainly those engaged in entertainment) will, however, first go to a pharmacist with the desire to obtain a remedy that triggers a haemorrhage. As a rule, overdosing is used in an abortive manner. If the bleeding does not occur and the woman is pregnant, she has an abortion (semi-legal). It is not out of the question, however, that pregnant*

		users do not want an abortion, although the Korean management does not believe in such cases. We could not obtain any information about the size of this group, nor were we able to obtain any indications of the incidence of abortion.'
14th July 1978	13210 page 20 (German)	Letter Ian Dodds-Smith (Schering solicitor) to Granitza dated 1/07/1978 and a memorandum of a Primodos status meeting
18 July 1978	13201 page 16 (German)	Letter from Ian Dodds-Smith (Schering solicitor) to Granitza dated 18/07/1978 and a memorandum of a on meeting between Schering and Roussel
19th July 1978 and 26th July 1978	13198 pages 102 - 104 (German)	Letter from Schering to Prof Acheson and reply.
21st July 1978	EWG Annex	Dr Isabel Gal submitted the report she had prepared on HPTs to Sir Roland Moyle and Jack Ashley MP. The report was titled Teratological adverse drug effects: Review of evidence implicating hormonal pregnancy tests. In it she examined the literature and commented upon the actions of the regulators.
7th August 1978	13190 page 72	HPTs were also being discussed in Germany, Dr Hannse, commented in an interview for Rias on 7 August 1978 *'After this suspicion was first raised in 1967, we have, of course made an effort to submit counterevidence. We, as a manufacturer of a pharmaceutical preparation, can normally only achieve this in animal testing. It is not possible, to conduct the necessary tests on pregnant women, simply due to ethical reasons. This is the reason why one speaks about a remaining risk to this day.'* The interview specifically asked about the situation in England *'But now, Mr. Dr Hannse, in England already, there the Sunday Times has printed and written it already, an association has formed of allegedly malformed children due to this pharmaceutical product. And yet through a minimal advertising expense over 1800 families have been in touch and have been persuaded to join or to affiliate with the association. This association now wants to file compensation test cases against Schering. How do you view this development that this movement originated in England at first and that such an initiative of parents could possibly also occur in the Federal Republic?* *Needless to say, we always have to expect compensation claims. You should know that nowadays approximately 1 – 2 % of all new-borns are born with more or less severe malformations. It is a terrible situation for the parents and they naturally ask for the reasons. For approximately one year now lay press and mass media in England report on*

		suspected connections between preparations which were used as hormonal pregnancy tests and such malformations. I consider it very understandable that parents then obviously agree to raise a compensation claim against the manufacturer. The question however is, how does a court assess the question of causality, hence, which means the correlation between the suspected cause DUOGYNON and the occurred damage malformations. From our point of view there is still no evidence or even a justification for this suspicion to this day after more than 10 years of discussion and after 10 years of surveys and scientific studies. We believe it is a coincidental concurrence of malformations and use of the preparation. This is also supported by the fact that due to the publicity of this preparation in England the use has decreased so enormously in the past years, so enormously that we ceased the sale in February. And nevertheless, the amount of malformation, which are reported, increase further.
16th August 1978		An article in the Sun made a call to donate to the Association for Children Damaged by Hormone Pregnancy Tests to fund litigation. The Sun had itself donated £700.
August/September 1978		Media interest in Germany increased with various articles published, for example 14/08/1978 Tagesthemen; 04/08/1978 die Zeit; 30/07/1978 Tagesspiegel; 21/07/1978 Berliner Extradienst. In her 4 August 1978 article in Die Zeit 'Pregnancy tests with consequences' Jutta Kampke wrote *"On the quiet Duogynon was used as an abortifacient, if it was taken in a sufficiently high doses. Schering denies this action. Studies were already known since 1960/61 that showed that women not only – as assumed until then – got bleedings after the administration of the hormone preparation when they were not pregnant. A minority of the examined women also had bleedings during the early pregnancy. 'This as such should already be a warning' says Dr. Graham Dukes from the Netherlands "commission for evaluation of medicines". Dukes, an internationally renowned expert for drug side effects concludes about this: "an abortion bleeding could follow or a disturbance of the embryonal development"* In the 30 July 1978 Tagesspiegel article Dr Gal's visit to Schering Berlin in 1969 is mentioned and she is quoted as follows "*At that time, they accepted that the hormonal pregnancy test leads to abortion*.", she said, "*However, they could not decide, whether my results, I mean the connection with the malformations, should be accepted or not."*
17th August 1978	BN116_11 Pg 32	Dr Gal's report was raised at the Committee of Safety of Medicines meeting. *'The Committee received a paper entitled TERATOLOGICAL ADVERSE DRUG EFFECTS –*

		REVIEW OF EVIDENCE IMPLICATING HORMONAL PREGNANCY TESTS, prepared by Dr Isabel Gal, MD and submitted to Minister of State (H). The Committee agreed that Dr Gal's paper should be referred to the Adverse Reactions Sub-Committee for them to consider, and report back to the Committee. Also if in considering the available evidence the Sub-Committee felt that there would be advantage in the setting up of a working party then there would be nothing to preclude them from making such a recommendation.'
18th August 1978	13223 Pg 82	In a memo from Dr Smolarek of Schering AG's Hannover office wrote *'In conversations about Duogynon it was highlighted that a surprisingly high percentage of physicians still swear by accomplishing an abort through Duogynon.'*
1st September 1978	Nora et al[94]	**Exogenous Progestogen and Estrogen Implicated in Birth Defects** A five-year study of the possible teratogenicity of exogenous female sex hormones included three case-control studies and one cohort study. Case-control study 1 – 32 cases, for 16 patients 2 patients to serve as controls who were referred for evaluation of heart murmurs. For the remaining 16 cases – children with functional murmurs but also normal births. Case-control studies 2 and 3 – 236 cases with congenital heart lesions 60 matched with patients with known single mutant gene and chromosomal disorders. For 176 cases 2 control matched with each congenital heart patient. Cohort study - 118 first trimester exposed cases and 118 controls. Authors conclude that because of the fall in HPT use, there were insufficient cases to address the question of whether maternal exposure to exogenous progestogen and estrogen during the first trimester represents a risk to the foetus. Nevertheless, the association of hormonal exposure with VACTERL provides the strongest evidence likely to become available from retrospective studies. The statistical differences are significant. Two of three prospective studies provide evidence consistent with an association between exogenous hormones and congenital heart disease; one does not. A 2-4 fold range of increase may be projected by combining the two positive studies. Furthermore, the weight

[94] Nora, J.J., et al., *Exogenous progestogen and estrogen implicated in birth defects.* JAMA, 1978. **240**(9): p. 837-843

		of evidence from studies conducted by several groups supports an association.
4-7 September 1978	European Teratology Society, 6 Conference, Budapest	**Teratogenic effects of Gestagene treatment during early pregnancy in mice** . Study in mice found no difference in resorption rate or average fetal weight, but increase in various malformations: exencephaly (irrespective of dose), cleft palate (dose dependent), kidney and bladder malformations (dose dependent), heart malformations (doubtful dose response).
7 September 1978	BN116_27 pages 11, 14, 16, 18 and 20	The Adverse Reactions Sub-Committee minutes record at point 8. *'The Sub-Committee had before them a paper submitted by Dr Isabel Gal in which she reiterated her view that hormonal pregnancy tests were a cause of congenital abnormalities. Ministers referred the paper to CSM for their advice. At their August meeting CSM agreed to pass the paper to the Adverse Reactions Sub-Committee for their consideration. An assessment of Dr Gal's paper by Dr Inman was also circulated to the Sub-Committee.'* The assessment of Dr Gal's report prepared by Dr Inman (CSM/AR/78/56A) also included a summary of the preliminary results of the German Research Association study. In his assessment of Dr Gal's review Dr Inman expresses various concerns over her selection of papers and the soundness of her conclusions, which are outlined in the 'conclusions' section below. In his review of the German data Dr Inman writes *'337 of 7,870 pregnancy women (4.3%) had used the hormonal pregnancy test. It was calculated that the expected number with major malformations was 5.4 and the observed number was 6. The expected number among mothers of babies with minor malformations was 74.8 while the observed number was 76. There were many associations with the use of HPT. The number of miscarriages and previous malformed children was greater, the pregnancy was more frequently undesired and inefficient methods of contraception had been more frequently used. More women who used HPT had previous chronic diseases.'* He then discusses the relative proportion of women using HPTs; 4.3% in Germany compared to 15.2% in the UK. He writes *'Possibly this difference is due to a greater reluctance on moral grounds to use these preparations for their abortifacient properties.'* The meeting minutes continue. *'After discussion of Dr Gal's paper 'Teratological Adverse Drug Effects: Review of Evidence Implicating Hormonal Pregnancy Tests', and Dr*

		Inman's comments on it, the Sub-Committee agreed to advise the Main Committee that:- *(i) Dr Gal's analysis of the literature was unsatisfactory from a scientific viewpoint;* *(ii) On the evidence now before them the Sub-Committee saw no reason to change their earlier views which were the basis for the warnings in the Adverse Reactions series leaflets No. 13 and 16.* *Before a further report was made to the Main Committee however, WHO should be asked for information about the review of world literature which they were known to be commissioning on the effects of all hormones in pregnancy.'*
28th September 1978	BN116_11 Page 17	At the next CSM meeting on Dr Gal's report on HPTs was discussed. The minutes at 7.4 read *'The Chairman explained that the Minster, to whom Dr Gal's report was addressed, would require a reasoned reply answering the points which she raised. It was agreed therefore that the reply should include the following five points:* *i. Dr Gal's study was scientifically unsatisfactory. The results of her publication in 1972, five years after her initial letter to Nature, showed that the majority of affected babies must have been exposed to HPT after the neural tube would normally have closed. HPT could not therefore have been responsible for failure of closure in children with spinabifida. Even in 1967, however, defects in the matching of cases and controls were apparent which cast serious doubt on her hypothesis at the time.* *ii. In her review, Dr Gal took together all forms of exposure to female sex-hormones including oral contraceptives and long term hormone support therapy, under the heading of HPT. In fact HPT could be separated clearly from the other hormones only in her own study, in that by the CSM, the RCGP, the German study and in one or two anecdotal accounts based on small groups of patients.* *iii. None of the large-scale prospective studies showed HPT to be a cause of birth defects. They merely demonstrated the fact that HPT increased the incidence of abortion.* *iv. Only the Gal study and that by the CSM showed a statistically significant trend in favour of her hypothesis. Her own study was not acceptable for the reasons stated above. In the CSM study, HPT was found to have been used by rather more mothers of abnormal babies than by control mothers. The CMS study had been intended to "signal" potential hazards, not to prove that the*

		signals generated are the results of a drug-induced abnormality. It was very likely that the small additional risk suggested by the Committee's study was due to some unidentifiable bias relating perhaps to the fact that it was not possible to match the patients closely; it was not known why HPT had been used, nor whether other factors might have caused the abnormalities, eg the smoking of cigarettes, of the use of non-prescribed medicines. *v. Women who used HPT were not typical of all women who became pregnant. Several of the studies quoted by Dr Gal indicated that women exposed to HPT were at greater risk of having an abnormal baby even before exposure in one study, for example, 18 of 22 mothers whose babies were exposed to HPT had repeatedly requested that pregnancy should be terminated.* *Other points raised for possible inclusion in the submission to Minister were:* *i. Dr Gal's list of studies was itself selective;* *ii. The statistical analysis which she employed in her review was not valid; it was agreed however that this should not be stressed* *iii. The Committee's warning could not reasonably have been given earlier in the light of the evidence then available.* *In answer to a question from the Committee Dr Inman stated that he did not believe that his report on Dr Gal's review report had omitted any significant studies though he had been unable to obtain all those papers listed eg the Israeli study. He advised members that a comprehensive report prepared by Schering Chemicals had reached conclusions identical to those set out in his CSM paper.*
10th October 1978	13192 page 10	Memo from Dr Granitza re. Dr Mobius (Dr Mobius was campaigning against HPT use in Germany) *'In my opinion the time has now also come for us to obstruct Dr. Möbius wherever possible and where there are objective reasons for this exist. As fair reporting can no longer be expected, in my opinion we should consider whether we should clarify internally, that Dr. Möbius of should not be given any further information at all on Schering or Schering employees.* *Are there any further opportunities to exclude him from the information flow (e.g. and delete him from distribution of any materials, such as press releases and similar items)?* *In my opinion we should also consider further whether we can find a journalist who is interested in the subject "Dr. Möbius conducts his affairs in fear". What Dr. Möbius is*

		doing at the moment in my opinion can no longer be supported in terms of healthcare policy. One would however certainly need to think about this further.'
10th-11th October 1978	13194 pg 74-76 also see 13219 page 89 & 95	Workshop on the Assessment of the Risks of Hormonal Treatments during the Early Pregnancy was held by the Federal Health Office at the Institute for Drugs offices in Berlin. This included experts from across the world, including Dr Gal, Dr Smithells, Dr Heinonen, and Prof Halle. Outcomes 1. Stop use of HPTs as pregnancy tests 2. Use of HPT for secondary amenorrhea only 8 weeks after last period and after 2 negative immunological pregnancy tests done at least 8 days apart Use of progesterone for threatened abortion/miscarriage should be subject to planned multi-centre clinical investigation on live fetuses
12 October 1978 13 October 1978	FDA Federal, Register 13 October 1978 (21 CFR 310.516)	US FDA requested that, required that starting on 11 December 1978 a lay-language brochure on progestins must be given to women by dispensing physician or pharmacists whenever a prescription is filled. The brochure points out that 'progestins' when taken by women in the first four months of pregnancy, may increase the risk of heart defects or deformed arms and legs in their children. The final regulation of the entries detailed at 22 July 1977
18 October 1978	13219 Page 104-5	In question time at the Bundestag the Federal Minister for Youth, Family and Health Herman Kroll-Schleuter described the conference as follows *'On October 10 and 11, 1978, a conference of experts from the Federal Health Office in Berlin took place with experts from Germany and abroad on the question of a possible relationship between the intake of certain hormone combinations in the early pregnancy period and the occurrence of malformations in newborns. In this meeting, all studies known world-wide were evaluated. In studies of more than 80,000 pregnancies, all malformations were recorded and analysed for type and frequency. The particular difficulties of their assessment were to distinguish the malformations observed possibly connected with the intake of drugs of the type and frequency of the malformations occurring without any recognizable causes. Among the examined pregnancies were several thousand, for which in the early pregnancy hormone preparations were applied for different reasons. The comparison of the frequency of malformation between the subgroups with and without hormone treatment showed so little differences that evidence of a causal link between malformations and drug intake cannot be demonstrated.* *However, in order to avoid any risk, the experts agreed that the use of hormone preparations for the detection or exclusion of pregnancy should be excluded as other suitable*

		methods are available. The treatment of secondary amenorrhea with such preparations is also to be carried out only if pregnancy is definitely excluded by immunological tests. The Medicines Committee of the Healers has been informed by the Federal Health Office and the Association of Pharmaceutical Industry of the result of the expert talk.'.
31st October 1978	13192 pages 98-99	In Presentation to board mtg:38/78 date 31/10/1978 *'The use of DUOGYNON as a pregnancy test apparently plays an extremely minor role in Korea. Duogynon is generally used as a treatment, occasionally apparently also with a belief in a supposed abortive effect. Should the latter not achieve its goal, as a general rule another form of termination is selected. According to statements by the practitioners asked by Dr. Granitza and Dr. Detering, it appears extremely unlikely that there will be pregnancies which run to term where DUOGYNON was used in the early phase.'*
23rd November 1978	13200 page 5	Minutes from Schering AG's Primodos working group meeting.
4 December 1978	13192 page 17 (German)	Memorandum of conference with Counsel Mr. Michael Tugendhat.
December 1978-January 1979	FDA drug bulletin, Vol. 8, No. 6, Page 36	**Patient Brochure for Progestins Warns Against Use in Pregnancy** *'Women must soon receive a lay language brochure on progestational drugs every time a physician or pharmacist dispenses one of these products. The brochure explains the risks associated with the use of progestational agents during the early stages of pregnancy'* It is reported that this action *'stems from reports in the literature that suggest an association between the use of progestins in the first 4 months of pregnancy and congenital anomalies, including congenital heart defects and limb reduction defects'* *'Since September 1977, physician labelling for progestational drugs has reflected these concerns, and also has included an addition contraindication and a boxed warning. The additional contraindication is against the use of progestational agents as a diagnostic test for pregnancy'* *'The boxed warning in physician labelling explains that although progestational agents have been used to prevent*

		habitual abortion or to treat threatened abortion, there is no adequate evidence that such use is effective. There is evidence of potential harm to the fetus when women take such drugs in the first 4 months of pregnancy' *'The approved indications for progestins are amenorrhea, endometriosis, and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology'* *'The patient brochure must be shipped and dispensed by pharmacists with all packages of progestins starting December 12, 1978. Physicians with unlabelled stock on hand will not have to dispense patient labelling until the supplies of progestational drugs they receive include the patient labelling'*
1979	13190 page 152 (German)	Side effects of Drugs Annual – 3 (1979) Chapter on 'Sex hormones and related compounds, including oral contraceptives. Teratological research is restricted to non-experimental design of passive data collection. *"Can at best, prove existence of, but not the cause for differences between groups.."* Goes on to review the studies Recent reviews of retrospective epidemiological studies, 7/15 no positive association between sex hormone administration and congenital malformations; 8 showed positive association; however, all studies have some methodological limitations. Nocke the author of chapter carried out review of literature, 8 studies, 105,000 mother-child pairs. Results contradictory: 5/8 no significant relation, 3/8 some positive associations. For example the US collaborative perinatal project (in SEDA-2) found RR of 2.0 for cardiovascular defects on exposure to any oestrogen and progestogen in first 4 lunar months. Relevance questioned e.g. development of heart and great vessels completed by end of 2nd lunar month; and discussion of the wider study (which looked at about 400 drugs in total).It concludes that the contradictory results of various studies, misinterpretation, public statements etc. have placed doctors in difficult position.
1979	Goujard et al 1979[95]	**Hormonal tests of pregnancy and congenital malformations** *INSERM has carried out two prospective inquiries centred on the evaluation of the teratogenic action of drugs on human beings. The first survey was between 1963 and 1969 and the second between 1975 and 1977 they were carried*

[95] Goujard, J., C. Rumeau-Rouquette, and M. Saurel-Cubizolles, *Hormonal tests of pregnancy and congenital malformatiHons.* J Gynecol Obstet Biol Reprod (Paris). 1979. **8**(6): p. 489-96.

		out in maternity hospitals. The first test, which was carried out on 12,764 women, had shown no overall association between the use of hormonal tests for the diagnosis of pregnancy (oestrogens-progestogens) and congenital malformation in the infant. The second study, which was carried out on 3,451 women who were questioned in the same way, shows that there is an excessive number of newborn babies with malformations when the mothers took certain products (oestrogens-progestogens when the progestogen was a derivative of testosterone). The problem of methodological bias is discussed as the results are interpreted in the light of epidemiological studies that have recently been carried out abroad.
1979	Shapiro & Slone[96]	**The effects of exogenous female hormones on the fetus** Review of evidence linking use of female hormones in pregnancy to various effects in fetus, including neoplasms, malformations, spontaneous abortion, prematurity and perinatal death. Authors conclusions are as follows: Congenital heart disease – the weight of the evidence points to a connection between female hormones (any) in early pregnancy and CHD. Neural tube defects – the evidence to support the hypothesis is conflicting but there are grounds for suspicion and further studies are needed. Limb reduction deficit – independent confirmation of this hypothesis is needed. VACTEL – evidence for existence of the syndrome are equivocal and if it does exist its association with hormones can be questioned on methodological grounds that include inadequate numbers and possible selection bias.
5th February 1979	MH156_278 Page 5	In the House of Commons debate on the Vaccine Damage Payments Bill Hugh Jenkins MP suggested that the bill should include provision for children who were born with congenital damage following their mother having taken an HPT. In a background note for the Permanent Secretary for Disability it says that the reply to Hugh Jenkins needs to make clear two points. *i) 'that there is no evidence to support the allegation and* *ii)* that even if there were, the damaged children would have no greater claim to *priority in disability*

[96] Shapiro, S. and D. Slone, *The effects of exogenous female hormones on the fetus.* Epidemiol Rev, 1979. **1**: p. 110-23.

		payment than other groups suffering adverse reactions to drugs (eg those who have suffered serious side-effects as a result of taking Eraldin (Practalol)) or indeed to all disabled people, whatever the cause of their disability. The distinguishing feature with vaccine-damaged children is that they were vaccinated as part of a public policy programme to benefit society as much as themselves. This is not the case with women who used hormonal pregnancy tests which were not provided by the Government and which provided a personal benefit.'
April 1979	Rothman et al[97]	**Exogenous hormones and other drug exposures of children with congenital heart disease** A retrospective case control study looking at case infants with congenital heart disease born in Massachusetts between 1973-5 (402 live and 58 dead cases identified). 1500 Control births were selected randomly from all births in the same county during the same time. 92% of cases and 89% of controls responded to the questionnaire/telephone interview. HPT/oral contraceptive use during early pregnancy – 54% cases vs 41% controls. Small positive association for each of the oral contraceptives, HPTs and progestogens. Individually each was compatible with sampling variability; combined RR 1.5 (1.0-2.1). HPTs strongly associated with total anomalous pulmonary venous return, prevalence ratio 11 (1.9-45) based on 2 cases. Trunco-conal defects as a group or individually were not associated with hormone exposure. Authors conclude that the data suggest with 95% confidence that the association between hormones and CHD is characterised by a prevalence of <2.1, and <2.0 for trunco-conal defects. Exogenous hormones, if they cause an increase in CHD, probably cause only a modest increase.
17th December 1979	13196 (German) page 38	**Reprotox Report 'Examination of ZK4.944 (I) and ZK5.422 (II) (1 + 500) on embryotoxic effects in Rhesus monkeys'** The report conclusions read *'The results in group 2 and 3, treated with 0.0004 + 0.2 and 0.004 + 2.0 mg/kg respectively, may indicate a slight*

[97] Rothman, K.J., et al., *Exogenous hormones and other drug exposures of children with congenital heart disease.* Am J Epidemiol, 1979. **109**(4): p. 433-9

		substance induced embryolethal effect (p > 0.10). In contrast, 0.04 + 20.0 mg/kg excerted clearly an embryolethal effect. *However, the examination of the foetuses gave no indication for other embryotoxic, including teratogenic effects after all tested dosages.'*
21st April 1980	Ferencz et al[98]	**Maternal hormone therapy and congenital heart disease** A study looking at a possible association between exogenous female sex hormones and conotruncal malformations. 110 infants with conotruncal cardiac malformation were identified. For each, 3 controls from birth population were selected (1 matched on 8 maternal factors related to likelihood of taking hormones; 2 matched on these plus infant's sex and birth weight; 3 chosen at random). Authors conclude that multilogistic regression analysis controlling for matching variables and scores for reproductive malformation and exposure risks revealed no association of prenatal sex hormone exposure and conotruncal heart disease.
22nd December 1980	Schardein, JL.[99]	**Congenital abnormalities and hormones during pregnancy: a clinical review** A review of the literature. The author concludes that there seems little doubt that hormones have an inherent androgenic potency that can masculinise certain female tissue of which NETA is one of the more potent agents. Realising the limitations of the published studies, when all present data are considered there seems no justification for undue concern over the induction of non-genital malformations through hormone use in pregnancy.
February 1981	BN116_359	The CSM Current Problems Issue 5 February 1981 starts with a piece entitled Medicines in Pregnancy, which reads *'Recent public reports of suspected damage to the fetus following the administration of drugs during pregnancy has led to widespread concern. The Committee on Safety of Medicines and the Committee on the Review of Medicines are constantly aware of the importance of considering the possible teratogenic effects of drugs. Because of the "background" incidence of congenital abnormality, of unknown aetiology, it is difficult to establish a causal*

[98] Ferencz, C., et al., *Maternal hormone therapy and congenital heart disease.* Teratology, 1980. **21**(2): p. 225-39.

[99] Schardein, JL. (1980) Congenital abnormalities and hormones during pregnancy: a clinical review. Teratology 22(3): 251-70

		relationship between a particular drug and fetal damage. At the same time it is impossible to prove beyond a shadow of a doubt that any drug is absolutely safe in pregnancy. The CSM supports the view that drugs should not be given during pregnancy unless they are essential.'
May 1981	Torfs et al[100]	**The relationship between hormonal pregnancy tests and congenital anomalies: a prospective study** A prospective study of 19,906 pregnancies, identified from women reporting for prenatal visit in the area between 1959 and 1966 who expected to deliver at the Kaiser hospital in San Francisco. Exposure to HPTs (n=227, 1.1%); exposure to control nonhormonal pregnancy test (n=876 biologic HCG tests, 4.4% or immunochemical HCG urine test n=415, 2.1%); 17,057 pregnancies with no test. Rate of foetal death was higher for all pregnancy test groups compared with non-test. Crude rates of serious anomalies: HPT 4.4% (n=9) vs serum HCG 4.4% (n=30) vs urine HCG 2.7% (n=9) vs no test 3.8% (n=640). Authors conclude that findings do not support the hypothesis that Estrogen /Progestagen HPTs are associated with an excess of severe congenital abnormalities; however the numbers involved are not large enough to definitively reject the hypothesis either.
1st November 1981	Wilson & Brent[101]	**Are female sex hormones teratogenic?** Review of the literature. Authors conclude that use of exogenous hormones during human pregnancy has not been proven to cause developmental abnormality in nongenital organs and tissues. The quality of epidemiological data does not, at this time, permit a definitive conclusion that sex hormones under as yet undefined conditions have some adverse effect on human prenatal development. If there are risks they are very small, may not be causal and are substantially below the risk of spontaneous malformation. Even in a malformed exposed population the vast majority of malformations could not be attributed to sex hormones. Even positive associations have been of low order of magnitude. In reality, there is no way anyone could state with certainty that a particular non-

[100] Torfs, C.P., L. Milkovich, and B.J. van den Berg, *The relationship between hormonal pregnancy tests and congenital anomalies: a prospective study.* Am J Epidemiol, 1981. **113**(5): p. 563-74

[101] Wilson, J.G. and R.L. Brent, *Are female sex hormones teratogenic?* Am J Obstet Gynecol, 1981. **141**(5): p. 567-80

		genital organ malformation was due to a sex steroid exposure in an individual pregnancy.
2nd July 1982	Bayer Evidence	The Primodos litigation was discontinued at the request of the claimant's counsel. Judge Bingham stated: *I approach this matter with very considerable sympathy with the Defendants' contentions. I remind myself that justice must be done to them as well as to the Plaintiffs, and if the Plaintiffs were adults I think it is exceedingly probably that I should accede to Mr Rougier's submission at least to the extent of giving leave to discontinue on the most stringent terms. As it is, I must bear in mind that these Plaintiffs are children and that although the claims, particularly in one case, are of some age since the child is now 14, nonetheless the claims are still well within the statutory limitation period governing claims by children. Accordingly I conclude that the Plaintiffs should have leave to discontinue, subject to the term that no further action should be brought in respect of the complaints the subject matter of this action without the leave of the Court on such terms as the Court may then impose. I shall not myself impose any term as to the previous payment of costs, although it may be that any Court to whom application was made would impose that term."*
14th July 1982	HC Deb 14 July 1982 vol 27 c408W	Written answers were provided to the following questions put forward by Renee Short MP. *'(1) what advice the Committee on Safety of Medicines gives to doctors concerning the prescribing of the pregnancy-testing drug Primodos; (2) what adverse reactions have been reported connected with the pregnancy-testing drug Primodos;(3) if he is satisfied with the safety aspects of the pregnancy-testing drug Primodos'* Kenneth Clark MP the Secretary of State for Social Services replies *'The indication for pregnancy-testing was removed from the product licences of a number of hormonal preparations, including Primodos, in 1975, because there was evidence of a possible association between taking these products and an increased incidence of congenital abnormalities. The Committee on Safety of Medicines—CSM—advised all doctors in June of that year that they should no longer be used for pregnancy-testing. No hormonal preparation is currently licensed for this indication. The product licence for Primodos expired in 1978 and it is therefore no longer marketed in the United Kingdom.* *The CSM has received 52 reports of adverse reactions suspected to have been associated with Primodos. These included reports of congenital malformations and of vascular disorders.'*

1982		Shortly after the discontinuation of the litigation the ACDHPT ceased active campaigning.
27th February 1983	Michaelis et al[102]	**Prospective study of suspected associations between certain drugs administered during early pregnancy and congenital malformations** Prospective cohort study of women in their first trimester of pregnancy, from 21 obstetrics departments in Germany between 1964-1972. The study was designed to test the hypothesis that there is an association between HPTs (and antiemetics) and teratogenic effects. Women examined initially then observed once monthly. Particular attention given to drug intake plus a number of other factors – recorded in diaries, also checked monthly. Children examined immediately after birth, days 3-5, 6wks, 40wks, 18 months and 36 months. All malformations checked by expert committee on human genetics and paediatricians. Authors conclude that HPT use is not significantly associated with an increase of major malformations. However, the upper 90% confidence intervals were rather high which could be regarded as being consistent with the positive findings of other studies and the lack of statistical significance interpreted as due to the small number of cases.
30th December 1984	Wiseman & Dodds-Smith[103]	**Cardiovascular birth defects and antenatal exposure to female sex hormones: a reevaluation of some base data** A re-evaluation by Schering of the base data as reported by Heinonen et al. from the Drug Epidemiology Unit of the Boston Collaborative Perinatal Project (records of all 19 cases hormone exposed with cardiac malformations and 100 of the 1023 exposed cases without cardiac malformations). The re-evaluation evaluated three matters not considered in the original study: 1. timing of administration 2. incidence of serious maternal bleeding 3. malformations in previous pregnancies Authors conclude that there was a number of inconsistencies in the original base data. Incidence of exposure to sex hormones during the critical period of cardiac organogenesis was not significantly different

[102] Michaelis, J., et al., *Prospective study of suspected associations between certain drugs administered during early pregnancy and congenital malformations.* Teratology, 1983. **27**(1): p. 57-64

[103] Wiseman, R.A. and I.C. Dodds-Smith, *Cardiovascular birth defects and antenatal exposure to female sex hormones: a reevaluation of some base data.* Teratology, 1984. **30**(3): p. 359-70

		statistically in those women whose children had cardiac lesions as compared with those without. *'Re-examination of base data of Boston CPP does not support the reported association between exposure to female sex hormones during pregnancy and the occurrence of serious cardiac malformations.'* See 1992 entry on the E. Hook re-evaluation of this study below.
1985	Polednak, AP.[104]	**Exogenous female sex hormones and birth defects** Critical review of evidence for an association between hormonal exposure in pregnancy and birth defects. Author concludes that there is little evidence for major, direct teratogenic effects of exogenous sex hormones. However there is evidence for slightly increased risks for certain defects including cardiac (perhaps 1.5-2 fold increase but paucity of data from prospective studies prohibit firm conclusions regarding causation), limb-reduction (association with HPT could be confounded by vaginal bleeding as bleeding has been associated with such defects), and multiple defects. Information on association between maternal sex hormone exposure and NTDs is limited. Further investigation is warranted for oral clefts and clubfoot.
April 1985	Resseguie et al[105]	**Congenital malformations among offspring exposed in utero to progestin, Olmsted County, Minnesota, 1936-1974** Medical records of 24,000 women who received prenatal care at the Mayo Clinic were reviewed to identify those exposed to sex hormones before birth (live and stillborn) between1936-1974. There was a higher rate of bleeding during pregnancy and prior foetal and neonatal deaths in the exposed cohort. No tendency for excess of cardiovascular (0.9% vs 0.9%), CNS (2.5% vs 2.3%) or limb reduction anomalies (0.1% vs. 0.2%) or hypospadias observed in exposed group versus unexposed group.

[104] P Polednak, A., *Exogenous female sex hormones and birth defects*. Vol. 13. 1985. 89-114

[105] Resseguie, L.J., et al., *Congenital malformations among offspring exposed in utero to progestins, Olmsted County, Minnesota, 1936-1974.* Fertil Steril, 1985. **43**(4): p. 514-9.

		Authors conclude that there is no support for concept that progestins cause anomalies when given exogenously to pregnant women.
June 1985	Katz et al[106]	**Teratogenicity of progestogens given during the first trimester of pregnancy** Controlled historic prospective study of 2754 infants born to mothers who had bled during the first trimester of pregnancy. The study group consisted of 1608 newborns whose mothers had been treated with progestogens (mostly medroxyprogesterone acetate) beginning in the first trimester. The control group comprised 1146 infants of untreated mothers. All newborns were subjected to thorough examination during the first days of life. No significant difference was found between the treated and the control groups with respect to malformations in any of the systems examined. The overall rate of malformations was 120 per 1000 in the study group and 123.9 per 1000 in the control group. Major malformations occurred at rates of 63.4 and 71.5 per 1000, respectively. The study thus fails to demonstrate an increase in teratogenicity after administration of gestagens during the first trimester of pregnancy.
13th June 1986	Lammer et al[107]	**Exogenous sex hormone exposure and the risk for major malformations** A case-control study of first-trimester sex hormone exposure among mothers of 1,091 infants with Down syndrome or at least one of 11 major malformations. Of the 12 defect categories analysed, only oesophageal atresia had a significant association with HPT exposure *'For each malformation category, the infants with other malformations served as the control group. Associations were found between oesophageal atresia and (1) any sex hormone exposure (odds ratio, 2.84); (2) progestins (odds ratio, 2.87); nonspecified sex hormones (odds ratio, 2.99) and (4) hormonal pregnancy tests (odds ratio, 2.81). We found no potentially confounding variables for this association. WE found no statistically significant association between any malformation category and oral contraceptive exposure. Even if relationship between oesophageal atresia*

[106] Katz, Z., et al., *Teratogenicity of progestogens given during the first trimester of pregnancy.* Obstet Gynecol, 1985. **65**(6): p. 775-8

[107] Lammer, E.J. and J.F. Cordero, *Exogenous sex hormone exposure and the risk for major malformations.* Jama, 1986. **255**(22): p. 3128-32.

		and noncontraceptive sex hormone exposure is causal, the absolute risk would be low, on the order of six per 10,000 exposed live births.'
1987	Bonnema & Dalebout [108]; Olszynko-Gryn[109]	Some of the more recent papers from less developed nations with restricted access to legal abortions appear to higher levels of HPT use, for example the Bonnema and Dalebout paper describing Peru in 1987
February 1987	Hendrickx et al[110]	**Embryotoxicity of sex steroidal hormone combinations in nonhuman primates: I. Norethisterone acetate + ethinylestradiol and progesterone + estradiol benzoate (Macaca mulatta, Macaca fascicularis, and Papio cynocephalus)** Study designed to determine embryo-toxicity of Oestrogen and Progesterone during early pregnancy in non-human primates. After confirmation of pregnancy 43 rhesus monkeys, 40 baboons and 61 cynomolgus monkeys were randomly split into groups then given control, 1x, 10x or 100x human dose equivalent of Norethisterone acetate + ethinylestradiol (for rhesus monkeys and baboons) or 100x, 300x and 1000x human dose equivalent for cynomolgus monkeys daily from day 20 – 50 of gestation. Critical dosage level for embryolethality in all 3 species is 100X HDE. No malformations were observed in the rhesus monkey or baboon but skeletal (scoliosis) or genital malformations were observed in the cynomolgus monkey from doses of 100x HDE. The scoliosis was considered to be a spontaneous occurrence as it was an isolated case. Overall incidence of defects was 1.3% (2 of 152) equivalent to incidence of spontaneous defects. Authors conclude that combined sex steroids such as those used in OCs and HPTs may be embryolethal at high doses but the effects of inadvertent exposure on surviving offspring are inconsequential.

[108] Bonnema, J. and J.A. Dalebout, *The abuse of high dose estrogen/progestin combination drugs in delay of menstruation: the assumptions and practices of doctors, midwives and pharmacists in a Peruvian city.* Soc Sci Med, 1992. **34**(3): p. 281-9

[109] Olszynko-Gryn, J. (2018) A historical argument for regulatory failure in the case of Primodos and other hormone pregnancy tests. Reproductive and Biomedicine Society Online 6: 34–44

[110] Hendrickx, A.G., et al., *Embryotoxicity of sex steroidal hormone combinations in nonhuman primates: I. Norethisterone acetate + ethinylestradiol and progesterone + estradiol benzoate (Macaca mulatta, Macaca fascicularis, and Papio cynocephalus).* Teratology, 1987. **35**(1): p. 119-127

September 1987	Sainz et al[111]	**Progestogens and estrogens in high doses (hormone pregnancy tests): the risk of appearance of spina bifida and anencephaly** The paper is in Spanish, the abstract reads *'A case control study of the teratogenic effect of the combination of high-dose estrogens and progestagens during the first trimester of pregnancy has been carried out. This epidemiological technique is very effective for the detection of unusual adverse side-effects such as congenital malformations.'* *'This study focussed on the association between the administration of these drugs to pregnant women and the increase in spina bifida and anencephalus in the newborn. The results have shown that the women exposed to these drugs have a risk of giving birth to a child with spina bifida or anencephalus 7 to 9 times higher than the non-exposed women, suggesting the additional possibility that sexual hormones may induce other types of malformations.'* (n=7, OR=8.57; 95%-CI 4.28-17.14)
12 January 1989	FDA Federal Register 12 January 1989 (54 FR 1243)	**FDA published revised guideline texts for patients and professional labelling for progestational drugs.** 'Progesterone or progesterone-like drugs have been used to prevent miscarriage in the first few months of pregnancy. No adequate evidence is available to show that they are effective for this purpose. Furthermore, most cases of early miscarriage are due to causes which could not be helped by taking these drugs. There is an increased risk of minor birth defects in children whose mothers take this drug during the first 4 months of pregnancy. Several reports suggest an association between mothers who take these drugs in the first trimester of pregnancy and genital abnormalities in male and female babies. The risk to male babies is the possibility of being born with a condition in which the opening of the penis is on the underside rather than the tip of the penis (hypospadias). Hypospadias occurs in 5 to 8 people per 1,000 male births and is doubled with exposure to these drugs. There is not enough information to quantify the risk to exposed female foetuses, but enlargement of the clitoris and fusion of the labia may occur, although rarely. Therefore, since drugs of this type may induce mild masculinization of the external genitalia of the female fetus

[111] Sainz, M.P., E. Rodriguez Pinilla, and M.L. Martinez Frias, *[Progestogens and estrogens in high doses (hormone pregnancy tests): the risk of appearance of spina bifida and anencephaly].* Med Clin (Barc), 1987. **89**(7): p. 272-4.

		as well as hypospadias in the male fetus, it is wise to avoid using the drug during the first trimester of pregnancy. These drugs have been used as a test for pregnancy but such use is no longer considered safe because of possible damage to a developing baby. Also, more rapid methods of testing for pregnancy are now available.
1992	Meyboom, R.H.B.[112]	**Causality Classification in Pharmacovigilance Centres in the European Community.** Paper on defining causality in pharmacovigilance.
1992	Hook, E.B.[113]	**Cardiovascular Birth Defects and Prenatal Exposure to Female Sex Hormones: A Reevaluation of Data Reanalysis From a Large Prospective Study** Hook re-evaluated the Wiseman & Dodds-Smith study and concluded that *'The study reported here reclassified the cases of the original DEU study in accord with the implications of the Wiseman and Dodds-Smith reanalysis of exposure and disease. After this reclassification, an effect magnitude measure of association, the relative risk rose from 2.33 to 2.48 and remained nominally significant statistically at the .05 level. Thus, if anything, the quantitative consequences of the Wiseman and Dodds-Smith review of the data, when applied in an unbiased manner, result in an increase in the measure of effect. The increase is consistent with the theoretical epidemiological expectation that correction of random errors in a database and of other non-differential misclassification, will tend to raise the estimate of an underlying association in the population studied. While these results reestablish the reported association, they do not, of course, prove that the positive association represents causal induction of defects in conceptuses by female sex hormones.'*
January 1998	Martinez et al[114]	**Prenatal exposure to sex hormones: a case-control study** Hospital-based case control from Spanish Collaborative Study of Congenital Malformations – including over 70 collaborating hospitals throughout Spain between 1976 - 1995. Looking at the effect of prenatal exposure to sex hormones on congenital anomalies

[112] Meyboom RHB, Royer RJ. Causality Classification in Pharmacovigilance Centres in the European Community. Pharmacoepidemiology and Drug Safety 1992; 1:87-97

[113] Hook, E.B., *Cardiovascular birth defects and prenatal exposure to female sex hormones: a reevaluation of data reanalysis from a large prospective study.* Teratology, 1992. **46**(3): p. 261-6

[114] Martinez-Frias, M.L., et al., *Prenatal exposure to sex hormones: a case-control study.* Teratology, 1998. **57**(1): p. 8-12

		20,388 liveborn malformed cases and 19,981 controls (next non-malformed infant of the same sex born in the same hospital as the case and from which same data was collected). The primary outcome measure was 1 of 600 different major and/or mild malformations identified within 3 days of birth, for which, 684 exposed cases (3.3%) 552 exposed controls (2.8%) were identified. Cases had more vaginal bleeding, more prior abortions, more fertility issues and substantially more family history of malformations than controls. Cleft lip and palate were associated with exposure to oral contraceptives and progesterone but the association became nonsignificant when results were stratified by the above mentioned confounding factors. Authors conclude that after controlling for potential confounding factors, the results do not support the hypothesis that prenatal exposure to sex hormones increases the risk of genital and non-genital malformations.
June 1999	Hemminki et al[115]	**Exposure to female hormone drugs during pregnancy: effect on malformations and cancer** Study aimed to investigate whether the use of female sex hormone drugs during pregnancy is a risk factor for subsequent breast and other oestrogen-dependent cancers among mothers/children and for genital malformations in the children. A retrospective cohort of 2052 hormone-drug exposed mothers, 2038 control mothers and their 4130 infants was collected from maternity centres in Helsinki from 1954 to 1963. Cancer cases were searched for in national registers through record linkage. Exposures were examined by the type of the drug (oestrogen, progestin only) and by timing (early in pregnancy, only late in pregnancy). There were no statistically significant differences between the groups with regard to mothers' cancer, either in total or in specified hormone-dependent cancers. The total number of malformations recorded, as well as malformations of the genitals in male infants, were higher among exposed children. The number of cancers among the offspring was small and none of the differences between groups were statistically significant.

[115] Hemminki, E., M. Gissler, and H. Toukomaa, *Exposure to female hormone drugs during pregnancy: effect on malformations and cancer.* Br J Cancer, 1999. **80**(7): p. 1092-7

		The authors conclude that the study supports the hypothesis that oestrogen or progestin drug therapy during pregnancy causes malformations among children who were exposed in utero but does not support the hypothesis that it causes cancer later in life in the mother; the power to study cancers in offspring, however, was very low. Non-existence of the risk, negative confounding, weak exposure or low study-power may explain the negative findings.
16th November 1999	FDA Federal Register 16 November 1999 (64 FR 62110)[116]	FDA revoked the previous rules on labelling of progestational drugs *'In the Federal Register of April 13, 1999 (64 FR 17985), FDA published a proposed rule to revoke its regulation requiring patient labeling for progestational drug products. FDA concluded that, based on a review of the scientific data, such labeling for all progestogens is not warranted. In addition, the diversity of drugs that can be described as progestational and the diversity of conditions these drugs may be used to treat make it inappropriate to consider these drugs a single class for labeling purposes. For more detailed descriptions of the scientific basis for revoking the rule and the history of the rule's adoption, see the proposed rule (64 FR 17985).'*
2007	Neogi, S.B.[117]	**Congenital malformations: unexplored causes** Neogi reports the use of progesterone analogues to test for pregnancy in India despite an official contraindication on use in pregnancy having been in place for over 30 years
2009	*EWG Documents submitted through public call for information*	In 2009 the ACDHPT was relaunched with Karl Murphy as president.
22nd February 2010	*Hansard*	Written answers Mike O'Brien MP provided the following in answer to questions from Mike Pennington MP. In response to being asked whether an estimate of the number of people there are in England who have been adversely affected by the drug Primodos had been made he replied that the MHRA collect Yellow card reports from the UK and that it is not possible to calculate the number of people affected from Yellow card reports. *'As of 12 February 2010, there are three retrospective cases for Primodos and 3,540 that have been recorded in our database for the combined drug substances norethisterone and ethinylestradiol.'* When asked what steps the Department of Health had taken to

[116] https://www.govinfo.gov/content/pkg/FR-1999-11-16/pdf/99-29854.pdf

[117] Neogi, S.B., *Congenital malformations: unexplored causes.* Indian Pediatr, 2007. **44**(12): p. 941

		assess the needs of those adversely affected by Primodos he replied *'We have made assessment. It is for local clinicians and multi-disciplinary teams to assess the health and care needs of people adversely affected by Primodos.'*
26th October 2010	*Hansard*	Written answers Lord Alton received answers to written questions on; the dosage of norethisterone and ethinylestradiol in Primodos; currently marketed drugs containing these ingredients, including what warnings were given with them and whether disabilities had occurred in children of women who used these drugs; what actions had been taken to assess needs of those affected; whether the Government would meet with those affected and with Bayer; and what assessments had been made of the safety of Primolut. In answer he was told that there were many preparations that contained these ingredients for a variety of indications, but none at the same dose as Primodos. That there are warnings of potential side effects in the patient information leaflet that accompanies each medicine, including information about use in pregnancy. All medicines on the UK market are continuously monitored to ensure the benefits outweigh the risks. *'As of 13 October 2010 the MHRA had received a total of 32 UK spontaneous "suspected" ADR reports associated with the combination of the drug ingredients norethisterone and ethinylestradiol (other than Primodos) which describe a congenital abnormality. These reports were received over a period of 45 years.'* The answer went on *'In the absence of any significant new scientific evidence that has become available since Primodos was discontinued, a meeting such as that suggested would be unlikely to benefit any of those concerned. Local clinicians and multidisciplinary teams assess the health and care needs of people who consider that they have been adversely affected by Primodos or other hormonal pregnancy tests. The MHRA therefore has no current plans to meet members of the Association for Children Damaged by Hormone Pregnancy Tests, people suspected to have been adversely affected by the drug Primodos, or with the pharmaceutical company, Bayer.'* The information given on Primulot ends *'As with all medicines used in the UK, the MHRA, together with advice from an independent advisory body, the Commission on Human Medicines, keeps the safety of Primolut N under continuous review. The MHRA is not aware of any current safety issues with Primolut N.'*
23rd January 2012	EWG minutes and COIs - Dr Laura	Legal aid was obtained to review new evidence arising since the discontinuation of the previous litigation in 1982. On 23 January 2012 the UK Teratology information service (UKTIS) were commissioned by Prof Steve Robson to produce a written review of the literature published post

	Yates statement	1982, on Primodos, OCs and Hormonal Pregnancy Tests. Prof Robson used the UKTIS review of the published data to write a legal report for XXX from XXX solicitors who was acting on behalf of individuals with birth defects whose mothers were exposed to primodos and who were seeking to bring a claim against Bayer on the basis it was a pharmaceutical teratogen. The UKTIS review of HPT and oral contraceptive (OC) exposure was subsequently published in the EWG evidence. Regarding HPTs the review concluded *'The single study published post-1982 on Primodos does not demonstrate an association between Primodos exposure in pregnancy and an increased overall risk or specific pattern of congenital malformation in exposed offspring. No reports regarding fetal outcome following the use of oral hormonal pregnancy tests other than Primodos were found in the published literature post-1982.'* On oral contraceptive pills the report concluded *'Data produced since 1982 do not suggest an association between maternal use of OC in pregnancy and congenital malformations in general, cardiac malformations, neural tube defects, or risk of neonatal or infant death. Conflicting findings have been produced by studies investigating the risk of limb reduction defects, genital defects and low birth weight.'* It goes on to finish *'Adequate data which has not been confounded or limited by methodology of data collection or analysis are lacking. Therefore, defining or excluding continued maternal OC or sex hormone exposure in pregnancy use as a contributory factor in the aetiology of these malformations and neonatal outcomes is not currently possible.* *Until more robust studies are available, which is unlikely given the circumstances of exposure, it will not be possible to definitively exclude an association between maternal OC use in early pregnancy and birth defects. Collective data published since 1982 however, do not provide sufficient evidence that an increased risk exists.'*
February and June 2012	Hansard	29 February 2012 an Early Day Motion calling for a public inquiry was tabled by Yasmin Qureshi MP. "*That this House notes that children were born with serious deformities due to hormone pregnancy test drugs taken by expectant mothers between 1953 and 1975; further notes with concern that as the surviving victims enter their 40s and 50s many of them face a host of new problems as their bodies continue to suffer; further notes that no official warnings were issued about these drugs until eight years after the first reports indicated possible dangers; further notes that some doctors continued to prescribe the drugs for pregnant women after official warnings from the Committee on Safety of Medicines; further notes that the Department of Health in the past has continuously rejected requests for an inquiry into these*

		matters; and calls on the Secretary of State for Health to set up an independent public inquiry." 21 June 2012 an identical Early Day Motion was tabled by Yasmin Qureshi MP
July 2012		MHRA met with Esther McVey MP, then Minister for Disabled People.
January 2014	'Assessment of historical evidence on Primodos and congenital malformations.'	MHRA met with Yasmin Qureshi MP and Dan Poulter MP, then Parliamentary Under Secretary of State for Health, who asked MHRA to provide a summary of findings from the historical evidence.
March 2014		The MHRA published 'Assessment of historical evidence on Primodos and congenital malformations.' This report looked at 36 published studies and concluded that *'The body of evidence for an association between HPTs and congenital anomalies is mixed, with some studies finding a strong association, some finding a weak association and many others finding no association. Although it is understandable to suspect that there may be an association between a medicine and a condition that develops after taking it, particularly when that medicine is taken during pregnancy, this may not necessarily be the case. The timing of exposure is critical and needs to occur during the period of gestation when the fetus is susceptible to the observed outcome. The association also needs to be plausible; in this case the observation of isolated but different anomalies in different studies is particularly difficult to interpret. If HPTs really were teratogenic, all studies should have observed increased numbers of all the observed that have been anomalies because women were exposed to HPTs at random times throughout gestation. In addition the scientific methodology needs to be sufficiently robust as to exclude false positive findings ie the possibility that other factors could have been responsible for the observed finding - this is not the case for the vast majority of studies. Having carefully considered the available published evidence, our position therefore remains that the data are not sufficient to conclude that there is a causal association between the use of Primodos (or any HPT) and congenital abnormalities.'*

June 2014	Tümmler et al[118]	**Congenital bladder exstrophy associated with Duogynon hormonal pregnancy tests – signal for teratogenicity or consumer report bias?** Study evaluating 296 consumer reports of the German Duogynon (Primodos in the UK) database and comparing the reported birth defects with data from a population-based birth registry. The abstract notes that *'The most striking result is an increase of bladder exstrophy (OR = 37.27; 95%-CI 14.56–95.28). Neural tube defects (OR = 2.99; 95%-CI 1.85–4.84) and renal agenesis (OR = 2.53; 95%-CI 1.17–5.45) were also significantly increased. Bladder exstrophy may be a yet undetected teratogenic effect of Duogynon, but may also represent a reporting bias. The present study highlights the difficulties of evaluating consumer reports which may be influenced by public media.'* In the paper the authors state *'The most remarkable result of our study is the 37-fold risk increase for bladder exstrophy (OR = 37.27, 95%-CI 14.56–95.28) in association with prenatal exposure to Duogynon. Bladder exstrophy is a rare major developmental defect caused by absence of mesodermal differentiation [11] between the 6th and 7th gestational week.'*
23rd October 2014	Hansard	A debate on Oral Hormone Pregnancy Tests took place, it was proposed by Yasmin Qureshi MP and was based on the same Early Day motion previously tabled. In this debate the history was reviewed, including newly discovered documents from the LandesArchiv and the Sky Documentary; the MHRA assessment of the historic evidence was criticized; the alleged destruction of medical records was raised; assertion of falsification of research records (not related to HPTs) by Professor Briggs (formerly of Schering) was noted; the integrity of witnesses in the litigation was questioned; the request for an expert panel to examine all the documentation held by the government and ALBs on this issue and to recommend an inquiry if necessary. At the conclusion of the Debate George Freeman MP the Parliamentary Under-Secretary of State for Health stated *'Members have asked that the Department fully disclose all documents on hormone pregnancy tests held between 1953 and 1978. While I support that request, I remind the House that we are talking about an era that mostly predated medicines legislation and companies were*

[118] Tummler, G., et al., *Congenital bladder exstrophy associated with Duogynon hormonal pregnancy tests-signal for teratogenicity or consumer report bias?* Reprod Toxicol, 2014. **45**: p. 14-9

		not required even to submit evidence to support the efficacy, quality and safety of their products—extraordinary though that may seem to us today. As a result of that, and the fact that the pregnancy tests were withdrawn from use more than 35 years ago, the Department holds very limited information and what it does hold is already in the public domain. That said, I am happy to confirm to the House this afternoon that I will instruct that all relevant documents held by the Department be released. *The MHRA will of course review any new data that emerge as a matter of priority and seek independent expert advice as needed. I am happy to go further and confirm to the House that I will instruct an independent review of the papers and all the evidence. I suggest that that be carried out by the Medicines for Women's Health Expert Advisory Group, which exists to advise the Department on such matters. It comprises independent members who are experts in their field, and I am happy to take submissions from colleagues to ensure that the association is properly represented and has a chance to give evidence.'*
November 2014 to October 2015		The CHM of the Expert Working Group on Hormone Pregnancy Tests was established. It investigated the issue of an association between the use of HPTs and congenital malformations. This included holding a public call for evidence, obtaining evidence from the National Archives and the LandesArchiv, and other published research.
14th October 2015	EWG Report Annexes [119]	The first meeting of the EWG. The minutes record the terms of reference at point 4 *'The terms of reference for the Group were therefore amended and agreed as follows: 1. To consider all available evidence on the possible association between exposure in pregnancy to HPTs and adverse outcomes in pregnancy (in particular congenital anomalies, miscarriage and stillbirth) including consideration of any potential mechanism of action; 2. To consider whether the Group's findings have any implications for currently licensed medicines in the UK or elsewhere; 3. To draw any lessons for how drug safety issues in pregnancy are identified, assessed and communicated in the present regulatory system and how the effectiveness of risk management is monitored; 4. To make recommendations.'*
4th December 2015	EWG Report Annexes	The second meeting of the EWG.

[119] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/667482/Minutes-declaration-of-interests-redacted.pdf

25th April 2016	EWG Report Annexes	The third meeting of the EWG.
May 2016	Coomarasamy A, et al[120]	PROMISE TRIAL 2016. In the results of the PROMISE trial were published. This was a randomised, double-blind, placebo-controlled, international multi-centre study on the effect of progesterone therapy on recurrent miscarriage conducted in hospital settings across the UK and the Netherlands. Each participant in the PROMISE trial received either micronised progesterone at a dose of 400 mg (two vaginal capsules of 200 mg) or placebo vaginal capsules twice daily, administered vaginally from the date of randomisation soon after a positive urinary pregnancy test (and no later than 6 weeks of gestation) until 12 completed weeks of gestation (or earlier if the pregnancy ended before 12 weeks). No statistically significant difference between the groups was found on miscarriage rates, still births and neonatal survival. Congenital abnormalities rates were also measured. These were non-significant: progesterone group 3.0% (8/266) vs. placebo group 4.0% (11/276); RR 0.75, 95% CI 0.31 to 1.85; $p = 0.54$].
11th August 2016	EWG Report Annexes	The fourth meeting of the EWG.
13th October 2016	Hansard	A debate on HPTs took place in the House of Commons '*That this House notes that an Expert Working Panel Group Inquiry was set up by the Government to investigate and assess evidence on children born with serious deformities due to hormone pregnancy test drugs taken by expectant mothers between 1953 and 1975; further notes with concern that the terms of reference as set out by the Medicines and Healthcare Products Regulatory Agency do not clearly allow for an investigation into the systematic regulatory failures of government bodies at the time; notes the conflict of interest of some panel members; further notes that all evidence must be presented to expert panel members as set out in the term of reference; calls on the Inquiry to ensure that all evidence is presented to the expert panel with sufficient time for due consideration; further calls on the inquiry to guarantee thorough background checks on all panel members; calls for the terms of reference to be amended to include an investigation into the conduct of the Committee on Safety of Medicines; further calls on the Government to ensure that the inquiry has the trust and confidence of the victims for whom it was set up; and believes that, unless these changes are made, the ability of the Inquiry to achieve a fair outcome will be significantly compromised.'* In this debate the regulatory history was reviewed. The scope of the Expert

[120] Coomarasamy A, et al *Health Technol Assess* 2016;20(41)

		Working Group review was criticized for not including regulatory failure and the workings of the EWG were criticized for; a lack of transparency and use of 'gagging clauses'; the way in which members of ACHPT had been treated by the EWG; conflicts of interest of EWG members and questioning the suitability of panel members, including specifically mentioning Laura Yates having used social media to promote research she had done suggesting a causal link between HPT use and congenital malformations could not be proven; not providing a clear finish date; not giving sufficient time for members to read large volumes of documentation; a difficulty in obtaining translations of documents in German held in Berlin. The Parliamentary Under-Secretary for Health, David Mowat MP, responded by saying *'We have heard some strong words today: "establishment whitewash", "sham inquiry" and "a blanket over the issues". I say again: nobody on the Government side of the House has any interest in anything other than getting to the truth, and the process that was put in place two years ago had that at its heart.'* He continued *'…we have heard that there was a regulatory failure and that the inquiry should look at it. I say to the House that if, when the expert group reports next spring, it finds a clear causal link, that will be the time to take further action on issues such as regulation and liability, and everything that goes with that. The first step we are taking is to establish the science. The group that has been set up is an expert group. It is science-led. It is important to make it clear in the House that we are not criticising individual members, because they are striving to get to the truth. It is a group of eminent people.* *It would be quite wrong if we conflated the possible eventual need to look at the regulatory actions that were taken, the legal liabilities and everything that goes with that, with the first step of the process, which is to establish whether the science leads us to that link. In spite of some of the comments that have been made today, that has not been done yet in any country. The first serious attempt to do it is the one that is going on now.'* He then stated that the MHRA had taken a vigorous approach to conflicts of interest and that the claims made earlier in debate about Dr Yates would be investigated and outlining how action had been taken to remove a member of the advisory group for a conflict of interested. He stated that all the evidence in German would be translated and put before the group, but that this was not a quick process, and that the confidence of the ACDHPT was essential and he would be happy to answer any letters from them.

Annex B: HPT Timeline – Key Events

18th October 2016	*EWG Report Annexes*	The fifth meeting of the EWG.
31st January 2017	Youtube[121]	A conference was held at Cambridge University 'The Contested History of Hormone Pregnancy Tests'. This was organized by Dr Jesse Olszynko-Gryn with support from the Wellcome Trust, History & Policy, and Generation to Reproduction. Participants included international academics and the programme included a screening of "Primodos: The Secret Drug Scandal", 1978 followed by various talks. Speakers included Mrs Lyon on documents obtained from the British National Archive and the Landesarchiv Berlin; Professor John Abrahams on UK drug regulation before and after thalidomide; Professor Tim Lewens about the difficulty of the decision-making process with evidential uncertainty; and Dr. Neil Vargesson on his research on the impact of Primodos components on embryonic development.
21st March 2017		On a Sky News documentary Primodos: The Secret Drug Scandal presented by Jason Farrell was released. This documentary used material from the LandesArchiv Berlin and the National Archives as well as interviewing affected individuals. This documentary covered the history of Primodos. The behaviour and knowledge of the manufacturer Schering was examined, including the extent of pre-market testing, keeping the product on the market after safety concerns had been raised, their awareness that the product was believed to act as an abortifacient in some countries and their relationship with the UK drug regulator. The actions of the UK drug regulator, in particular of Dr Bill Inman, was a focus, including their alleged inaction over HPTs, Dr Inman's advice to Schering of a 5:1 relative risk of anomalies among children born to women who had used an HPT, the destruction of medical records on which studies were based, and Dr Inman acting as a witness for Schering in the subsequent litigation.
27th March 2017	EWG Report Annexes[122]	The sixth meeting of the EWG.
24th April 2017	EWG Report Annexes	The 7th and final meeting of the EWG.

[121] Playlist: https://www.youtube.com/playlist?list=PLWSzZ44spEiBmhRniZsf9VzNLbQFzdtke

[122] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/667482/Minutes-declaration-of-interests-redacted.pdf

15th November 2017	Expert Working Group	The report set out to address three key issues and to make recommendations. *'**To consider all available evidence on the possible association between exposure in pregnancy to HPTs and adverse outcomes in pregnancy (in particular congenital anomalies, miscarriage and stillbirth) including consideration of any potential mechanism of action** The EWG's overall finding is that the available scientific evidence, taking all aspects into consideration, does not support a causal association between the use of HPTs, such as Primodos, during early pregnancy and adverse outcomes, either with regard to miscarriage, stillbirth or congenital anomalies. All the available relevant evidence on a possible association has been extensively and thoroughly reviewed with the benefit of up-to-date knowledge by experts from the relevant specialisms.'* *'**On whether the Expert Working Group's findings have any implications for currently licensed medicines.** The findings of the review for HPTs, including Primodos, on a possible association between exposure in pregnancy to HPTs and adverse outcomes in pregnancy do not have implications for any currently licensed medicines. They are in fact considered to be reassuring for women who may inadvertently become pregnant whilst taking these hormones for contraception or gynaecological indications.'* ***'To draw any lessons for how drug safety issues in pregnancy are identified, assessed, and communicated in the present regulatory system and how the effectiveness of risk management is monitored.** There have been substantial and far-reaching advances in all areas of the development, regulation, study and use of medicines in pregnancy since HPTs were available in the UK, whereas there was a lack of transparency in the past. Nevertheless, ways to strengthen further how safety concerns in pregnancy are detected, managed, evaluated and communicated should be taken forward.'* The following recommendations were made *'The EWG considered that a number of steps could be taken to safeguard future generations through strengthening the systems in place for detecting, evaluating, managing and communicating risk with exposure to medicines in early pregnancy. These include:* *• undertaking an annual review of all reported congenital anomalies with independent scientific advice of CHM, published in its annual report*

		• facilitating research by optimising the collection of, access to and use of data on medicines in pregnancy *• safeguarding future generations through improved training and guidance of healthcare professionals* *• working to improve the impact of safety messages on the risks of medicines in pregnancy.* *• In addition, families of the Association for Children Damaged by HPTs, whose lives have been impacted by adverse pregnancy outcomes and who were given HPTs to diagnose pregnancy should be offered a full up-to-date genetic clinical evaluation.'* Concerns were raised about the EWG process throughout. Minutes of the meetings can be found here.
15th November 2017		A press release was held and considerable dissatisfaction was expressed at the report and the organization of the press release, for example Yasmin Qureshi MP is quoted in the Guardian newspaper the following day *"I am completely disgusted by the report. They clearly have not looked at the evidence that was presented to them. If they had looked at the evidence presented to them they could never have arrived at the conclusion they have now. This report is a complete whitewash. It is not worth the paper it has been printed on."*
13th December 2017		Nick Dobrick, the independent observer was reported by Sky News as not endorsing EWG report. '*The Government is facing embarrassment after an expert said he was angry after being used to endorse last month's report into pregnancy test drug Primodos. Thalidomide campaigner Nick Dobrik told Sky News he disagrees with the report's conclusions, describing them as "plainly and simply wrong".'*
14th December 2017	Hansard	Parliamentary debate proposed by Sir Mike Penning *'That this House regrets that the terms of reference for the Commission on Human Medicines Expert Working Group on Hormone Pregnancy Tests asked the Commission to consider evidence on a possible association between exposure in pregnancy to hormone pregnancy tests and adverse outcomes in pregnancy, but the Commission's Report concluded that there was no causal association between the use of hormone pregnancy tests and babies born with deformities between 1953 and 1975, even though it was not asked to find a causal link; believes that the inquiry was flawed because it did not consider systematic regulatory failures of the Committee on Safety in Medicines and did not give careful consideration to the evidence presented to it; and calls on the Government, after consultation with the families affected so they have confidence in the process, to establish a Statutory Inquiry*

		under the Inquiries Act 2005 to review the evidence on a possible association with hormone pregnancy tests on pregnancies and to consider the regulatory failures of the Committee on Safety in Medicines.' These issues were all debated. As was the legal action and payment of compensation in an American case, the treatment of ACDHPT member when they went to give evidence to the EWG, the use of 'gagging clauses' on observers. In answer the Parliamentary Under-Secretary of State for Health, Steve Brine replied *'The terms of reference set out the scope of the review, and I do not believe that they changed. They were endorsed by the CHM in December 2014 a few weeks after the previous debate, and confirmed by the then Minister, my hon. Friend the Member for Mid Norfolk, in a letter to the all-party group in September 2015. In the same letter, the all-party group was informed:* *"it is important to review the scientific evidence to establish whether there is any causal association between use of HPTs and subsequent birth defects in the child."* *It is implicit and integral to any scientific assessment of evidence on medicines and associated harms to see whether the medicine is actually responsible for causing the harm rather than simply being associated with it.'* He went on and *'I know that many Members are concerned about differences in the draft and final reports, and especially over the removal of the sentence that said:* *"limitations of the methodology of the time and the relative scarcity of the evidence means it is not possible to reach a definitive conclusion."* *That sentence in the draft report was followed immediately by the group's overall finding* *"that the available scientific evidence does not support a causal association between the use of HPTs such as Primodos, during early pregnancy and adverse outcomes."* *The CHM quite rightly considered the two sentences together to be misleading, and advised that the report should be revised to better reflect the scientific—I stress, scientific—conclusion of the group, and that is set out on page 100 of the final report'* The regulatory aspects were outlined. 'Ministers have always been clear that issues of historic regulatory process were outside the scope of this review because there first needed to be clarity on whether there might be a link between HPTs and birth defects. On transparency he stated *'…the transparency issue and the "gagging order". As I said during the urgent question, I can assure the House that, in being asked to sign a confidentiality undertaking, Mrs Lyon, who is here today—and I pay great tribute to her for her work—was not in any way treated differently from other panel members. This is standard procedure so that discussions can be held freely*

		and openly in the group without external interference or a running commentary in, God forbid, the media. Despite being an observer throughout the review, Mrs Lyon was invited to speak after every agenda item and asked to give a presentation to the group on the evidence she had provided for the review.'
13th February 2018	**Brown et al 2018[123]**	**The Primodos components Norethisterone acetate and Ethinyl estradiol induce developmental abnormalities in zebrafish embryos** Brown et al was published on in Nature Scientific Notes in February. Findings include limb deformities, vascular disruption, yolk sac and eye abnormalities when zebrafish embyros are exposed to the components of primodos. *'We show that Norethisterone acetate and Ethinyl estradiol cause embryonic damage in a dose and time responsive manner. The damage occurs rapidly after drug exposure, affecting multiple organ systems. Moreover, we found that the Norethisterone acetate and Ethinyl estradiol mixture can affect nerve outgrowth and blood vessel patterning directly and accumulates in the forming embryo for at least 24 hrs. These data demonstrate that Norethisterone acetate and Ethinyl estradiol are potentially teratogenic, depending on dose and embryonic stage of development in the zebrafish. Further work in mammalian model species are now required to build on these findings and determine if placental embryos also are affected by synthetic sex hormones and their mechanisms of action.'*
Early 2018	CHM website	Following the publication of Brown et al the CHM convened a different group of scientists from the original EWG, the zebrafish ad hoc expert working group to examine i. the suitability of the zebrafish model for evaluating effects of norethisterone and EE in human pregnancy; ii. the robustness of the study; and iii. any clinical implications.
May 2018	CHMP website	The MHRA also made a referral to the European Medicines Agency under article 5(3) of Regulation EC 726/2004. This asked the Committee for Medicinal Products for Human Use (CHMP) to provide a scientific opinion. A report is prepared by a rapporteur and co-rapporteur who are from a different member state to the country making the request and to each other. This report is then put the CHMP for them to consider, and, if necessary, to vote on. A scientific opinion will be

[123] Brown, S., et al., *The Primodos components Norethisterone acetate and Ethinyl estradiol induce developmental abnormalities in zebrafish embryos.* Scientific Reports, 2018. **8**(1): p. 2917

		adopted if quorum is reached (two thirds of members present) and either a consensus is reached by all member states or if consensus cannot be reached a majority vote in favour. The UK sought an opinion on i. The suitability of the zebrafish model for evaluating effects of norethisterone and EE in human pregnancy; ii. the robustness of the study; and iii. any clinical implications.
5th October 2018	CHM	The zebrafish ad hoc working group convened to consider the Brown et al paper, including a presentation from Professor Vargesson.
18th August 2018	Olszynko-Gryn, J. (2018)[124]	An analysis of the historical evidence which concluded that there had been regulatory failure in the cases of Primodos and other hormone pregnancy tests.
18th October 2018	CHMP[125]	The CHMP report was published. It was agreed by consensus. It stated *'If appropriately qualified, a well-performed zebrafish embryotoxicity test may contribute to the evaluation of the teratogenic potential of a compound as part of an integrated testing strategy. A proper qualification of a Zebrafish embryotoxicity test has not yet been performed and it is premature to conclude on its suitability to predict potential teratogenic effects of norethisterone and ethinylestradiol in human pregnancy. The results of such a study still needs to be evaluated together with all available in vivo non-clinical and human data, including exposure data, as part of an integrated risk assessment approach.* *The data evaluated as part of this procedure indicates effects on survival and development of the zebrafish embryo following direct exposure of a mixture of NA and EE in a ratio of 500:1 at multiple orders of magnitude higher than free plasma exposure in humans after intake to Primodos. However, the reliability of the performed studies could not be fully evaluated due to methodological limitations. The available data is not considered sufficient for establishing a direct teratogenic effect of the NA/EE mixture or of the individual components. Overall due to the multiple limitations of the study described in the manuscript (Brown et al., 2018) the results of this study do not add to the current knowledge regarding adverse events in early pregnancy in human. The CHMP concluded that there are*

[124] Olszynko-Gryn, J. (2018) A historical argument for regulatory failure in the case of Primodos and other hormone pregnancy tests. Reproductive and Biomedicine Society Online 6: 34–44

[125] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Assessment report Procedure under Article 5(3) of Regulation (EC) No 726/2004 INN/active substance: norethisterone and ethinylestradiol Procedure no: EMEA/H/A-5(3)/1470 https://www.ema.europa.eu/en/documents/report/assessment-report-article-53-procedure-norethisterone-ethinylestradiol_en.pdf

		no new clinical implications based on the results of the presented zebrafish study.'
19th October 2018	CHM	The CHM published the zebrafish ad hoc working group report. The minutes record that the following conclusions were agreed unanimously. ***'8.1 The suitability of the zebrafish model for evaluating the effects of norethisterone and ethinylestradiol in human pregnancy:*** *8.1.1 The Group considered that zebrafish can be a useful model system for studying developmental toxicity but there are currently limitations such that translation of the observed effects to human pregnancy outcomes is not possible. Although developmental processes are highly conserved between fish and humans there are molecular and physiological differences that can affect the specificity of a response. The model has been used for identifying potential mechanisms at the molecular target level and generating information for key events in an adverse outcome pathway rather than direct extrapolation to humans. The model in general can be used to complement, rather than provide an alternative to, established regulatory mammalian developmental toxicity assays.* *8.1.2 The Group concluded that the zebrafish model can provide information on qualitative effects of chemicals in general, however, for NETA/EE, there is a lack of information on the pharmacology, pharmacokinetics and mechanisms that makes interpreting the relevance of the observed findings for humans challenging.* *8.2 The robustness of the study:* *8.2.1 The Group acknowledged that the Brown et al., 2018 study was generally well conducted and that the limitations of the study were recognised by the authors. The Group concluded that the observed developmental effects were general and occurred in a range of different organ systems. It was noted that effects occurred on a steep concentration gradient and that lethality overlapped with developmental effects. The group determined that the effects were pleiotropic in nature and that further investigation could reveal additional effects. There are no mechanistic explanations for the observed effects, many of which are most likely non-classical receptor mediated.* ***8.3Any clinical implications:*** *8.3.1 The Group concluded that knowledge gaps existed and that information on the pharmacokinetics, pharmacology and phenotypes of the responses would be required to fully elucidate the translational relevance of this data to humans. Developmental effects occurred at concentrations in the zebrafish embryo that were several orders of magnitude*

		higher than would occur following clinical doses. Consequently, the Group considered that the Brown et al., 2018 study should be considered with the existing evidence as part of the overall weight of evidence and concluded that the study does not raise any new safety concerns for products in clinical use containing norethisterone acetate and ethinylestradiol'
31st October 2018	Heneghan et al 2018[126]	**Oral hormone pregnancy tests and the risks of congenital malformations: a systematic review and meta-analysis** Version one of the Heneghan meta-analysis published. (It has subsequently been updated to version 2) The article states *'**Results:** We found 16 case control studies and 10 prospective cohort studies, together including 71 330 women, of whom 4,209 were exposed to HPTs. Exposure to oral HPTs was associated with a 40% increased risk of all congenital malformations: pooled odds ratio (OR) = 1.40 (95% CI 1.18 to 1.66; P<0.0001; I^2 = 0%). Exposure to HPTs was associated with an increased risk of congenital heart malformations: pooled OR = 1.89 (95% CI 1.32 to 2.72; P = 0.0006; I^2=0%); nervous system malformations OR = 2.98 (95% CI 1.32 to 6.76; P = 0.0109 I^2 = 78%); gastrointestinal malformations, OR = 4.50 (95% CI 0.63 to 32.20; P = 0.13; I^2 = 54%); musculoskeletal malformations, OR = 2.24 (95% CI 1.23 to 4.08; P= 0.009; I^2 = 0%); the VACTERL syndrome (Vertebral defects, Anal atresia, Cardiovascular anomalies, Tracheoesophageal fistula, Esophageal atresia, Renal anomalies, and Limb defects), OR = 7.47 (95% CI 2.92 to 19.07; P < 0.0001; I^2 = 0%).* ***Conclusions:** This systematic review and meta-analysis shows that use of oral HPTs in pregnancy is associated with increased risks of congenital malformations.'*
November 2018	CHM	Following the publication of Heneghan et al the CHM convened a new ad hoc expert working group to examine i. the suitability and robustness of the methodology, including the selection and application of the data quality score; ii. any clinical implications.
27th November 2018	CHMP website	The MHRA also made a referral to CHMP at the European Medicines Agency under article 5(3) of Regulation EC 726/2004. i. the suitability and robustness of the methodology, including the selection and application of the data quality score;

[126] Heneghan C, Aronson JK, Spencer E *et al.* Oral hormone pregnancy tests and the risks of congenital malformations: a systematic review and meta-analysis [version 2; peer review: 3 approved]. *F1000Research* 2019, **7**:1725 (https://doi.org/10.12688/f1000research.16758.2)

		ii. any clinical implications.
27th November 2018	Sky Documentary	Sky report by Jason Farrell Exclusive: Oxford University study links pregnancy drug Primodos to birth defects
January – March 2019		On 30 January 2019 an FOI request was made by Yasmin Qureshi to MHRA for the raw data used by the EWG. Further requests were emailed MHRA in February. The requested information was emailed on 8 March with the email stating *'The forest plots included in the EWG report display the results from the published studies. No further analysis or meta-analysis on the raw data presented in the published studies was performed and the forest plots were created only as a graphical display of the data to aid interpretation and discussion during the EWG. Where the original studies reported an odds ratio or relative risk with 95% confidence intervals these were used directly for the forest plots. Some studies however did not calculate an odds ratio or relative risk and presented absolute numbers only. At the request of the EWG, in order that these studies could be included in the forest plots, odds ratios or relative risks and 95% confidence intervals were calculated using the published raw data in the papers. All raw data that was used in the forest plots is available in the published papers.'*
18th March 2019		The EWG ad hoc group convene (different membership to original EWG, chaired by Prof. Hannaford) to consider the Heneghan meta-analysis.
23rd April 2019	Hansard[127]	Westminster Hall debate on Hormone pregnancy tests was held. Various points were raised; that the EWG report had not considered the regulatory actions around HPTs; transparency and gagging clauses; the issue of possible v causal association; the independence of EWG members and the fact that MHRA is part funded by the pharmaceutical industry; the FOI request for the raw data; changes of wording between the draft and final report.
26th April 2019	EMA[128]	**Assessment report - Procedure under Article 5(3) of Regulation (EC) No 726/2004 Norethisterone and ethinylestradiol** Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

[127] Hansard. Hormone Pregnancy Tests. Westminster Hall debate. 23 April 2019. Volume 658

[128] https://www.ema.europa.eu/en/documents/referral/assessment-report-article-53-procedure-norethisterone-ethinylestradiol-emea/h/53/1477_en.pdf

6th May 2019		The CHMP report was published. It was agreed by consensus. It concludes *'Therefore, the quality of most studies used is questioned and, as a result, the conclusions of the metaanalysis cannot be considered reliable. Due to the multiple limitations of the meta-analysis study, the results described in this manuscript cannot be used to further expand clinical knowledge. The results of this meta-analysis, thus, have no clinical implications. As a consequence, the conclusion that current clinical data available do not support a signal of teratogenicity of a combination of norethisterone/ethinylestradiol remains valid. The CHMP therefore did not recommend any further regulatory actions based on the above data.'*
6th May 2019		EWG ad hoc report was also published. The minutes note *'Having considered the meta-analysis by Heneghan et al. at length the Members advised that the methods used were not in line with best practice, the application and choice of NOS was questionable, and the study could not be considered robust. The Members further advised that due to limitations in the design, reporting and analysis of the included studies there would be little value in re-analysing the data.'* They continue *'On the basis of the Group's findings, no implications for currently authorised medicines could be concluded.'* There is a **post meeting note** in the Ad Hoc group minutes which notes that in response to some of the questions that were raised at the meeting Professor Heneghan provided *'further details of the selection of controls and reasons for exclusion of some control women from the analysis; selection of confounding variables across studies; an analysis of the data from studies that took account of a previous history of congenital malformations. Professor Heneghan also provided:* • *a protocol, date stamped 23rd October 2018, which was also published online on 25th March 2019* • *a link to an article by the authors, dated 15th March 2019, on assessing bias in studies of harms* • *a meta-analysis of the results presented in the report of the CHM Expert Working Group on HPTs, published in November 2017.* *All additional information provided by Professor Heneghan was sent to the Group on 5th April 2019. The Group was asked whether anything in the responses changed their overall conclusion on the suitability and robustness of the methodology, the selection and application of the data quality score and any clinical implications of the meta-analysis by Heneghan et al. The Group advised that the*

		additional information did not alter the conclusions that had been reached at its meeting on 18th March.'
mid August 2019		The ACDHPT announced that they are preparing to take legal action against Bayer, Sanofi and the regulators.

Oral contraceptives

The following events relating to how regulators responded to the thromboembolism risk associated with the first generation of oral contraceptives have been mentioned in evidence supplied to us. As they concern oral contraceptives, they fall outside our Terms of Reference.[129] However, oral contraceptives and HPTs contained the same ingredients, albeit in different doses, so, for completeness, they are detailed below.

As Oral Contraceptives fall outside of our Terms of Reference, we did not obtain National Archives files relating to them during our evidence gathering. Due to Covid19 we cannot visit the National Archive and they are not currently digitising files. We have not been able to verify for ourselves the information contained in the entries in blue.

Date	Source	Key Event, Opinion, etc.
March 1964	MH148/570	Minutes of CSD meeting – discussion of adverse reactions to Oral Contraceptives
February? 1965 (These minutes mention approving the minutes of the meeting held on 28 January 1965)	MH148/570	Committee (CSD?) minutes *6. Special Report on Oral Contraceptives* *The Committee had before them a paper from the Senior Medical Officers reporting significant and disturbing changes in the type of adverse reactions being recorded. There was a continuing flow of venous thrombosis and pulmonary embolus but some of the latest reports related to arterial thrombosis. Arrangements were in hand for the part-time medical officers to follow up the reports.* *The Committee considered that it was essential to establish the correct classification of the reactions and the action being taken by the part-time medial officers would enable this to be done. It was also necessary to ascertain the incidence of vascular accidents in women who used oral contraceptives and in those who did not. The Chairman reported that information about the incidence of thrombo-embolic episodes in women was being sought of the F.D.A. but it was doubtful whether it would be of much value. There were, however, other sources of information open to the Committee. The Family Planning Association had called a meeting for 3rd March to discuss the problem of oral contraception and the Chairman and Dr. Inman had been invited. The Committee hoped that the Association would be prepared to carry out a study of the incidence of vascular episodes in women of child bearing age, for which they had facilities.*

[129] https://www.immdsreview.org.uk/terms-of-reference.html

		The Hospital In-patient Enquiry might have statistics on the incidence of thrombo-embolic episodes in women of the relevant age group and pathologists might be able to carry out a survey of autopsies performed on women in that group who have had vascular accidents and supply details of the drugs (including oral contraceptives) take by the women. The Committee asked the Secretariat to add oral contraceptives to the list of specially monitored drugs: to approach the Hospital In-patient Enquiry for information and to seek the cooperation of the Association of Clinical Pathologists.'
22 June 1965	MH171/50	**CSD(65) Sixth Meeting** The minutes read *7. Oral Contraceptives (Minute 8 of 65/3; 3 of 65/4; 9 of 65/5.* *The Chairman reported that the Sub-Committee on adverse reactions had some information from the Hospital In-Patient Enquiry for 1963, which together with the information already provided for the years 1960-1962 showed the incidence of cerebro-vascular disorders in females (excluding sub-arachnoid haemorrhage) had increased by 61% in the 3 year period during which "the pill" had been generally available. The estimated number of National Health Service prescriptions for oral contraceptives had increased from 60,000 in 1961 to 400,000 in 1964 (the rate of increase approximately doubling each year). The Chairman informed the Committee that Professor Wade and Dr. Inman were meeting representatives from the College of General Practitioners, the Medical Research Council and the Family Planning Association to discuss what action should be taken for a full investigation of the problem. An interim report for possible publication would be prepared as soon as the figures were available to show the age distribution of women taking "the pill" against the incidence of thrombo-embolic episodes in women. It was hoped that a paper would be ready for the July meeting of the Sub-Committee on Adverse Reactions.*
28 October 1965	MH171/50	**CSD(65) Tenth(?) Meeting** The minutes read *5. Oral Contraceptives – Press Release (Minutes 8 of 65/3; 3 of 65/4; 9 of 65/5; 7 of 65/6 10 of 65/8)* *The Committee had before them a draft letter for publication in the professional journals and a paper by Mrs. C. Palmer and Dr. W. H. W. Inman on thrombo-*

		embolic phenomena associated with the use of oral contraceptives. *Professor Witts reported that earlier in the day the Adverse Reactions Sub-Committee had carefully considered the draft. While the Sub-Committee were in general agreement with its content, they considered that it should be carefully re-drafted to meet the possible mis-interpretation of the figures given the deaths and for women taking oral contraceptives. The extent to which the Committee were involved not only in the mortality – but also in the morbidity due to thrombosis or embolism of women taking oral contraceptives should also be clarified…* The minutes continue, but subsequent pages have not been supplied to the IMMDS Review.
13 November 1965	Cahal 1965[130]	**Safety of Oral Contraceptives.** In this Letter Dr Cahal the Medical Assessor of CSD wrote *'In the 12-month period under review there were reported from the United Kingdom to the Committee on Safety of Drugs 16 deaths due to thrombo-embolic episodes in women taking oral contraceptives (cerebral thrombosis or embolism two deaths, coronary occlusion five deaths, pulmonary embolism or infarction eight deaths, mesenteric infarction one death). The application of the General Register Office mortality statistics for England and Wales for 1964 to the estimated age distribution of women taking oral contraceptives indicates that 13 of 400,000 women between the ages of 15 and 45 would normally be expected to die from these four causes during the same period (from cerebral thrombosis or embolism two, from coronary occlusion nine, from pulmonary embolism or infarction two, and from mesenteric infarction nil).'* The letter concludes *'The Committee are also well aware that not all reactions of this type may have been reported to them. Therefore the deaths reported to the Committee may represent an underestimate of their true incidence. The Committee wish to emphasize that no firm conclusion can be drawn from the data at present available and again urge doctors to report to them all suspected adverse reactions to oral contraceptives and to make particular inquiries about the use of these preparations in women of child-bearing age who experience or die from thrombo-embolic episodes. In the meantime the Committee do not feel justified in objecting to the marketing of oral contraceptives.'*

[130] Safety of oral contraceptives. *Br Med J* **2**, 1180 (1965).

16 December 1965	MH148/570	**Sub-Committee on Adverse Reactions.** **CSD(AR)(65) Eleventh Meeting** The minutes 'Contents' lists 3. Action initiated on reports of adverse reactions. 4. Senior Medical Officer's Report. 6. Oral Contraceptives. 10. List of Specially Monitored Drugs The minutes read *3.(h) Oral Contraceptives. The Committee had an oral report from Mr. Turner on the press conference and subsequent publicity. It was considered that the experiment of meeting the press before the Committee's letter had appeared in the Journals had been successful, since the reports the national press had been responsible and had kept the Committee's letter in the desired perspective.* *Mr. Turner also reported that following this publicity the Government had been asked in the House of Lords if they intended to withdraw all oral contraceptives pending the Committee's investigation. The Government's spokesman had said that they had been assured by the Committee that they did not consider that these drugs should be withdrawn, and that in the present state of their knowledge the Committee did not consider that there was cause for concern by women using "the pill". A further letter had now appeared in the press asking that the numbers of cases and all relevant information should be made generally available. In consequence a further question had been put on the Order Paper of the House of Commons.* *The question now arose as to what information should be made available, not only to the Ministry of Health, but also to general practitioners and others who have notified suspected adverse reactions to "the pill". The Committee agreed that:-* *(i) The Minister of Health should be advised that it would be misleading to quote figures, and* *(ii) acknowledgments to doctors reporting suspected adverse reactions should not quote figures.* *The Committee had before them a preliminary report prepared by the Senior Medical Officer setting out the available data on reports of suspected reactions, and they noted that the reports received covered all the oral contraceptives which were available.* *A further paper received from Dr. Bickerstaff of the Midland Centre for Neurosurgery and Neurology giving a preliminary list of figures over the last 10 years of women patients under the of 40 who had cerebral arterial occlusions was noted. The Secretariat were*

		instructed to write and thank Dr. Bickerstaff for his letter which had been of great interest. *Two papers prepared by Dr Heasman on "Oral Contraceptive and the causation of thrombo-embolic episodes" and "Thrombolic Disease – Hospital Discharges and Mortality rates" were also before the Committee. They agreed that the approach suggested by Dr. Heasman in the first paper was fight and offered a method for considering the problem. The first thing would be to obtain from the Family Planning Association and the College of General Practitioners the age distribution of women taking "the pill". The Committee noted that Dr. Heasman had already established a preliminary contact with these bodies on this problem. Other points which would need to be taken into account before reaching a conclusion were social differences and high fertility. It was expected that it would take 3/4 years for all the necessary investigations to be completed.* *4. Senior Medical Officer's Report.* *Dr. Inman presented his report, and said that his now included reports about oral contraceptives, and that the left-hand column for this item showed the total numbers of each suspected reaction. There had not been a flood of reports following the recent publicity. The Committee's attention was drawn to the 4 cases of Stevens-Johnson Syndrome associated with the use of Sulphamethoxypyridazine which have now been reported from the United Kingdom and 5 cases of impaired liver function in cases treated with Lasix.* Section 6 on Oral Contraceptives was not supplied to the IMMDS Review. *10. List of Specially Monitored Drugs* *A list of 36 drugs that had available for at least 2 years was submitted to the Committee for possible withdrawal from the list of specially Monitored Drugs. The Committee decided that the following drugs should be retained on the List and reviewed at a later date:-* *[There are no hormone preparations in this list]* *and that the following drugs should be withdrawn:-* *ETHYNODIOL DIACETATE WITH "Metrulen"* *MESTRANOL "Ovulen"* *LYNOESTRENOL "Lyndiol"*

		MEGESTROL ACETATE WITH ETHINYLOESTRADIOL — *"Volidan"* *NORETHISTERONE WITH MESTRANOL* — *"Ortho-Novin"* *NORETHISTERONE WITH ETHINYLOESTRADIOL* — *"Anovlar"* *"Gynovlar"* *"Norlestrin"* *NORETHYNODREL WITH MESTRANOL* — *"Conovid"* *"Conovid E"* *"Feminor"* *"Previson"* *The Committee asked the Secretariat to submit to the next meeting an up-to-date list of specially monitored drugs and their code numbers.*
6 May 1967	BMJ[131]	**Risk of Thromboembolic Disease in Women Taking Oral Contraceptives: A Preliminary Communication to the Medical Research Council by a Subcommittee** The report outlines that on the issue of oral contraceptives and thromboembolism *'It was clear that more evidence was required on so important a problem, and in January 1966, at the request of the Committee on Safety of Drugs, the Ministry of Health asked the Medical Research Council for their views. The Council accordingly set up a subcommittee under the chairmanship of Lord (then Sir Robert) Platt, on the recommendation of which two retrospective investigations of morbidity were undertaken. In this present paper we report the preliminary results of these studies, together with those of a study of mortality which had already been set up by the Committee on Safety of Drugs.'* The preliminary findings of investigations by the College of General Practitioners, the MRC and the CSD are detailed. The report states *'Two of the studies are as yet incomplete, and their results cannot be properly assessed until the full accounts are published in detail. The sum of the evidence, however, is so strong that there can be no reasonable doubt that some types of thromboembolic disorder are associated with the use of oral contraceptives. The association with oral*

[131] Risk of thromboembolic disease in women taking oral contraceptives. A preliminary communication to the Medical Research Council by a Subcommittee. *British Medical Journal* **2**, 355-359 (1967)

		contraceptives is particularly strong in the group of women with no known medical condition predisposing to thrombosis. We cannot envisage any common factor which may have been responsible both for the production of the disease and for the use of these prespeparations. We conclude, therefore, that the oral contraceptives are themselves a factor in the production of the disease.'
6 May 1967	BMJ[132]	The Editorial on the above paper begins *According to the Medical Research Council report published at page 355 of this week's B.M.J.* " there can be no reasonable doubt that some types of thromboembolic disorder are associated with the use of oral contraceptives." *The report therefore takes us distinctly further than previous official pronouncements in blaming on the pill some forms of thromboembolic disease. On this point it is much more definite than the Food and Drug Administration report in the United States.' It also supersedes the report of the expert committee of the World Health Organization, which concluded that no cause-and-effect relationship between oral contraceptives and thrombosis had been established.'* It concludes *'Oral contraceptives cause a small amount of morbidity and mortality. Compared with the large amount of thromboembolic disease contributed by other causes the fraction contributed by oral contraceptives is so small that it can be detected only by careful statistical techniques. Nevertheless, many doctors will regard the prescribing of the present oral contraceptives as an interim measure until safer means are available.'*
22 June 1967	MH171_67 pages 265-271	CSD Interim Senior Medical Officer's Report The report states *'Oral Contraceptives* *Intercontinental Medical Statistics Limited (I.M.S), have recently supplied some valuable estimates for purchases of oral contraceptives from chemists in 1964, 1965 and 1966.'* The report describes the market and concludes 'Conclusions. (1) Minor side-effects, of which the five selected above are common examples, appear to be rather more frequently associated with ethinyloestradiol.

[132] Oral contraceptives and thromboembolic disease. *British Medical Journal* **2**, 327-328 (1967).

		(2) Reports of pulmonary embolism and cerebral thrombo-embolism associated with the use of mestranol are more than twice as frequent as would be expected from the I.M.S. data. (3) No difference has been detected between any of the progestogens which could not be accounted for by their combination with one or other oestrogen.' In the minutes of the CSD AR subcommittee meeting on 22 June 1967 point 3 records *'3. Action initiated on reports of adverse reactions.* *(a) ORAL CONTRACEPTIVES* *The Committee received a further interim report from the Senior Medical Officer on the number and type of adverse reactions attributed to oral contraceptives. This examined the Committee's data in relation to the oestrogen and progestogen component of the individual preparations and indicated possible differences between the reactions associated with the oestrogens, mestranol and ethinyloestradiol.* *The Committee noted that further data were being collected with a view to establishing whether or not the differences were significant. At this stage no special action was warranted.'*
Dec 1967	Not specified	CSD Statement on Oral Contraceptives.
? January(?) 1968 (The date of the next meeting is detailed in these minutes as 28 March 1968)	MH171/53	Minutes of the CSD. *7. Oral contraceptives – Thrombo-embolic risks* *The Chairman informed the meeting that the British Medical Journal would shortly be publishing a report by Dr. W. H. W. Inman and Dr. M. P. Vessey, Medical Research Council, on the Committee's investigation of deaths from pulmonary, coronary and cerebral thrombosis and embolism in women of child-bearing age and one by Dr. Vessey and Dr. R. Doll pm the Medical Research Council's investigation of the relationship between the use of oral contraceptives and thrombo-embolic disease. Copies of the reports had been sent to the Ministry of Health and the Ministry was seeking informally the Committee's advice on what action should be taken in light of the findings of the investigations. The reports would inevitably arouse much interest, particularly in the lay Press, and the Committee might therefore wish to consider the line that should be taken by the Secretariat in dealing with enquiries.* *From the reports it could be concluded that the risk of death from thrombo-embolic conditions was somewhat greater in women who used oral contraceptives than in*

		those who did not and that there was a definite relationship between the use of such preparations and deaths from pulmonary embolism or cerebral thrombosis in the absence of predisposing conditions. The morbidity due to thrombo-embolism of sufficient gravity to warrant hospital treatment was considerably higher in women using oral contraceptives than in those who did not. The Committee considered therefore that there was more than a "slightly" increased risk of thrombo-embolic conditions arising in women taking oral contraceptives. These preparations had a considerable therapeutic as well as a social value, however, and the Committee did not feel justified in recommending to the Minister that they should be withdrawn from the market provided they remained available only on prescription and doctors and patients were ware of the degree of risk which their use involved. *The Committee was informed that the reports that had been accepted for publication were abridged versions of those already issued to members. Although the conclusions remained the same, in the case of the Medical Research Council's report they were now presented in a different way and it seemed highly probable that in the revised form the figures for morbidity in terms of hospital admissions would attract a great deal of attention and might cause some controversy and alarm. Copies of the revises Summary and Conclusions to the Council's report were before the Committee. Some doubt was expressed about the terms in which this was couched and the Committee felt that in the absence of the latest version of the full report it could not interpret the figures on morbidity in such a way as to make them meaningful to enquirers. Since it would fall to the Secretariat to answer enquiries it was essential that it should have some guidance on the significance of the conclusions reached by the Medical Research Council. The Committee asked the Secretariat to obtain a copy of the latest version of the Council's report and suggested that Sir Austin Bradford Hill might be willing to prepare a commentary on this. Sir Austin agreed to do this.'*
1968?	MH 171/24	CSD ***DRAFT ANNUAL REPORT*** ***Adverse Reactions to Drugs***. *Oral Contraceptives* *The Committee published its final report on the investigation of the relationship between the use of*

		oral contraceptives and thrombo-embolism in April 1968[1]. This work commenced in January 1966 and the study was the first in the world to show that a definite risk of thrombo-embolism existed. It was established that the risk of death of a healthy woman from cerebral thrombosis or pulmonary embolism was increased approximately ten-times if she was using oral contraceptives. The risk of one year's treatment was comparable to the risk of thrombosis during one pregnancy. Subsequent studies by the Medical Research Council[2] on women admitted to hospital with thrombo-embolism, and by the Royal College of Practitioners[3] also confirmed the causal relationship between the use of oral contraceptives and thrombo-embolic disorders. The Committee has not altered its view, expressed in its report for 1967, that there is no justification for withdrawal of oral contraceptives provided they are only prescribed by doctors with knowledge that their use involves some risk. 1. *Inman and Vessey (1968) Brit. Med. J. 2, 193* 2. *Vessey and Doll (1968) Brit. Med. J. 2, 199* 3. *J. Roy. Col. Gen. Practit. (1967) 13, 267.*
19 December 1968	Appendix A from CSD meeting on 19/12/1968 (MH171/53)	Appendix A to the Minutes of the CSD meeting. Appendix A contained the recommendations of the Sub-Committee on Toxicity and Clinical trials and the Decision of the Main Committee on applications for Ovran (produced by John Wyeth & Bros) and Ablacton (produced by Schering). Ovran. Ovran was a monophasic oral contraceptive (21/28 250 µg Levonorgestrel, 50 µg Ethinylestradiol). The application was refused as *'The evidence required was stated in the publications of June 1966 and agreed further in detail with the manufacturers in December 1966. Such evidence is not contained in the present application.'* The Decision (which was sent to the manufacturer) records. *'On the evidence before them, the Committee do not agree to the release for marketing of this preparation for the purposes indicated by the manufacturer in his submission, since the evidence provided on the long term toxicity in animals is not in accordance with the details agreed with the manufacturers of oral contraceptives at the meeting held on 14th December 1966.'* Ovran was subsequently granted a marketing authorisation and remained on the UK market until 2002 when it was withdrawn by the manufacturer.

		Ablacton. Ablacton was used for the suppression of lactation.[133] It is not clear from the available evidence if it had any other indications. It was an ampule containing 5 mg estradiol benzoate, 8 mg estradiol valerianate, 20mg ethinylnortestosterone acetate, and180 mg testosterone enantate in oily solution.[134] It was administered as an intramuscular injection after the baby was born. The application was refused as *'Any possible benefits from this preparation are considered to be significantly outweighed by known toxic hazards.'* The Decision (which was sent to the manufacturer) records. *'On the evidence before them, the Committee do not agree to the marketing of this product, since any possible benefits from the preparation are, in the Committee's view, considerably outweighed by known side effects.'* Ablacton was available in other countries.
27 February 1969	MH171/24	Minutes of the CSD. 9. *Oral contraceptives and pregnancy* Professor Wade, reporting form the Sub-Committee on Adverse Reactions, informed the Committee that the efficacy of sequential oral contraceptives had been discussed by the Sub-Committee at its meeting that day. There was no evidence that thrombosis was any less frequent with the sequential than the combined oral contraceptives but there appeared to be strong circumstantial evidence that the sequential preparations were less effective than the combined. In the Sub-Committee's view this should be made known to the medical profession and it recommended that a suitable leaflet should be issued to all doctors after the manufacturers concerned had met the Secretariat to discuss the problem. The Committee agreed with the action proposed and asked the Secretariat to draft a paper that might be issued.
22 April 1970	MH171/21	Dear Dr letter from CSD concerning oral contraceptives and thromboembolism risk embargoed until 24 April 1970 to allow their report to be published.

[133] *Chapter XI Pregnancy* by Paul Keller at page 696 in A Labhart's *Clinical Endocrinology: Theory and Practice* (1974, Springer Verlag); R. Slunsky, A. Mullauer, [Weaning with an injection of Schering ablacton]. *Zentralblatt fur Gynakologie* **94**, 596-599 (1972).

[134] *Chapter XI Pregnancy* by Paul Keller at page 696 in A Labhart's *Clinical Endocrinology: Theory and Practice* (1974, Springer Verlag; H. Welti, F. Paiva, J. P. Felber, Prevention and interruption of postpartum lactation with bromocriptine (Parlodel) and effect on plasma prolactin, compared with a hormonal preparation (Ablacton). *European journal of obstetrics, gynecology, and reproductive biology* **9**, 35-39 (1979)

		'I am writing to let you know that the full analysis of the data on which the Committee on Safety of Drugs based its warning statement in December last year (No. 9 in the Adverse Reaction Series) has now been completed and will be published at the end of this week in the British Medical Journal together with a statement by the Committee. *As you know, the Committee has been concerned for some years with the association between the use of oral contraceptives and thromboembolic disorders. By last December, sufficient evidence accumulated to convince the Committee of the broad relationship between oestrogen content of such preparations and the liability to these complications.* *At that time it was apparent that deaths from pulmonary embolism had been reported more than three times as frequently among women taking oral contraceptives containing 75 micrograms of oestrogen than among those using products containing 50 micrograms. Preparations containing 75 micrograms or more and those containing 50 micrograms were used by equal numbers of women.* *The Committee recognised that further evidence was necessary and that the reports or reactions to individual preparations must be examined. It did not feel, however, that it should wait until this analysis was complete before issuing an early warning to the medical profession. Each month, many women would be unnecessarily at risk from thrombosis, and some would die.* *The Committee has considered and accepted the detailed scientific report on the work carried out on its behalf. Since publication in the British Medical Journal is likely to lead to discussion by the general press on the Friday morning before you have had an opportunity of reading the report, I thought it right to let you know that the publication is imminent. I hope this letter will reach all doctors before anything appears in the public press ,that they may be the first to be informed of the main findings.* *The detailed evidence presented in the report confirms and strengthens the conclusion reached in December. The number of adverse reaction reports relating to thromboembolic complications made to the Committee was 30 per cent higher with oral contraceptives containing 100 micrograms or more of oestrogen and 20 per cent lower with those containing less than 100 micrograms than would be expected from the known use of these preparations.*

		These results also demonstrate that a change to oral contraceptives of lower oestrogen dose could reduce the total deaths by 50 per cent and the morbidity from major thrombosis by at least 25 per cent. They further demonstrate that the trend in all forms of thrombotic hazard is related to the dose of oestrogen, but certain discrepancies affecting a small number of products need further investigation. *The Committee recognises that serious thromboembolic complications with oral contraceptives are fortunately uncommon. Nevertheless, it is estimated that about 1½ million women in the United Kingdom are taking oral contraceptives and there are therefore good grounds for hoping that there could be a substantial reduction in both mortality and morbidity by the use of the combined preparations which contain the lower dose of oestrogen. This indicates a way to secure greater safety without loss of contraceptive efficacy.'*
25 April 1970	Inman et al 1970[135] and Statement by CSD 1970[136]	The paper described the findings of the CSD study. In the statement. There is mention of comparisons with the Danish and Swedish ADR data *In short, the reports made to the Committee are double the number expected with 150 µg. of oestrogen, and 20% above expectation with 100 µg.; with 75 and 50 µg. they are 18 and 21% below expectation.* *These data we have been able to compare with similar reports made in Denmark and Sweden. In both countries there is the same trend as we have found in the United Kingdom, which provides independent evidence of its reality.* The paper concludes *'It was the broad demonstration of this dose relationship of oestrogen content to thrombotic episodes which led the Committee to issue an early warning. At the time of that warning the overall figures showed that deaths from pulmonary embolism were three times higher in women taking preparations containing 100 µg than in those who were taking 50 µg of oestrogen. The number of women on these two doses was almost equal, and together they covered between 80 and 90% of the market. The change from 100 to 50 µg could therefore result in a reduction of total mortality by 50%. By 1969 it was estimated that*

[135] W. H. Inman, M. P. Vessey, B. Westerholm, A. Engelund, Thromboembolic disease and the steroidal content of oral contraceptives. A report to the Committee on Safety of Drugs. *Br Med J* **2**, 203-209 (1970).
[136] Combined oral contraceptives. A statement by the committee on safety of drugs. *Br Med J* **2**, 231-232 (1970).

		1.5 million-women in the United Kingdom were taking oral contraceptives, so that the scope for the reduction of deaths is by no means negligible. The morbidity from major venous thrombosis with or without pulmonary embolism is, of course, much greater, and comparison of the numbers of the more serious thromboembolic episodes occurring with 100 and 50 µg of oestrogen respectively showed that a reduction of at least 25% could be expected by a change to the lower dose. It was also noted that the less frequent but dangerous arterial thromboses followed the same trends, and similar reductions in mortality and morbidity could be expected. The Committee recognized that the incidence of thromboembolic disorders in women taking oral contraceptives is fortunately uncommon. Nevertheless, the number of women using these preparations is very large, and any advice which would reduce substantially both the mortality and morbidity should be given at the earliest opportunity, particularly since the action required could be undertaken without reducing contraceptive efficacy. The Committee therefore did not feel that it could delay for months for a detailed analysis of the individual preparations, since during each month several women would die unnecessarily and many would suffer from avoidable hazard. In this situation the Committee regarded an early warning as imperative.'
October 1972	CSM 1972[137]	**Carcinogenicity Tests of Oral Contraceptives** The Committee on Safety of Medicines published their report into the teratogenicity of oral contraceptive in mouse and rat models. The Committee stated *'Although a carcinogenic effect can be produced when some of the preparations are used in high doses throughout the life span in certain strains of rat and mouse, this evidence cannot be interpreted as constituting a carcinogenic hazard to women when these preparations are used as oral contraceptives.'*
28 October 1972	Editorial BMJ[138]	This editorial expresses some concerns over the CSM report. *'The report is a masterpiece of brevity, compressing the findings of studies on over 13,000 animals into 15 pages and 7 tables, but the experimentalist used to scrutinizing data from long-term animal studies will note that some important information is missing. For*

[137] Committee on Safety of Medicines *Carcinogenicity Tests of Oral Contraceptives,* London, HMSO November 1972

[138] Tests on the pill for carcinogenicity. *Br Med J* **4**, 190 (1972).

		example, the report states: "In some instances the high doses of the compounds led to premature death of the animals, either from general toxicity or from certain tumours. As a result, the incidence of other tumours may have been -reduced. This needs to be borne in mind when assessing tumour yield." The last sentence is very true, but the reader of the report is left with a, problem on his mind because data on early deaths are not given. Another important omission is any information on whether treatment of female animals with the compounds was associated with suppression of ovulation. If not, can there be any assurance that exposure reproduced the hormonal state of women taking the "pill"? If the risk of cancer is altered in either direction in women on the pill, the change in risk is likely to be attributable to interference with the delicate feedback mechanisms which control menstruation and ovulation. Massive exposure to hormones of species in which the control mechanisms are basically different is a priori unlikely to provide interpretable results. Readers unfamiliar with laboratory rats and mice may well be surprised at the high incidences of some types of neoplasms found in untreated control animals. The tables in the report show incidences of 25% of lung tumours and 17% of liver tumours in control mice and 26% adrenal tumours, 30% pituitary tumours, and 99% mammary tumours in control rats. It is difficult to see how experiments on strains of animals so exceedingly liable to develop tumours of these various kinds can throw useful light on the carcinogenicity of any compound for man. Indeed the value of the mouse as a species for carcinogenicity testing has recently been seriously questioned because of a high incidence of tumours in untreated controls. *Many people who feel oppressed by the increasing threat of world overpopulation would desperately like the "pill" to be found safe from the point of view of cancer. The studies now reported neither incriminate oral contraceptives as carcinogens nor exonerate them. We shall simply have to wait and see what the epidemiologists learn from prospective studies.'*
11th March 2010	Hannaford et al[139]	**Mortality among contraceptive pill users: cohort evidence from Royal College of General Practitioners' Oral Contraceptive Study.**

[139] P. C. Hannaford *et al.*, Mortality among contraceptive pill users: cohort evidence from Royal College of General Practitioners' Oral Contraception Study. *BMJ* **340**, c927 (2010)

		Results 1747 deaths occurred in never users of oral contraception and 2864 in ever users. Compared with never users, ever users of oral contraception had a significantly lower rate of death from any cause (adjusted relative risk 0.88, 95% confidence interval 0.82 to 0.93). They also had significantly lower rates of death from all cancers; large bowel/rectum, uterine body, and ovarian cancer; main gynaecological cancers combined; all circulatory disease; ischaemic heart disease; and all other diseases. They had higher rates of violent deaths. No association between overall mortality and duration of oral contraceptive use was observed, although some disease specific relations were apparent. An increased relative risk of death from any cause between ever users and never users was observed in women aged under 45 years who had stopped using oral contraceptives 5-9 years previously but not in those with more distant use. The estimated absolute reduction in all cause mortality among ever users of oral contraception was 52 per 100 000 woman years. **Conclusion** Oral contraception was not associated with an increased long term risk of death in this large UK cohort; indeed, a net benefit was apparent. The balance of risks and benefits, however, may vary globally, depending on patterns of oral contraception usage and background risk of disease. **Funding**: The study received funding from the Royal College of General Practitioners, Medical Research Council, Imperial Cancer Research Fund, British Heart Foundation, Cruden Foundation, Schering AG, Schering Health Care, Wyeth Ayerst International, Ortho Cilag, and Searle. None of the funders had a role in the data collection, analysis, or interpretation or in the writing of this paper