The Independent
MEDICINES & MEDICAL DEVICES
Safety Review

The Independent Medicines and Medical Devices Safety Review

Written Evidence

Patient Groups: Hormone Pregnancy Tests

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Disclaimer

The statements made and the opinions expressed in response to the Independent Medicines and Medical Devices Safety Review's ('IMMDSR) Call for Evidence and in the video recording of the IMMDSR's oral hearings are those of the authors. They do not purport to reflect the opinions, views or conclusions of the IMMDSR or its members. 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

WARNING: Please be aware some evidence contains descriptions, pictures and audio of the harm suffered by individuals. Some may find this distressing.

Association for Children Damaged by Hormone Pregnancy Tests

The ACDHPT submitted the following:

1: Letter from MHRA to genetic testing centres regarding outcome of the Expert Working Group on Hormonal Pregnancy Tests (February 2018)

Referral letter :

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/679097/Referral_letter_for_genetic_testing.docx

2. The Contested History of Hormone Pregnancy Tests – Youtube Playlist

Professor John Abraham and others:
https://www.youtube.com/watch?v=kG8Jj8gYYDg&list=PLWSzZ44spEiBmhRniZsf9VzNLbQFzdtke&index=7

3. Comments on the CHM Primodos Report from Professor John Abraham.
Also submitted by Professor Abraham, please see Clinicians, academics and other individuals – Hormone Pregnancy Tests to read this in full.

4. Presentation given to the CHM on the 6th October, 2017

PRESENTATION TO THE C.H.M. - 6TH OCTOBER, 2017

THANK YOU FOR YOUR INVITATION TO COMMENT ON THE EWG REVIEW, IT'S CONCLUSIONS AND RECOMMENDATIONS.

I WOULD LIKE TO THANK THE MEMBERS OF THE EXPERT WORKING GROUP FOR THE TIME THEY SPENT CONSIDERING THE ISSUES DISCUSSED IN THEIR REPORT. A VAST ARRAY OF SCIENTIFIC EVIDENCE WAS PRESENTED TO THE GROUP, **HOWEVER** I WOULD POINT OUT THAT NOT ALL THE EVIDENCE FORWARDED FOR THEIR CONSIDERATION WAS REVIEWED.

I APPRECIATE THAT THIS WAS A DIFFICULT TASK FOR THE GROUP, AS DOCUMENTS WERE OFTEN RECEIVED JUST A FEW DAYS BEFORE THE MEETINGS AND CONSISTED OF VAST NUMBERS OF PAGES FOR REVIEW. e.**g. 2,000 PAGES**. COMPOUNDING THIS DIFFICULTY, PRESENTATIONS WERE

SOMETIMES DELIVERED, WITHOUT THE ABILITY TO SUBSTANTIATE THE DATA AND BASED ON AVAILABLE EVIDENCE WITH **SOME** LIMITATIONS.

WHEN CHALLENGING THE DATA PRESENTED, RESPONSES INCLUDED "THIS WAS THE BEST WE COULD FIND"" NOT SURE WHERE WE GOT THE INFORMATION FROM" NOT THE USUAL QUALITY AND QUANTITY OF DATA. THERE IS A DEFAULT ASSUMPTION WE USUALLY MAKE"

ON THIS BASIS I **WOULD NOT** EXPECT THE GROUP TO REACH A **DEFINITIVE** CONCLUSION ON A *CAUSAL LINK*

THE *POSSIBLE LINK* HOWEVER, WHICH **IS** EXPLICIT IN THE TERMS OF REFERENCE, IS NOT REFERERED TO IN **EITHER THE CONTENT** OR CONCLUSIONS OF THE REPORT, WHICH **CONSISTENTLY** AND **INCORRECTLY REFERS TO A *CAUSAL LINK***

THE STATEMENT "THE EWG ARE **CONFIDENT** IN THEIR FINAL CONCLUSIONS AND ASSURED THEY HAVE DONE ALL THEY COULD WITH THE *AVAILABLE DATA* WOULD SUGGEST THAT THE EWG DID **NOT** HAVE SUFFICIENT EVIDENCE TO **SUPPORT** THE CONCLUSIONS IN THE REPORT, BUT WERE CONSTRAINED TO BASE THEIR CONCLUSIONS ON *AVAILABLE DATA*

THIS IS NOT A CRITICISM OF THE GROUP, BUT AN OBSERVATION ON THE LACK OF DATA

THE STATEMENT "ASSUMPTIONS HAD TO BE MADE ON THE SCIENTIFIC EVIDENCE PRESENTED". FOR EXAMPLE "A SMALL AMOUNT OF NET/EE AT THE DOSES FOUND IN PRIMODOS **COULD** HAVE REACHED THE FETUS DURING DEVELOPMENT, EVERYTHING ELSE WAS *UNCLEAR*

FROM THIS, THE EWG CONCLUDED THERE WAS "INSUFFICIENT EVIDENCE TO DETERMINE WHETHER PRIMODOS COULD HAVE REACHED AND HAD AN EFFECT ON THE FETUS". HOWEVER THIS DOES **NOT** JUSTIFY THE CONCLUSION *NO CAUSAL LINK* IN THE REPORT, BUT **DOES** SUPPORT THE *POSSIBLE LINK* IN THE T.O.R.

ALSO REFERENCED IN THE REPORT: "THE TOTALITY OF THE AVAILABLE EVIDENCE FOR A *CAUSAL* ASSOCIATION" IS INSUFFICIENT, THEREFORE ONCE AGAIN, HOW CAN A CONCLUSION BE REACHED.

THE STATEMENT"THE EFFECT OF EE AS AN ABORTIFACIENT EFFECT IN HIGH DOSES ,WAS OBSERVED IN MANY STUDIES AND IS CONSIDERED TO BE A WELL ESTABLISHED FACT, **WITHOUT UNDERSTANDING THE MECHANISM,** BUT MAY INVOLVE DISRUPTION OF THE FETAL MATERNAL ENDROCRINE RELATIONSHIP REQUIRED TO MAINTAIN PREGNANCY"

HOW IS THIS ACCEPTED AS A WELL ESTABLISHED *FACT* WHEN THE MECHANISM IS **NOT UNDERSTOOD.** HPT'S ARE REQUIRED TO PROVE THE MECHANISM BEFORE A LINK CAN BE ACKNOWLEDGED 47 YEARS AFTER THE PRODUCT WAS WITHDRAWN.

"IT IS **NOW KNOWN** THAT THE MATERNAL HORMONES AND ANTIBODIES READILY CROSS THE PLACENTA".

THIS KNOWLEDGE HOWEVER, **COULD** INDICATE A POSSIBLE MECHANISM, WHICH IS PART OF REMIT IN THE T.O.R .

"IN ADDITION TO THE *KNOWN* EFFECTS OF NET ON GENITAL TISSUES, THE FOLLOWING ADVERSE EFFECTS WERE NOTED: FETAL LOSS, SKELETAL VARIATIONS **AND EQUIVOCAL** INCREASE IN MALFORMATIONS, IN ONE SCHERING RABBIT STUDY, IN DOSES HIGHER THAN THOSE IN HPT'S" .

WERE THESE DOSES BASED ON THE FDA CURRENT GUIDLINES, WHICH **SUBSTANTIALLY DECREASE** THE DOSE EFFECT WHEN USED ON BODY SURFACE AREA INSTEAD OF WEIGHT.

"CONSISTENT FINDINGS WERE SHOWN IN STUDIES WITH NETA AND EE ACROSS MICE, RATS, GUINEA PIGS AND RABBITS, ALTHOUGH AGAIN *HIGH DOSES* ARE QUOTED. HOWEVER, SCHERING SCIENTISTS COMMENTS WERE **NOT REFERENCED** WHICH EXPRESS CONCERNS ABOUT THESE STUDIES AND STATE: "INCREASE IN MALFORMATIONS IN THIS STUDY SHOULD BE CONSIDERED DRUG RELATED" FURTHER STUDIES ARE NEEDED TO PROVE SAFETY".

THE STATEMENT "THERE IS EVIDENCE THAT COMBINED NET/EE , INCREASED THE FREQUENCY OF SKELETAL VARIATIONS. SUCH EFFECTS WERE ***NOT CONSIDERED*** MECHANISTICALLY LINKED TO MALFORMATIONS* *NOT CONSIDERED* SHOULD NOT BE EXPRESSED AS **NO EVIDENCE** AND DOES NOT SUPPORT THIS CONCLUSION, WHEN EVIDENCE OF **INCREASED FREQUENCY** WAS DOCUMENTED.

WHEN COMPARING PATTERNS OF CONGENTIAL ANOMALIES, THE REPORT DOCUMENTS A HIGHER PROPORTION OF LIMB REDUCTIONS AND OTHER MORE SERIOUS DEFECTS, BUT STATES THE **LIMITATIONS** OF THE DATA DO NOT ALLOW ANY CONCLUSIONS TO BE DRAWN.

I F CONCLUSIONS CANNOT BE DRAWN FROM THIS **LIMITED DATA,** HOW CAN THE CONCLUSION OF **NO CAUSAL** LINK IN THE REPORT, BE VALIDATED..

EVIDENCE THAT "EMBRYOLETHAL DOSES OF NETA WERE GENERALLY HIGHER THAN THOSE USED IN PRIMODOS", **FAILS** TO ACKNOWLEDGE THAT IN **RABBITS** THE EFFECT WAS ESTABLISHED **AT 1/3RD** HED - SCHERING STUDY 2300 - 1976

STUDY 2221 - FOUND THAT **ONLY** THE HED OF **1/10TH** DID NOT KILL OFF ALL FETUSES.

THE **EQUIVOCAL** INCREASE IN MALFORMATIONS IN **RABBITS** IS MISLEADING. THIS REFERS TO THE AVAILABILITY OF ONLY 3 FETAL REMANANTS AFTER RESORPTIONS. WITHIN THOSE **3** REMNANTS THERE WERE 2 MALFORMATIONS, WHICH WOULD INDICATE THIS RESULTS WAS UNEQUIVACAL

"THERE ARE FEW DATA ON **HOW THE** EFFECT OF ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION OF MEDICINES, AFFECT THE BODY DURING PREGNANCY" . THIS IS A STRONG MESSAGE THAT FURTHER RESEARCH IS NEEDED TO ADDRESS THIS FAILING.

TODAY WITH ALMOST UNLIMITED RESCOURCES AND SIGNIFICANT ADVANCES IN MEDICAL SCIENCE, WE ARE STILL UNABLE TO DETERMINE A DEFINITIVE CAUSATION ON STATINS, YET THE CONCLUSIONS OF THE REPORT ARE MAKING A FIRM STATEMENT OF *NO CAUSAL LINK* BASED ON RELATIVE SCARCITY OF EVIDENCE WHICH IS INSUFFICIENT TO SUPPORT THEIR CONCLUSIONS.

T HE VAST AMOUNT OF STUDIES AND REPORTS AVAILABLE FROM 1958 GIVE A CLEAR INDICATION OF THE STRENGTH OF DOUBT ABOUT THE SAFETY OF HPT'S, WHICH PROMPTED THE MEDICAL AND SCIENTIFIC COMMUNITY TO INITIATE THE STUDIES UNDER REVIEW.

" OVERALL CONCLUSIONS OF THE EWG ON THE AVAILABLE EVIDENCE"

"HAVING REVIEWED ALL THE AVAILABLE RELEVANT EVIDENCE, WITH THE BENEFIT OF UP TO DATE KNOWLEDGE, WITHIN THE RELEVANT SPECIALISMS, THE LIMITATIONS OF THE METHODOLOGY OF THE TIME AND THE RELATIVE SCARCITY OF EVIDENCE, MEANS IT IS **NOT POSSIBLE TO REACH A DEFINITIVE CONCLUSION.**

THE PARAGRAPH IMMEDIATELY FOLLOWING THIS STATEMENT IS CONTRADICTORY AND NEEDS TO BE EXCLUDED FROM THE REPORT

"NEVERTHELESS, BASED ON AN EXTENSIVE AND THOROUGH REVIEW OF THE EWG OVERALL FINDINGS , THE SCIENTIFIC EVIDENCE DOES NOT SUPPORT A CAUSAL ASSOCIATION BETWEEN THE USE OF HPT'S SUCH AS PRIMODOS DURING EARLY PREGNANCY AND ADVERSE OUTCOMES.

IN CONCLUSION:

THERE WAS POOR QUALITY OF DATA

THEREFORE NO DEFINITE CONCLUSIONS CAN BE REACHED

THERE IS AN OBVIOUS NEED FOR FURTHER RESEARCH

FUNDING FOR THIS RESEARCH MUST BE A PRIORITY

5. Review of the EWG Report and Causality - Marie Lyon and Tobias Arndt - 9-7-18

Review of the EWG Report and Causality

Warnings for Adverse reactions are inserted in all packages of medicines. They are intended as a warning of *possible* reactions and the *degree of likelihood* they may occur. (eg: "More than 1 in 10: headache ... , less than 1 in 10: vomiting, etc..) This means that not everyone who takes the same medication will be affected in the same way. It should therefore be accepted that not all women who took a hormone pregnancy test would have been affected or that the anomalies would have followed a particular pattern.

"*In practice few adverse reactions are 'certain' or 'unlikely'; most are somewhere in between these extremes, i.e. 'possible' or 'probable'. In an attempt to solve this problem many systems have been developed for a structured and harmonised assessment of causality*" The WHO paper of reference for assessment of causality of adverse effects defines a range of **categories for causality** (see table below) varying between certain, probable, possible to unlikely causality.

This standard procedure is accepted by the CHM and it would have been expected to have been applied when assessing the causality in the EWG review (see paper WHO-UMC causality assessment attached).

Table 2. WHO-UMC Causality Categories

Causality term	Assessment criteria*
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

*All points should be reasonably complied with

The Terms of Reference of the EWG was to review evidence for a **Possible** association between HPT's and adverse effects. The actual wording of the conclusions of the report *was altered* to a **Causal** association, which was **not** explicit in the T.O.R. and therefore did not fulfil the remit accepted by the MHRA and CHM.

When this arbitrary alteration to **Causal** was applied, in accordance with the above detailed standard of the CHM procedure, to assess which category of Causal has to be investigated ,the task for the EWG would have been to look into **possible causality** and the standard criteria set out for identifying this category of causality

WHO Upsala Monitoring Centre paper on assessment of causality defines **possible causality** as:

• Event or laboratory test abnormality, with reasonable time relationship to drug intake"

<u>Criteria met:</u>

- **Animal studies showing malformations and embryo lethality**
    - E.g. page XV **in EWG Review** "*Death of the developing embryo with high doses of estrogens has been consistently observed in animal studies and is now considered to be a well-established effect. A similar effect has been observed in studies with norethisterone (or related progestogens). As may be expected, the combination of norethisterone and ethinylestradiol also showed consistent embryo-lethality in different animal species.*"

    - The clear majority (26) of 34 epidemiological studies presented in the EWG reviews tables (pages 71-74) support an association between hormones in pregnancy and malformations. Out of these 34 studies **seven** are even **statistically significant** and all seven statistically significant studies are in support of an association.
      It is important to note there is **no** single study, which does not show an association, has statistical significance.

- **Time relationship to drug intake is fully acknowledged by the EWG Report**
    - See EWG Review on page 28: "*the likely window for HPT use (…) is, 4 to 12 weeks of pregnancy (2 to 10 developmental weeks). Since this covers most of the critical period of fetal development the first criterion for a possible drug-related effect was considered met.*"

The two other criteria from the **table above and referenced below** are not conditional and therefore do not require explanation.

• Could also be explained by disease or other drugs
• Information on drug withdrawal may be lacking or unclear

CONCLUSIONS

The conclusions of the EWG Report have not taken into consideration that it is generally recognised that there are various categories of causality.

The categories range from Certain to Unlikely, yet this very important distinction was not referenced in any of the EWG report. To use the term causal only, serves to give the impression that there is **only** certain causality, which is patently unrealistic and disingenuous: "*In practice few adverse reactions are 'certain' or 'unlikely'; most are somewhere in between these extremes, i.e. 'possible' or 'probable'."*

It is important to reference the Thalidomide case. Thalidomide is widely believed to be the medicine where the association to malformations are proven with the degree of **certain causality**. Latest research presented at a conference at the WHO in Geneva in 2014 (see conference report attached) suggests that this is **not correct** even for thalidomide.

- "It is (...) difficult to specify exact diagnostic parameters of thalidomide embryopathy"
- "Thalidomide embryopathy **can** phenocopy genetic defects"
- "One would have to accept that there may be other effects of Thalidomide which are not being diagnosed and there may be effects **not** due to Thalidomide that overlap with the Thalidomide effects"

It is astounding that the conclusions of the EWG Report do not take into consideration the above factors, i.e. Causality Categories and the contents of the WHO conference in Geneva in 2014, which was produced before the EWG Review commenced and was easily accessible.

It is also difficult to understand, when the clear majority of epidemiological studies which demonstrate an association and were contained in the report, were obviously not accepted as credible evidence of association. This is particularly concerning as epidemiology is generally accepted as the methodology to detect adverse drug reactions.

6 - 12. Correspondence from 1967

The Review does not have permission to publish these at this point.

13. Primodos Prescription Totals for 1968 – 1977.

P6 of 17 of Annex 12 from the EWG report https://mhra.filecamp.com/public/files/2ou7-p1dlcbo2, with annotated calculations of number of prescriptions for pregnancy testing.

14. Presentation on the Landesarchiv Berlin Files

PRESENTATION LANDESARCHIV BERLIN FILES – MARIE LYON

PREPARING THIS PRESENTATION WAS A HUGE CHALLENGE. THE CHALLENGE WAS NOT TO FIND EVIDENCE TO PRESENT, BUT TO DECIDE WHICH DOCUMENTS TO LEAVE OUT.

THIS IS A SMALL SAMPLE OF THE DOCUMENTS CONTAINED IN THE FILE, TO REPRESENT THE CHRONOLOGY OF EVENTS, THE SCIENTIFIC EVIDENCE OF ADVERSE EFFECTS. THE FAILURES OF THE

REGULATORY AUTHORITIES, BOTH IN THE UK AND GERMANY. ALSO INCLUDED ARE THE FACTORS INFLUENCING THE DECISION OF BAYER/SCHERING & THE GVT. HEALTH AUTHORITIES ,TO KEEP PRIMODOS/DUOGYNON/CUMORIT ON THE MARKET.

THERE WERE TWO TESTS CONDUCTED BY SCHERING, BEFORE THE INTRODUCTION OF PRIMODOS IN 1958, NEITHER OF WHICH WERE FOR TOXICITY.

WE HAVE NO DATA ON THE RESULTS OF THESE TESTS, HOWEVER ON PAGE 25 OF MHRA DOCUMENT (2) REFERENCE IS MADE TO SCHERING STUDIES (SH376) CARRIED OUT ON ACTIVE SUBSTANCES IN 1956-57 FOR ONE YEAR, ON 5MG OF NE. 1957-1958 FOR A YEAR AND A HALF, ON 10MG NE. AND 1961-62 3 YEARS AFTER PRIMODOS WAS ON THE MARKET, FOR ABOUT ONE YEAR. THERE WERE NO DETAILS OF THE RESULTS AND METHODOLOGY OF THE TESTS INCLUDED. THE DATA HAS NOT BEEN SUPPLIED BY BAYER/SCHERING

TWO YEARS AFTER THE INTRODUCTION OF PRIMODOS IN THE UK, RELIABLE, NON INVASIVE TESTS WERE AVAILABLE, WHICH WERE RISK FREE. EVIDENCE BEGAN TO CIRCULATE THAT PRIMODOS COULD BE HIGH RISK AND OF DOUBTFUL BENEFIT TO WOMEN. THESE WARNINGS BEGAN IN 1958 WITH WARNINGS FROM PROF. DUKES (LWT DOCUMENTARY) AND DR. EDWARDS.

THERE WAS NO THERAPEUTIC VALUE TO HPT'S. IF A RISK/BENEFIT ASSESSMENT HAD BEEN APPLIED THE RESULTS WOULD HAVE WEIGHED HEAVILY ON THE RISK AND VERY LITTLE ON THE BENEFIT, EXCEPT TO THE DRUG COMPANY.

DESPITE MANY WARNINGS RECEIVED BY THE CSD/CSM, THE DRUG CONTINUED TO BE MARKETED FOR USE IN PREGNANCY IN THE UK, WITH ANTICIPATED FIGURES IN EXCESS OF 1.5 MILLION PRESCRIPTIONS. 20/10/1967 - LETTER FROM DR. M.P. CARTER TO THE CSD - AFTER HPT USE - 5 MALFORMATIONS, EXPECTED 2.5, ABORTIONS 11, EXPECTED 4.5, TOTAL WASTAGE 16 EXPECTED 7.5. AMENERONE FORTE APPEARED TO BE ONE OF THE CHIEF OFFENDERS.

THE COMPONENTS OF PRIMODOS CONTAINED EE AND NET, WHICH WAS ALSO CONTAINED IN SCHERING'S ORAL CONTRACEPTIVE PILL. CONCERNS WERE EXPRESSED THAT IF THESE WARNINGS WERE MADE PUBLIC, THIS WOULD IMPACT ON SALES OF SCHERING'S O.C. WHICH FROM 1964 TO 1979 HAD TOTAL SALES OF 403 MILLION PACKETS IN THE UK ALONE.

THIS WAS A HUGE MOTIVATION TO SUPPRESS ANY CONCERNS ABOUT PRIMODOS FOR BOTH SCHERING AND DR. WILLIAM INMAN . THERE HAD BEEN MANY DEATHS AND DISABILITIES SUFFERED BY WOMEN FROM THROMBOEMBOLIC EVENTS, RELATING TO THE ORIGINAL SCHERING O.C ONTRACEPTIVE PILL. (INFORMATION IN KEW ARCHIVES)

DR. INMAN DID NOT DISCLOSE THIS INFORMATION TO THE MEDICAL PROFESSION, BUT INSTEAD CHOSE TO WORK WITH SCHERING TO REDUCE THE DOSE AND THEREFORE THE RISK. ONLY WHEN THE DOSAGE WAS REDUCED TO AN ACCEPTABLE LEVEL WAS THIS DATA ACKNOWLEDGED AND THE MEDICAL PROFESSION INFORMED. DR. INMAN WAS KNOWN AS *THE FATHER OF THE MINI PILL*

BEFORE PRESENTING AN OVERVIEW OF SOME OF THE STUDIES CONTAINED IN THE LANDESARCHIVE I HAVE REFERENCED A DOCUMENT FROM THE FDA, SLIDE (1) THIS CONTAINS ESTIMATES OF THE HUMAN EQUIVALENT DOSE (HED) FOR ANIMAL STUDIES, WHICH RELATE TO THE BODY SURFACE AREA OF THE RESPECTIVE SPECIES. THE MG/KG DOSE SHOULD BE DIVIDED BY A FACTOR OF 6.2. FOR RATS AND BY A FACTOR OF 3.1 FOR RABBITS.

THESE ESTIMATES HAVE BEEN REFERENCED IN THE FOLLOWING STUDIES, WHICH WERE PRODUCED BY SCHERING SCIENTISTS, THE EARLIEST FROM 1966.

IN THESE STUDIES,THERE WERE FINDINGS OF EXCESS EMBRYOLETHALITY AT CLOSE TO HUMAN DOSE AND POSSIBLE LINKS TO TERATOGENICTY. SCHERING SCIENTIST STATED IN BOTH THE APRIL AND AUGUST, 1973 STUDIES " A TERATOGENIC EFFECT CANNOT BE RULED OUT"

THE INTENDED USE AS AN ABORTIFACIENT IS ALSO REFERENCED BOTH IN STUDIES AND IN DOCUMENTS INTHE LANDESARCHIV FILES.

CONTAINED IN THE APRIL, 1970 STUDY, IS THIS STATEMENT BY A SCHERING SCIENTIST. " WITH THESE TERATOGENIC FINDINGS A CONNECTION CANNOT BE RULED OUT WITH ABSOLUTE CERTAINTY" SCHERING UK SCIENTISTS ALSO NOTED "THERE IS NO PROOF OF SAFETY"

I REFERENCE THIS SMALL SELECTION OF STUDIES TO SHOW THAT SCHERING DID HAVE SCIENTIFIC INFORMATION WHICH SHOULD HAVE BEEN DISCLOSED, AS MANY OF THE FINDINGS WERE INDICATIVE OF ADVERSE EFFECTS. THESE FINDINGS SHOULD HAVE BEEN FOLLOWED UP BY SCHERING WITH FURTHER STUDIES. A FREQUENT REQUEST BY CHIEF SCIENTISTS AT UK SCHERING.

INSTEAD THEY CONTINUED TO MARKET PRIMODOS TO PREGNANT WOMEN, WITHOUT DISCLOSING THE RISKS OR LACK OF PROOF OF SAFETY, TO THE MEDICAL PROFESSION.

TO COMPOUND THIS DELIBERATE OMISSION, THE FILES CONTAIN A LETTER FROM DR. HETHERINGTON CRITICISING THE SCHERING STATEMENT MADE IN 1961 *IF A PREGNANCY EXISTS, IT IS IN NO WAY AFFECTED* DR. HETHERINGTON ALSO REFERS TO A BOOKLET SENT OUT IN 1966 WHEN THE FIRST TEST WAS COMPLETED, WHICH STATES *NO HARMFUL EFFECTS WERE NOTED TO THE FOETUS*

THESE STATEMENTS ARE DISINGENUOUS AT BEST.

SCHERING STUDIES – EE, NETA, AND COMBINATION

- **<u>EE/NETA RELATING TO THE PRIMODOS COMBINATION DATED 27.4.1970</u> (LANDESACHIVE 13227 P114 - P125 GERMAN ORIGINAL[1] SLIDE (2)**
    - **AFTER 25HD RABBITS & RATS (8HED, RATS 4HED)**
        - **RABBITS 100% RESORPTIONS**
        - **RATS LOWER WEIGHT GAIN; ANOMALIES IN TWO FOETUSES (OEDOMATIC BODIES;**
        - **ANOPHTHALMIA (TWO EYES MISSING) AND ERRONEOUS BRAIN DEVELOPMENT)**
        - **COMMENT:" WITH THESE TERATOGENIC FINDINGS A CONNECTION CANNOT BE RULED OUT WITH CERTAINTY".**

[1] Landesarchive 13227 p114 ff. (p125 ff. German original)

- **THE TEST WITH 2.5HD (CONVERTED RABBITS: 0.8 HED; RATS: 0.4 HED) IS LESS THAN THE HED IN BOTH SPECIES AND THUS THE ABSENCE OF FINDINGS IS UNSURPRISING.**

- **AS THERE ARE NO TESTING RESULTS AVAILABLE BETWEEN THE DOSES OF 2.5HD (RABBITS: 0.8 HED) AND 25HD (RABBITS: 8 HED) THE THRESHOLD FOR 100% EMBRYO LETHALITY MAY LIE BETWEEN THOSE TWO VALUES, AND MAY WELL BE FAR BELOW THE HIGHEST DOSE**

- **NETA – RABBITS RESORPTIONS OF 29% AFTER ½ HUMAN DOSE (0.16 HED CONVERTED) 12.7.1976 LANDESARCHIV 12227 P 71 FF. – GERMAN ORIGINAL P76 +.) SLIDE (3)**

- **NETA – TOXICOLOGICAL AND GENERATIONAL EXPERIMENTS USING 17-ETHINYL-19-NORTESTOSTERONE ACETATE IN RATS APRIL 1966 (LANDESARCHIVE 13227 P23 FF., P34 FF. GERMAN ORIGINAL)** [2] **SLIDE (4)**

  - **EARLIEST STUDY IN THE LANDESARCHIV FILE, PRIOR TO GAL: SHOW DOSE RELATED EMBRYO TOXICITY UP TO ALMOST 100% AT THE HIGHEST DOSE (30 MG = 90MG/KG 450 HD 72HED). THE STUDY STIPULATES AT THE LOWER DOSE (10 MG = 30MG/KG, 135HD; 24HED) "IN PRINCIPLE THE SAME PHENOMENA (EMBRYO TOXICITY) OCCURRED", AND AT (0.3 MG = 0.9MG/KG, 4.5 HD; 0.72HED) "IMPAIRED FOETAL DEVELOPMENT WAS ONLY ESTABLISHED IN INDIVIDUAL ANIMALS". THE STUDY IS NOT CONCLUSIVE ABOUT MALFORMATIONS AS: "NO MALFORMATIONS WERE SEEN IN THE LIVING YOUNG ". IT DID DEMONSTRATED SERIOUS SYMPTOMS OF PREGNANCY DISRUPTIONS (UTERINE BLEEDING, HYALINOSIS AND OEDEMA OF THE PLACENTA, HAEMORRHAGING AND NECROSES OF THE UTERUS).**

  - **EE - TESTING FOR EMBRYOTOXIC EFFECTS ON RABBITS 27.8.1973 (LANDESARCHIV 13226 P 167FF., P 204 FF. GERMAN ORIGINAL)**[3] **SLIDE (5)**

  - **HEAD DEFORMITIES FOR ONE FOETUS FOR BOTH 0.03 (75HD; 24HED) AND 0.1 (250HD; 80HED) MG/KG - COMMENT : "A TERATOGENIC EFFECT CANNOT BE RULED OUT WITH ABSOLUTE CERTAINTY FOR THE DOSES OF 0.03 AND 0.1MG/KG."**
  - **FURTHER TEST POSTPONED BECAUSE THE DRUG IS FOR ABORTIFACIENT "INTENDED USE FOR ADMINISTRATION IN POST-COITAL EMERGENCY SITUATIONS"**
  - **AFTER 0.01 (25HD; 8HED), 0.03 (75HD; 24HED) AND 0.1MG/KG BODY WEIGHT.(250HD; 80HED), EMBRYO-LETHAL EFFECTS WERE IDENTIFIED (21.9%, 33.6% AND 52.3% OF IMPLANTATIONS, RESPECTIVELY), (IN THE CONTROL GROUP: 9.3%).**

[2] Landesarchive 13227 p23 ff., p34 ff. German original

[3] Landesarchive 13226 p 167ff., p 204 ff. German Original

- **EE – RABBITS - PRELIMINARY REPORT 773 – FOR DOSE DETERMINATION 28.12.1972[4] (SLIDE 6)**
    - **AFTER 0.1 MG/PER KG BODY WEIGHT (250HD; 80HED): 50% FOETUSES DIED OFF (24 OF 50) – SURVIVING ALL SHOWED CLEAR SIGNS OF RETARDATION. ALL CONTROLS SHOWED NORMAL RESULTS.**

- **EE - TESTING FOR EMBRYOTOXIC EFFECTS IN RATS 17.4.1973 (13226 P132 FF. GERMAN ORIGINAL P165 FF.)[5] SLIDE (7)**
    - **SEVERE DOSE-DEPENDENT REDUCTION IN THE AVERAGE BODY WEIGHT GAIN - 0.03 (75HD; 24HED), 0.1 (250HD; 80HED), 0.3 (750HD; 240HED) MG/PER KG BODY WEIGHT**
    - **20 % OF ALL IMPLANTED EMBRYOS RESORBED AFTER 0.1 (250HD; 80HED) AND MORE THAN 50 % AFTER 0.3 MG/KG (750HD; 240HED) – RESORBTIONS WITHOUT FETAL REMNANTS – THIS LOSS IN EARLY PREGNANCY COULD BE CAUSED BY A MALFORMATION**
    - **AFTER 0.3 MG/KG (750HD; 240HED): AGNATHY OF THE LOWER JAW, PIG TAIL, A RUDIMENTARY TAIL AND OEDEMATOUS SWELLING OF THE WHOLE BODY – 4 ABNORMALITIES IN 88 LIVING FOETUSES AFTER MORE THAN 50% HAD BEEN RESORBED. COMMENT SAYS: "A TERATOGENIC EFFECT AFTER 0.3 MG / KG CANNOT BE RULED OUT"**
      11 OUT OF 20 MOTHER ANIMALS HAD VAGINAL BLEEDINGS, THREE HAD NO LIVING OFFSPRING
    - **CONCLUSION: NO NEED TO FOLLOW UP BECAUSE PRODUCT IS AN ABORTIFACIENT "ITS INTENDED USE IS FOR DISCONTINUING PREGNANCY, (P.C. "EMERGENCY MEDICATION")**

ISSUES WITH METHODOLOGY WERE EXPRESSED IN A LETTER SENT TO DR. INMAN FROM DR. PITCHFORD, SCHERING UK ABOUT USINGSTUDIES ON RATS. (LANDERSARCHIV 13198 P12 – ENGLISH) SLIDE (8)

- **17.2.1969 "DR. PITCHFORD WROTE TO DR. INMAN TO ADVISE HIM ON THE CONTENTS OF A LETTER RECEIVED FROM DR. LACHNIT, SCHERING. HE STATES "THE RAT WAS NOT A SUITABLE MODEL FOR TESTING." THIS DID NOT HOWEVER, INITIATE WITHDRAWAL OF PRIMODOS BY EITHER SCHERING OR THE COMMITEE, UNTIL FURTHER STUDIES WERE COMPLETED.**

COMMITTEE ON SAFETY OF DRUG/MEDICINES
SLIDE (9)

[4]Landesarchive 13226 p 155ff., p 142ff. German Original

[5] 13226 p132 ff. (German original p165 ff.); 13226 p 130 (166 German original); P 13 (167 German original)

1958 - EDWARDS - THE FIRST SUGGESTION THAT THE MECHANISM OF ACTION OF HPTS COULD CAUSE MALFORMATIONS

1959 - STUDY GROUPS IN HOLLAND: CAN CAUSE ABORTION, VIRILISATION IS POSSIBLE, PSEUDO-HERMAPHRODIDISM. TEST NOT VERY EFFICIENT. PROF. DUKES - BLEEDING EVEN WHEN PREGNANT (LWT DOC)

1962 - DUBOWITZ POSSIBLE VIRILISATION IN THE FEMALE INFANT. REFERENCED MANY TIMES IN BOTH LANDESARCHIV AND KEW ARCHIVE FILES. VIRILISATION WAS ACCEPTED BY BAYER AS AN EFFECT. VIRILISATION IS AN ABNORMALITY.

1962 – LETTER DR. CARTER TO MINISTRY OF HEALTH: OF 15 MOTHERS GIVEN AMENERONE FORTE (HPT) 3 (20%) ABORTED

1964 – WHEATLEY - GENERAL PRACTITIONER RESEARCH GROUP SURVEY: FETAL ABNORMALITIES OCCURRED IN 8.2% OF 60 PATIENTS GIVEN FEMALE SEX HORMONES. [BMJ]

SLIDE (10)

1966 - SUB COMMITTEE ON ADVERSE REACTIONS: REPORTED 15.15% OF CASES RELATED TO PRIMODOS.

1967 - LETTER FROM PROF WITTS (CSD) TO DR INMAN: REFUTES DR. INMAN'S HYPOTHESIS THAT OTHER FACTORS COULD BE THE CAUSE. "THE CIRCUMSTANCES OF THE ORAL PREGNANCY TEST ARE UNIQUE. A BIG DOSE OF PROGESTOGEN BEING GIVEN AT A TIME WHEN THE EMBRYO IS MOST VULNERABLE."

1967 – STUDY BY DR. GAL - DISPUTED BY DR. INMAN, WHO EXPRESSED DOUBT ON THE RESULTS OF THE STUDY, BUT ALSO ADMITTED, IT WAS !!!!!

1967 – DR. INMAN WRITES TO DR. GAL AND AGREES SHE HAS PRODUCED PRIMA FACIE EVIDENCE.

1967 – DR. INMAN'S RESPONSE TO DR. CARTER: "THERE IS NO CONVINCING EVIDENCE ON AN EFFECT BUT SUCH AN EFFECT CANNOT BE EXCLUDED "

1967 NOVEMBER - SIGNIFICANT STATISTICAL LINK FOUND BY DENNIS COOKE, A HIGHLY RESPECTED STATISTICIAN WHO REQUESTED AN URGENT FOLLOW UP - THE STATISTICAL ANALYSIS WAS COMMISSIONED BY DR. BRIGGS, SCHERING CHIEF MEDICAL OFFICER UK. RESULTS WERE RELAYED TO DR. INMAN.

SLIDE (11)

1969 -DR. CARR REFERS TO FINDINGS 10/27 ABORTIONS SHOW POLYPLOID CONFIGURATIONS = 37% 11/227 = 4.8% ONLY IN UNSELECTED GROUP. REQUESTS URGENT NEED FOR FURTHER INVESTIGATION.

7TH AUGUST 1969 – DR. INMAN LETTER TO DR. KEUNSSBERG RCGP, REFERS TO "DISTURBING CORRESPONDENCE RELATING TO ANIMAL DATA" WHERE IS THE DATA? WHY WAS IT NOT PUBLISHED. SCHERING WERE SENT THE RESULTS, BUT HAVE NOT DISCLOSED THEM. ALSO NOT DISCLOSED IS THE RCGP FOLLOW UP STUDY. WHY DID ONE OF THE SCIENTISTS WORKING ON THE STUDY WRITE *HE HAD A BAD CONSCIENCE ABOUT THE STUDY. ALSO STATED "THE RESULTS OF THIS STUDY WOULD BE OF GREAT BENEFIT TO THE PLAINTIFFS.

21ST AUGUST 1969 – LETTER FROM DR. KEUNSSBERG TO DR. INMAN? AT A RISK OF 3.79% WE CANNOT AFFORD TO IGNORE WARNINGS.

17.10.70 - LETTER FROM DR. CROMBIE ROYAL COLLEGE OF GENERAL PRACTITIONERS, STATES *THESE RESULTS ARE HIGHLY SIGNIFICANT*

1971 - SUB COMMITTEE ON ADVERSE REACTIONS, REPORTED 11 CASES OF CONGENITAL ABNORMALITIES LINKED TO HPT'S, AT LEAST 4 WITH REDUCTION OF LIMBS.

MARCH 1973 - SUB COMMITTEE ON ADVERSE REACTIONS UPDATE ON RCGP STUDY SHOWS *POTENTIALLY STRIKING FINDINGS.*

SLIDE (12)

APRIL 1973 - NORA & NORA STUDY. THIS STUDY WAS USED IN THE USA TO SECURE A HIGH MILLION DOLLAR SETTLEMENT FROM SQUIBB FOR THEIR HPT, GESTEST, WITH COMPONENTS MANUFACTURED BY SCHERING. DOCUMENTS IN THE FILE DEMONSTRATE THE LEVEL OF CONCERN SCHERING HAD ABOUT THE OUTCOME OF THIS LEGAL ACTION, WHICH DOCUMENTS ATTENDANCE OF SCHERING SCIENTISTS IN THE USA. SCHERING SCIENTISTS ATTENDED EVERY DAY OF THE HEARING.

MAY 1973 – DR. INMAN TO DR. REID *UPDATE ON MATERNAL STUDY NOTES THAT IN BOTH GROUPS (CLEFT PALATE & OTHER ABNORMALITIES) THERE IS AN APPARENT EXCESS OF THE USE OF HPTS. FINDINGS WERE REPORTED TO SUB COMMITTEE ON ADVERSE REACTIONS AND ALL PRESENT WERE ADVISED TO KEEP THIS INFORMATION CONFIDENTIAL.

1975 - LETTER FROM DR. INMAN - WE ARE DEFENCELESS IN THE 8 YEAR DELAY.

I THINK IT IS IMPORTANT TO STATE THAT ALL THE ABOVE WARNINGS WERE RELATED TO EFFECTS ON PREGNANT WOMEN AND NOT ANIMAL STUDIES. THIS IS A VERY SMALL EXAMPLE OF THE HUGE AMOUNT OF HUMAN STUDIES AVAILABLE, WHERE HPT'S WERE USED TO DETERMINE PREGNANCY. THIS DOES NOT NEGATE THE RELEVANCE OF ANIMAL STUDIES, AS THEY PROVIDE A WARNING SIGNAL TO POSSIBLE EFFECTS IN HUMANS. THIS POINT WAS REINFORCED BY THE PRESENTATION FROM SWEDEN AT ONE OF THE EWG MEETINGS.

SLIDE (13)

- **FEBRUARY, 1970 - DR. INMAN (APPROBATION OF QUIETLY DELETING INDICATION PREGNANCY TEST (DOCUMENT IN LANDESARCHIV 13198 P105)** [6]

- **QUOTE: "SCHERING QUIETLY CHANGED THE INDICATION FOR PREGNANCY AND NEVER ADDED AN EXPLICIT WARNING OR DREW PUBLIC ATTENTION TO THE INDICATION (BY APPROBATION OF DR. INMAN REPRESENTING THE BRITISH PUBLIC HEALTH AUTHORITY) AS THE SUSPICION SEEMED TO BE UNFOUNDED.**

- **22ND JANUARY, 1975 DR. INMAN INFORMS SCL ABOUT A 5:1 RISK FOR MALFORMATIONS (LANDESARCHIV 13198 P15 P23 GERMAN ORIGINAL AND 13222 P29 – P31 GERMAN ORIGINAL) ASSOCIATED WITH MOTHERS WHO TOOK HPTS.**

[6] Landesarchiv 13198 p105

- **EXPECTS PUBLICATION OF HIS STUDY IN 6 MONTHS. WANTED TO WARN SCHERING TO AVOID MEDICO LEGAL PROBLEMS, SO CHOSE TO INFORM THEM IN AN "UNOFFICIAL" WAY BEFORE MAKING HIS FINDINGS PUBLIC .[7] THIS FIGURE IS QUOTED IN THE DOCUMENTS MORE THAN ONCE AND IS INDISPUTABLE.**

SLIDE (14)

- **CSM (DR. INMAN) ASKS TO BE SUBPOENAED AS A WITNESS IN THE LITIGATION BROUGHT BY THE ASSOCIATION FOR CHILDREN DAMAGED BY HPT'S.**

- **EXTRACT OF MEETING NOTE WITH LEGAL CONSULTANT MR CLOTHIER – 23.12.1977 (LANDESARCHIV 13201 P 307 FF.)**

  DR. INMAN WANTED THE OPPORTUNITY TO DISTANCE HIMSELF FROM THE RESULTS OF HIS AND DR. GREENBERGS STUDY.

  "ON THE QUESTION WHETHER THE CSM SHOULD BE CALLED AS WITNESSES. THE LEGAL TEAM WOULD BE RELUCTANT AND IT MIGHT BE THAT HE WOULD HAVE TO BE SUBPOENAED. WHILST THEY WOULD PROBABLY SUPPORT SCHERING, THE COURT WOULD SAY THAT THEY WERE BOUND TO DO SO BECAUSE OF THE DECISION THAT THEY (THE CSM) HAD MADE IN REGARD TO PRIMODOS"

SLIDE (15)

- **DR. INMAN *CONVERSATION IN BERMUDA RE: DESTROYED DOCUMENTS (LANDESARCHIV 13198 P86 FF., P187 FF. GERMAN ORIGINAL): CONVERSATION WITH DR. DETERING (SCHERING)**

- **"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 FROM 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"[8]**

SLIDE (16)

- **LEGAL SITUATION IN GERMANY AND THE UK WERE SIMILAR (LANDESARCHIVE 13199 P95-100): STATED BY THE LEGAL COUNSEL REPRESENTING SCHERING. CONTERGAN DISCONTINUATION ORDER STATES *GIVEN THE SERIOUSNESS OF MALFORMATIONS AS SIDE EFFECTS, A PHARMACEUTICAL MANUFACTURER HAS AN OBLIGATION TO REMOVE A**

[7] Landesarchive 13198 p 15

[8] Landesarchiv 13198 p86 ff., p187 ff. German original

DRUG TEMPORARILY FROM THE MARKET, IF ONLY THE REMOTE POSSIBILITY EXISTS, UNTIL SUFFICIENT TESTING IS CONCLUDED.[9]

- **SLIDE (17)**

LEGISLATION WAS IN PLACE IN 1968:

- **1968 MEDICINES ACT: P.67 (ITEM 2.G) MANDATE ON REMOVAL OF PRODUCT IS JUSTIFIED IF (1) THE PRODUCT CAN NO LONGER BE REGARDED AS SAFE TO ADMINISTER FOR THE PURPOSE INDICATED IN THE LICENCE, OR CAN NO LONGER BE REGARDED AS EFFICACIOUS FOR THIS PURPOSE**

- **(4.B) THAT A MATERIAL CHANGE OF CIRCUMSTANCES HAS OCCURRED: (E.G.AVAILABILITY OF NON INVASIVE TESTS. REPORTS OF ADVERSE EFFECTS AND MALFORMATIONS SHOULD ALSO INDICATE A CHANGE OF CIRCUMSTANCES)**
-
- **SECTION 118 OF MEDICINES ACT 1968 - IT IS AN OFFENCE TO DISCLOSE TO ANY PERSON ANY INFORMATION, UNLESS THIS DISCLOSURE WAS MADE IN THE PERFORMANCE OF HIS DUTY. DID DR. INMAN COMMIT AN OFFENCE BY GIVING SCHERING ADVANCE WARNING OF HIS STUDY RESULTS?**

- **DR. INMAN'S DUTY (EMPLOYED IN A GOVERNMENT HEALTH AGENCY) WAS TO PROTECT THE HEALTH OF THE PEOPLE, NOT THE INTERESTS OF THE PHARMA CO'S.**

COMPLICITY OF GERMAN AUTHORITIES BGA

- **SLIDE (18)**

- **THE DEPARTMENT HEAD OF THE GERMAN HEALTH AUTHORITIES IN CHARGE OF SUPERVISING DUOGYNON THE GERMAN EQUIVALENT OF PRIMODOS WAS PROF. VON EICKSTEDT:**

    - **(LANDESARCHIVE 13199 P75-76) PROF. EICKSTEDT CALLED HIMSELF AND THE HEALTH AUTHORITY ADVOCATES FOR SCHERING - 03.08.78[10]**

    - **ASK SCHERING TO PROVIDE (LANDESARCHIV 13199 P60) "STUDIES WHICH DO NOT YIELD ANY STATISTICALLY SIGNIFICANT CORRELATION BETWEEN THE USE OF SEXUAL HORMONES IN EARLY PREGNANCY AND DEFORMITIES"[11]**

[9] Landesarchive 13199 p95-100

[10] Landesarchive 13199 p75-76

[11] Landesarchiv 13199 p60

- **ARGUES IN A MINISTRY MEETING CONSIDERING THE MARKET REMOVAL OF DUOGYNON, AGAINST SUCH A MEASURE: (LANDESARCHIV 13199 P 68-69)"NO ONE *BELIEVES* IN A CAUSATIVE RELATIONSHIP BETWEEN THE USE OF SEX HORMONES AND THE OCCURRENCE OF DEFORMITIES"[12]**

- **INSTEAD BLAMES *CONSUMERS* RATHER THAN THE MANUFACTURER(LANDESARCHIV 13199 P77-79): "*VON EICKSTEDT STATED IT COULD BE A PREGNANCY DISORDER, OR IT COULD BE A WOMAN WHO IS MORE INTERESTED IN THE APPEARANCE OF A PERIOD THAN IN AN EXISTING PREGNANCY.*"[13]**

SLIDE (19)

CORRESPONDENCE BETWEEN SCHERING AG AND SCHERING UK.

SCL (UK) TO SCHERING AG REQUESTING URGENT MARKET WITHDRAWAL OF PRIMODOS LANDESARCHIV 13198 P5 - ENGLISH):
TWO LETTERS IN THE FILES FROM 1968 AND A FURTHER REQUEST IN 1969. FROM SENIOR SCIENTISTS SCHERING UK.

THESE AND OTHER LETTERS WERE REMOVED BY A SENIOR MANAGER FROM SCHERING AND GIVEN TO THE PRESS.

"MR. EHRICH (SCHERING AG) WAS ASKED IF HE KNEW WHICH DOCUMENTS HAD FALLEN INTO THE HANDS OF THE PRIVATE DETECTIVE. HE SAID IT WAS A FOLDER CONTAINING CORRESPONDENCE BETWEEN DR. PITCHFORD AND SCHERING BERLIN, IN WHICH DR. PITCHFORD EXPRESSED SEVERAL TIMES, THAT PRIMODOS SHOULD BE WITHDRAWN FROM THE MARKET, OR THAT MEASURES HAD TO AT LEAST BE TAKEN. THE HEADQUARTERS HAD RESPONDED DISMISSIVELY TO EACH REQUEST, SUPPORTED BY DR. INMAN WHO WROTE

"MY OPINION IS THERE IS NOT ENOUGH EVIDENCE TO CONSIDER TAKING PRIMODOS OFF THE MARKET"

SLIDE (20)

LEGAL DEPARTMENT 22.12.1977 (LANDESARCHIV 13201 P80 FF. ENGLISH)[14]:
"ON THE BASIS OF THE ABOVE-MENTIONED CORRESPONDENCE ("SOME LETTERS ARE DYNAMITE IN THE HANDS OF THE CLAIMANTS"),

MR. CLOTHIER STATES THAT A "BREACH OF DUTY" AND A CHARGE OF NEGLIGENCE BY SCHERING, WOULD PRESUMABLY BE DETERMINED BY A JUDGE."

SLIDE (21)

[12] Landesarchiv 13199 p 68-69

[13] Landesarchiv 13199 p77-79

[14] [source unclear]

- **27TH MARCH 1975, DR. PITCHFORD (SCL) TO DR. ESCHE (SAG) (LANDESARHIV 13198 P.17 – ENGLISH):**

  THE DOCUMENT STATES "WE WERE THIS SITUATION MORE THAN 7 YEARS AFTER THE ORIGINAL SUSPICIONS AGAINST THE SAFETY OF HORMONAL PREGNANCY TESTS CAME TO OUR ATTENTION. SHOULD THIS ISSUE BE PUBLICLY DISCUSSED, THE COMPANY WOULD BE THOROUGHLY QUESTIONED, WHY NO REAL EFFORTS HAD BEEN MADE DURING THESE SEVEN YEARS TO PROVE THE SAFETY OF OUR PREPARATIONS."

USE OF DUOGYNON/PRIMODOS AS ABORTIFACIENT

- **SLIDE (22)**
- **SCHERING MEETING OF PRIMODOS WORKING GROUP ON THE 23RD MAY 1978 DISCUSSING RISK-BENEFIT OF THE PRODUCT FOR THE COMPANY (LANDESARCHIV 13200 P183 - ENGLISH)[15]**
    - **ABORTION USE AS MISUSE "IN NO WAY A NEW STATE OF AFFAIRS FOR US" THEREFORE SHOULD NOT PLAY TOO SIGNIFICANT A ROLE IN OUR CURRENT DECISION MAKING.**
- **SUCCESSFUL IN-HOUSE EXPERIMENTS WITH DUOGYNON SIMPLEX AS ABORTIFACIENT**
- **"EXAMINATION OF THE IMPACT OF SH 70804 ON THE IMPLANTATION IN THE RAT" - 1.3.1971 (LANDESARCHIV 13227 P83 +. (GERMAN)[16]**
    - **"NO IMPLANTATION COULD BE OBSERVED IN ANY OF THE TREATED DAMS, HENCE, THE SUBSTANCES APPLIED TO THE DAMS RESULTED IN THE DYING OFF OF THE SEEDS IN THE EARLIEST PHASE OF DEVELOPMENT AND/OR TO THE PREVENTION OF THE IMPLANTATION OF THESE SEEDS."**

SLIDE (23)

- **ÄRZTEBLATT (EQUIVALENT OF BMJ) ON REFORM OF ABORTION LAW - 9.2.1978 (LANDESARCHIV 13224 P19 ENGLISH)**
    - **DISCUSSION ON MORTALITY RISKS OF WOMEN DURING AN ABORTION: "FOR INSTANCE, THE USE OF DUOGYNON TABLETS AND "SYRINGES" SHOULD DEFINITELY BE A THING OF THE PAST! UNFORTUNATELY, THESE KINDS OF PRACTICES, WHICH ARE HARDLY ACCEPTABLE, ARE REPORTED IN THE COUNSELLING CENTRES QUITE OFTEN."**
- **DOCTORS WIDESPREAD USE OF DUOGYNON/PRIMODOS AS ABORTIFACIENT – REPORT FROM SCIENTIFIC SALES IN HANNOVER 18. 8. 78 – LANDESARCHIV 13223 P 82 - ENGLISH**

[15] Landesarchiv 13200 p183

[16] Landesarchiv 13227 p83 ff.

- **"IN CONVERSATIONS ABOUT DUOGYNON IT WAS HIGHLIGHTED THAT A SURPRISINGLY HIGH PERCENTAGE OF PHYSICIANS STILL SWEAR BY ACCOMPLISHING AN ABORTION THROUGH DUOGYNON."**

CONCLUSIONS (1)

THERE IS ROBUST DOCUMENTED EVIDENCE, CONTAINED IN BOTH LANDESARCHIV AND KEW ARCHIVES TO PROVE COMPLICITY TO WITHHOLD EVIDENCE EXISTED BETWEEN THE UK AND GERMAN GVT. HEALTH AGENCIES AND BAYER/SCHERING

THERE IS DOCUMENTED EVIDENCE TO SHOW THE SUPPRESSION OF ADVERSE EFFECTS FOR BOTH THE ORAL CONTRACEPTIVE AND PRIMODOS/DUOGYNON/ THEY WERE ALL NEGLIGENT IN FAILING TO INFORM THE MEDICAL PROFESSION UNTIL AFTER THE PROBLEMS HAD BEEN RESOLVED, OR WERE FORCED INTO THE POSITION BY THE MEDIA. DURING THIS TIME THE MANUFACTURERS WERE KEPT FULLY INFORMED, THROUGH UNOFFICIAL DISCLOSURE.

DOCUMENTED EVIDENCE TO SHOW THEY ALL FAILED IN THEIR MORAL DUTY TO PROTECT THE UNBORN CHILD, WHEN EVIDENCE OF MALFORMATIONS WAS GROWING STEADILY, EVEN BEFORE DR. GAL'S STUDY AND NON INVASIVE TESTS HAD BEEN AVAILABLE SINCE 1960.

IT WAS AN ACT OF DELIBERATE NEGLIGENCE TO DELAY NOTIFYING THE MEDICAL PROFESSION FOR 5 YEARS AFTER*DISCRETELY WITHDRAWING THE INDICATION FOR PREGNANCY IN 1970. DR. INMAN ALSO WAITED 8 YEARS AFTER CONFIRMING A *PRIMA FACIE* CASE TO DR. GAL. THIS HE FREELY ADMITS *WE ARE DEFENCELESS IN THE 8 YEAR DELAY* THE BGA ALSO DECLARED THEMSELVES *ADVOCATES FOR SCHERING* AND COLLUDED TO KEEP DUOGYNON ON THE MARKET IN GERMANY, BY ASKING FOR RESULTS *WITHOUT* MALFORMATIONS

THERE IS OVERWHELMING EVIDENCE IN THE FILES, OF CONCERNS FROM ALL PARTIES, THAT ORAL CONTRACEPTIVE SALES WOULD BE AFFECTED IF THE LINK WAS MADE BETWEEN THE COMPONENTS OF PRIMODOS AND SCHERING'S O.C.

CONCLUSIONS (2) THE TERMS OF REFERENCE:

THE INITIAL T.O.R. INCLUDED PROOF OF A CAUSAL LINK, WHICH I FELT WAS NOT ACHIEVABLE. IN A SCIENTIFIC STUDY, CAUSALITY HAS TO BE OBSERVABLE, PREDICTABLE AND REPRODUCTABLE AND IS DIFFICULT TO PROVE. IT WOULD BE UNETHICAL TO REPRODUCE A CAUSAL LINK, AS PRIMODOS IS CONTRAINDICATED FOR USE IN A PREGNANT WOMAN.

I ACCEPTED A CHANGE IN TERMINOLOGY FROM THE COMMISSION ON HUMAN MEDICINES AND AGREED TO THE WORD MECHANISM. UNFORTUNATELY I DID NOT REALISE THAT THE WORD MAY BE DIFFERENT BUT THE OBJECTIVE IS THE SAME. MECHANISM IS DESCRIBED AS *THE DETAILED DESCRIPTION OF A REACTION PATHWAY* E.G. CHEMICAL REACTIONS OCCURING WITHIN A CELL. THESE TESTS WOULD REQUIRE ANIMAL STUDIES WHICH COULD SHOW THE PROBABLILITY OF A LINK. MECHANISM IS EQUIVALENT TO CAUSAL LINK AND SHOULD BE REMOVED FROM THE TOR.

THE STUDY BY NEIL VARGESSON WAS INFORMATIVE AND GENERATED GREAT INTEREST BY THE EWGT. INITIAL RESULTS WERE REVALATIONERY. ALREADY THE STUDY HAD DEMONSTRATED EVIDENCE OF MALFORMATIONS. MR. VARGESSON STATED *IF WE WERE TESTING THIS DRUG TODAY, IT WOULD NOT BE PROGRESSED ANY FURTHER WITH THE RESULTS WE HAVE DISCOVERED.

THIS STUDY IS EXPECTED TO BE PEER REVIEWED AND ACCEPTED IN A PRESTIGEOUS SCIENTIFIC PUBLICATION WITHIN THE NEXT FEW MONTHS. THE STUDY SHOULD BE CONSIDERED BEFORE THE EWG FINALISES IT'S CONCLUSIONS.

IF *THE MECHANISM* CONTINUES TO BE PART OF THE T.O.R, THE NUMEROUS STUDIES AVAILABLE WHICH WERE CARRIED OUT IN LIVE SITUATIONS, ON PREGNANT WOMEN FROM 1967, TOGETHER WITH HUMAN STUDIES BEFORE THAT DATE, SHOULD BE MADE AVAILABLE IN FULL TO THE EWG, DESPITE CONFOUNDING FACTORS AND SAMPLE SIZE.

THESE STUDIES ARE A VALID INDICATION OF THE LEVEL OF CONCERN FELT BY THE MEDICAL PROFESSION ABOUT THE SAFETY OF HPT'S, AT THAT TIME.

THERE ARE TOO MANY HUMAN STUDIES TO BE DISCOUNTED AND IT IS ALSO WORTH REITERATING THE T.O.R. STATE *POSSIBLE LINK* NOT CONCLUSIVE LINK.

THE ALARMING STATISTICAL LINK PROVIDED BY DENNIS COOKE SHOULD ALSO BE FULLY CONSIDERED. I REFERENCE AN ARTICLE ON *CAUSATION/EPIDEMIOLOGY* OBSERVATIONS OF A STATISTICAL ASSOCIATION BETWEEN EXPOSURE AND DISEASE MAY BE EVIDENCE OF CAUSATION. SCHERING OBVIOUSLY THOUGHT SO, AS THEY PROVIDED THEIR OWN STATISTICAL ANALYSIS, BUT THEY DID NOT DECLARE THE DIFFERENT MEASUREMENT CRITERIA. SCHERING ALSO REFERENCED THE REDUCTION IN HPT SALES. EVIDENCE IN THE FILES SHOW *1,000* PACKAGES PER MONTH WERE SHIPPED TO NORTHERN IRELAND IN 1978. (ABORTION WAS STILL ILLEGAL IN N.I.)

THE BURDEN OF PROOF THROUGHOUT THIS PROCESS, TO FIND EVIDENCE OF CAUSATION OR A POSSIBLE LINK, IS ONCE AGAIN PLACED ON THE PEOPLE WHO FEEL THEY HAVE BEEN HARMED.

WHERE IS THE REQUEST TO BAYER/SCHERING FOR PROOF OF SAFETY. * THEIR OWN SCIENTIST STATED, WHEN BEGGING FOR THE DRUG TO BE TAKEN OFF THE MARKET *THERE IS NO PROOF OF SAFETY*

WHERE IS THE REQUEST TO BAYER/SCHERING FOR RCGP STUDY RESULTS AND THE RESULTS OF THE TWO TESTS THEY CONDUCTED BEFORE MARKETING PRIMODOS?

15. Translation of Thalidomide Court Decision (Germany)

The Review does not have permission to publish this translation, but please see Tobias Arndt's submission in Clinicians, academics and other individuals – Hormone Pregnancy Tests for a summary of the important points.

16. Translation of Schering documents

The IMMDS Review does not currently have permission to publish these files.

17. Federal Register Notice

Department of Health, Education and Welfare
Food and Drug Administration
COMBINATION
[DESI **12872;** Docket No. **FDC-D-572; NDA 12-8721]**
Federal Register 38(25): Wednesday, February 7, 1973

COMBINATION DRUG CONTAINING NORETHINDRONE ACETATE AND ETHINYL ESTRADIOL
Notice of Opportunity for Hearing on Pro**posal** To Withdraw **Approval** of New Drug Application; Drugs for Human **Use;** Drug **Efficacy Study Implementation**

https://heinonline.org/HOL/P?h=hein.fedreg/038025&i=38

18. FDA Drug Bulletin

FDA Drug Bulletin 5(1): January – March 1975

Warning On Use of Sex Hormones in Pregnancy

19. Olszynko-Gryn (2016) Risky hormones, birth defects and the business of pregnancy testing I

https://perceptionsofpregnancy.com/2016/11/22/risky-hormones-birth-defects-and-the-business-of-pregnancy-testing-pt-i/

20. Olszynko-Gryn (2016) Risky hormones, birth defects and the business of pregnancy testing II

https://perceptionsofpregnancy.com/2016/12/12/risky-hormones-birth-defects-and-the-business-of-pregnancy-testing-part-ii/

21. Email exchange regarding previous legal cases

From: Jesse Olszynko-Gryn

Date: 25-Nov-16

To: Marie Lyon

Subject: Re: Contact Form Submission

Yes, Schering had the patent, but it was licensed to Squibb and Squibb sold it in the US as Delalutin. Schering called it Proluton. It is the same thing.

Proluton + Progynon = Duogyon

Delalutin + Delestrogen = Gestest

Roussel, in contrast, had it's own patented progestogen called Ethisterone and was in Amenorone and Amenorone Forte.

It does get confusing with all the different names, but the records are very clear and I am starting to sort them out, e.g.:

Trade name	**Duogynon oral (2 tablets)**	**Primodos (2 tablets)**	**Gestest (4 tablets)**
Company	Schering AG, Berlin	Pharmethicals, UK subsidiary of Schering AG	Squibb (licensed from Schering AG)
Progestogen	Norethisterone acetate (5 mg / tablet) (10 mg)	Norethisterone acetate (5 mg / tablet) (10 mg / test)	Norethisterone acetate (2.5 mg / tablet) (10 mg / test)
Estrogen	Ethinyl oestradiol (0.01 mg / tablet)(0.02 mg)	Ethinyl oestradiol (0.01 mg / tablet) (0.02 mg / test)	Ethinyl oestradiol (0.05 mg / tablet) (0.2 / test)
Ratio	500:1	500:1	50:1

Jesse

On 24 Nov 2016, Marie Lyon wrote:

Yes the case was Barson v Squibb. I thought Schering had the patent for Norethisterone and Ethinylestradiol, but would have to check. I am not sure which was the most damaging, but I think it may have been the Ethinylestradiol. Would have to check.

-------*Original Message*-------

From: **Jesse** Olszynko-Gryn

Date: 24-Nov-16

Subject: Re: Contact Form Submission

You previously mentioned the case was Barson v ER Squibb. And I'd have to check, but probably yes to maintain pregnancies. It is Squibb's trade name for Norethisterone, the progestogen component of Gestest and Primodos/Duogynon. Do you have a clear sense whether the progestogen or estrogen in Primodos was the more implicated teratogen or would xxxxxxxxx know about this?

On 24 Nov 2016, Marie Lyon wrote:

Absolutely worth mentioning. Was it used to maintain pregnancy? Not sure, but I think it was and similar synthetic hormones.

-------Original Message-------

From: Jesse Olszynko-Gryn

Date: 24-Nov-16

Subject: Re: Contact Form Submission

Yes, Delalutin was licensed from Schering as well, in 1956. The agreement is very clear on this and there is no ambiguity. It was the same product as Schering's Proluton. Perhaps this would be worth mentioning in my next article.

On 24 Nov 2016, Marie Lyon wrote:

Great. There was another Squibb case and I am sure it was Delalutin. I have it in my documents if you need to see it. I am fairly sure Schering were involved in that also, but haven't really paid much attention, as Gestest has been my main focus.

-------Original Message-------

From: Jesse Olszynko-Gryn

Date: 24-Nov-16

Subject: Re: Contact Form Submission

Thanks, he found the names I was looking for on page 7 of the docket, which I hadn't seen.

On 24 Nov 2016, Marie Lyon wrote:

Hi Jesse, This is the first email I received from [redacted]. I had contacted [redacted] on 28th May, but [redacted] didn't receive my email. I had given [redacted] details to [redacted], the German documentary Producer, who did manage to get [redacted] email through to [redacted].

I researched the Doctors in [redacted], who were [redacted] and [redacted]. I am sure [redacted] would share the information with you if you emailed [redacted] direct, but I will also look because I feel I have this information somewhere in the masses of paperwork.

Good luck. Marie

-------Original Message-------

Response: *The Review does not currently have permission to publish this.*

22. To-day's Drugs, BMJ 1958

British Medical Journal (1958) To-day's Drugs. 1:1352 (Published 07 June)

On Primodos Oral

https://doi.org/10.1136/bmj.1.5083.1352

Shared by email by Olszynko-Gryn to Marie Lyon, with the following comments:

A different, higher test dosage (estradiol: 0.05 vs. 0.02 mg) from 1958 and also 'fears' dismissed based on absence of evidence of harm, which of course is not the same thing as evidence of safety.

23. Document prepared for Lord O'Shaughnessy

DOCUMENT PREPARED FOR LORD O'SHAUGHNESSY

I would like to bring to your attention the results of a review, produced at the request of the APPG members, supporting the Association for children damaged by Hormone Pregnancy Tests. The revue is focussed on files in LandesArchiv, Berlin and the Archives in Kew.

We have prepared this document to highlight concerns resulting from this review and after viewing the London Weekend Television documentary, produced in 1978. A copy is enclosed

The LWT film was part of a Conference on "The Contested History of Hormone Pregnancy Tests" which took place in Cambridge on 27th January, 2017. The conference was attended by Experts from Norway, Sweden, France, Germany and the UK. The conference was supported by the Wellcome Trust.

Issues were raised during discussions, regarding the independence of the MHRA to provide Secretariat support. It was also suggested that the review should be a full Independent Legal Inquiry, where all evidence is assessed and scrutinised independently to check for bias.

We are concerned that the MHRA continue to display "Assessment of historical evidence on Primodos and congenital malformations **(2014)** on their website[17]. This paper concludes, under findings "*The studies are i**nconsistent** in their findings for an association between use of HPTs and congenital anomalies and are **not considered** sufficient to conclude that an association exists.*" The APPG have a copy of this report.

The APPG members find it highly questionable that a body conducting an independent investigation, continues to display this study on their website. This would indicate an opinion, with regard to the possible outcome of such an investigation. More crucially, the study is to a great extent based on biased material and we are advised by our Researcher, that **many important studies**, which suggested a link, were readily available in 2014. It raises the question why these other studies were not included. How can we be assured that **all** relevant studies relating to HPT's, will be presented to the EWG, for consideration.

We are unable to gain assurance from the MHRA, that prior to presentation of documents to the EWG, all information has been subjected to full scrutiny, to assess for bias. This is particularly important when checking the source of the documents, which can result in biased conclusions. These sources would include Schering employees and Schering consultants, plus Scientists whose work was funded or otherwise supported by Schering. An example of this is the study by Tummler, which was produced with the assistance of Prof. Schaefer, during a time he was remunerated by Bayer in 2012. This information is available in the documentation relating to German litigation during that period.

A report on base data relating to key epidemiological studies by R.A. Wiseman[18], represents a critical review of epidemiological studies, which had shown a positive association between the use of female sexual hormones during pregnancy and birth defects. The Author, R.A. Wiseman was a Senior Schering employee. This unpublished paper had originally been produced as defence material for the Association's litigation against Schering in the early 1980s. This document is susceptible to being bias and should not have been submitted to the EWG. However, on reviewing this document, it is apparent that the *claimed* independent data was from an in house source of Schering. The *benchmark index* presented as independent market research, was in fact produced by the Company *Intercontinental Medical Statistics Ltd* which was set up by Schering's legal advisors, McKenna & Co.

These are just two examples of information, which could have an effect on the ultimate conclusion of the EWG.

We are aware that material, including presentation documents and annexes with a total of app. 2 500 pages, were sent to the EWG in a period commencing two weeks, to final receipt six days prior to the meeting. This makes it practically impossible for the EWG to review the material with the required due diligence. This raises issues about the pressure placed on the EWG to process the full scope of the evidence provided in these complex documents. This is an unacceptable burden to place on EWG members. .

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[17] http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con404471.pdf - verified on 31.12.2016

[18] Report on some base data relating to key epidemiological studies – RA Wiseman 1983. Not published

Extract of Documents contained in the LandesArchiv files:

- **1/10th** human dose of Duogynon had been found to be the dose that does **not kill** all embryos, **1/3rd** human dose caused 98% of embryo loss (Report No. 2221)[19]
- Duogynon had been tested as an abortifacient and 100% of foetuses **died off or** were not implanted (Report No. 2121)[20]
- Further investigation, relating to malformations found in a series of animal experiments with Ethinylestradiol, were not executed, because the product was
- for pregnancy interruption ("emergency preparation") The product information also recommended **"an abortion was to be executed in case of a failure (Report No. 983)**
- 1115)[21]50% embryo loss and **all** the surviving embryos showed pronounced characteristics of **retardation** (document only says **50%** loss and retardation) (Report No. 773)[22]

The use of Primodos (Duogynon) as an abortifacient was known to Schering from the initial marketing of the drug. When discussing the product information with the Scientific Director **Dr.Ufer** on **26.11.1951**. stated: "for psychological reasons it does not seem advantageous to point out the indication for abortion too much, in the information leaflet for Duogynon/Primodos, or even have the word abortion appear, as we can **assume with certainty that abortion** will play an important role. However this will not be in the sense of a prophylaxis or a therapy." This is a clear indication that *abortion use* is not meant in prevention or termination for medical reasons, but will be used for **illegal abortions**

This knowledge is documented in a range of Schering-in house animal studies. (Several of which demonstrate all foetuses die off under Duogynon/Primodos treatment at even the low dosage of a **third** of the **dose** for women. Also displayed were other embryo toxic effects.

Schering also conducted studies with Duogynon and Norethisterone acetate specifically as an abortifacient. This is further evidence of Schering's involvement in developing Primodos/Duogynon for abortion use, also evidenced by **two patents** held by Schering.

While Schering always denied that Primodos or Duogynon could have been used as an abortifacient they did however execute experiments in this area, with remarkable results. A report on experiments with rats from 1971 was titled: "Examination of the impact of SH 70804 (= Duogynon simplex) on the implantation in the rat". It found that all fruits had died off or were not implanted.

The cover up of the abortifacient use in Germany has to be seen in connection with the **German criminal** code which banned abortifacient drugs until the mid 1970s. This was also the situation in many countries where Schering sold the drugs, e.g. Ireland.

Schering successful in-house experiments with Duogynon as abortifacient.

Schering in-house study "Examination of the impact of SH 70804 (Duogynon simplex) on the implantation in the rat" - 1.3.1971[23]

[19] Schering study Schering no. 2221 "Duogynon/Primodos - examination for embryotoxic action in the rat"
[20] Schering study 2121 "Duogynon -examination on the impact on implantation in the rat"
[21] Schering study 983 "ethinylestradiole – examination for embryotoxic action in the rat"
[22] Schering study 773 "examination of ethinylestradiole for embryotoxic action – preliminary tests - in the rabbit"
[22] Cancer Chemotherapeutic Agents as Human Teratogens, Selig et al. 2012 analyses 22 cases from a birth
[23] Landesarchive file 13227 p 83 – 1.3.1971

Summary section: *"No implantation could be observed in any of the treated dams after the application of 10 mg/kg I + 0.6 mg/kg II . Additionally, corpus luteum could not be found in any of these animals. Hence, the substances applied to the dams resulted in the* ***dying off of all the seeds*** *in the earliest phase of development and/or to the prevention of the implantation of these seeds"*

Schering studies *with Duogynon showed* ***100%*** *embryo lethality –* ***further studies*** *determined the dose where* ***not*** *all foetuses die off as* ***1/10*** *of the dose for women*

Schering in-house study "Examination of ZK. 5.356 + 4.902 on embryo toxic action in rats" with report from 1.3.1971[24]

> *"Two earlier examinations resulted in the dying off of all implanted seeds. The object of the present examination is to find a dose that does* ***not*** *any more or only* ***partly*** *result in the dying off of the foetuses."*

The result of the experiment was:

> *"With (0.1 mg I/kg + 0.006 mg II/kg) the dose has been found that only partly acts embryotoxically."*

The dose found to be **not** completely embryo lethal, was just one tenth or **10%** of the human dose[25]
.

A study on rhesus monkeys from 1976 and 1977 **confirms** this action in **primates:**

> "*The intramuscular administration of 0.5 ml SH 804 (= Duogynon simplex) /kg to rhesus monkeys at two days during the early pregnancy results in an embryo lethal action of almost all fruits."*[26]

Schering study on Norethisterone acetate showed retardation or dying off of all foetuses and damages to uterus and placenta.

Schering in-house: Toxicological and reproductive experiments with 17a-Aethinyl-19-nortestosteronacetat (norethisterone acetate) in rats, April 1966

"A one-time dose of ***30mg,*** *independent from the time of administration, or killing for examination, showed the foetuses of all animals were retarded or had died off and were more or less strongly resorped. There was* ***bleeding*** *of the uterus.*

The histological examination showed in different severity, ***hyalinosis and oedema of the placenta as well as haemorrhages, partly even small necrosis of the uterus****. At a one-time dose of 10mg/animal/day, showed the same phenomena emerged, after 30 mg, however the percentage of animals without or with only mildly disturbed foetal development was higher."*

Schering also found teratogenic actions of the HPT substances.

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[24] Landesarchiv 13226 p62 – Schering in-house study "Examination of ZK. 5.356 + 4.902 on embryotoxic action in rats" with report from 1.3.1971.

[25] The human dose of Duogynon simplex was 1mg progesterone + 0.06 mg estradial-benzoate per kg bodyweight

[26] Landesarchive 13226 p62. "Comment on the report of the Laboratorium für Pharmakologie und Toxikologie, Prof. Dr.F. Leuschner, from 24.11.1977 (last amendment from 17.04.1978): "Examination of the impact of ZK 4981 + ZK 4902 in the formulation of Duogynon simplex – here named SH 804 – on pregnant rhesus monkeys and their foetuses at intramuscular application" from 29.05.1978

A report on experiments from a Schering in house study in 1970 "Examination for teratogenic and embryo toxic action in rats", concludes: [27]

*"A connection with the application of the substance and the two anomalies (**subcutaneous oedema** on the entire body, **anophthalmy** on both sides **malformation** of the brain) found in group 3 (5, O mg I plus O.01 mg II /kg) can **not** be excluded with certainty."*

Official journal of the German medical profession confirms abortifacient use.

Deutsches Ärzteblatt 9.2.1978[28]

"Has the reform of section 218 failed? - (section 218 of the criminal code is on abortion-law)
*"**Mortality** (of pregnant women) in the first two month amounts to 0,6 in 100 000 terminations, whereas it rises to more than the 10-times (7.0) from 13th to 15th week and from the 16th week of gravitation it increases even to the 30-times (18.8). To stall with, e.g. **Duogynon-tablets** and "shots" should therefore finally be a thing of the past! Unfortunately, such **barely justifiable practices** are being reported again and again in the information centres."* [29]

The Author was the head of a network of information centres for women who wanted to have an abortion executed.

It was essential to cover up the use, as abortion drugs were illegal

German law criminal code (StGB) section 218 documents that the use of abortion drugs was illegal until 1974[30]**.**

The versions of the German Criminal Code until 19. June 1974 contained number 4: *„A person who supplies a substance or an object to aborticide the fruit of the womb will be punished with imprisonment of up to five years, in particularly severe cases with imprisonment of one to ten years.*"

Legal Dept, comments, on Schering Duogynon/Primodos off label use as abortifacient.

Extract from notes relating to the legal department of Schering dated, 23 May 1978, [31] contained in the LandesArchiv documents confirms that Schering had knowledge about this usage:

*"In what do we see the **abuse?** - Just in the use of the preparation in pregnancy or also in the use as **abortifacient, (the last is not a new fact** for us and should therefore not play a too big role in the current decision taking)"*

[27] Schering in-house study "Examination for teratogenic and embryotoxic action in rats" with report from 27.4.1970
[28] Landesarchiv Berlin 13224 p 96-98
[29] Landesarchiv Berlin B058-13224 p 96-98
[30] § 218 StGB as implemented from 15. Mai 1871 – 19. June 1974. The versions of the law until 19. June 1974 contained number 4: „A person who supplies a substance or an object to aborticide the fruit of the womb will be punished with imprisonment of up to five years, in particularly severe cases with imprisonment of one to ten years"
[31] Landesarchive 13200 p234

Doctors widespread use of Duogynon/Primodos as abortifacient.

Report from a Schering sales representative[32]

"During conversations about Duogynon it was clear that a surprisingly high amount of physicians are still **positive** about executing abortions with Duogynon"

When used as pregnancy test - abortion was also suggested*.*

Letter Schering Yugoslavia to Schering Berlin, regarding scientific sales statements to doctors[33]**:**

> *"This preparation could be used for pregnancy testing, but also **exclusively** for women who will anyway have an abortion."* [34]

Schering internal documents

Minutes (extracts) Schering Board Meeting 30.10.78 [35]

> *The use as a pregnancy test obviously plays a completely **subordinate** role in Korea. Duogynon is usually used as a therapeutic, sometimes obviously, also in the belief of an assumed abortive action. If this does not lead to the desired effect another form of pregnancy termination is sought. Following statements of experts by Dr. Granitza and. Dr. Detering (**Schering)** "it seems **improbable** that pregnancies would be continued in which **Duogynon** was used at early stage".*

Schering in-house study ZK 4.944, Ethinylestradiol – examination for embryotoxic action on rabbits - 17.4.1974

After the administration of ethinylestradiole an abortion **has** to be performed.

"The following findings related to the substance were as follows:

1. A dosage related pronounced decrease of the average gain of body weight after 0.03; 0.1 and 0.3 mg/kg.
2. An embryolethal action at 0.1 and 0.3 mg/kg(20% or about 50% of all implanted seeds were resorbed).
3. A decrease of the foetal weight after administration of 0.3 mg/kg
4. A **teratogenic** action after 0.3 mg/kg can **not be excluded, because in this group foetuses with externally visible anomalies ha**ve been observed, one case of **agnathia** of the lawer jaw, and a **pig tail,** rudimentary development of the tail and **oedema** like swelling of the entire body)

Schering's Conclusions:

No indications resulted from the present experiment that would **speak against** a use of ZK 4.944 up to a doses of 0.03 mg/kg in humans during pregnancy.

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[32] Landesarchive 13123 p122

[33] Evidence, 29, 78 Setsevits

[34] Beschwerde Schriftsatz Siegbert Setsevits im Verfahren AZ: 1 Wi Js 329/78 - 30.6.1981, p 8, reference to evidence folder 29, 78: „*dass man dieses Präparat auch zur Diagnose früher Schwangerschaft verwenden darf, aber ausschliesslich bei den Frauen, die einen Abort machen lassen werden.*"

[35] Landesarchiv 13192 p 131

The question if ZK 4.944 generates any teratogenic action in the dosage zone above 0.03 mg/kg in which a **partly embryolethal** effect occurs, **should be examined** in the long term in **further** experiments.

We **do not** consider these further experiments **are necessary** at present, due to the **planned use** as a **pregnancy interruption** (*abortifacient*) ("p.c. emergency preparation") it will be indicated in the preparations information that **at failure** of the drug, an interruption **has** to be executed. (see minutes of the 46th meeting of the theme group sexual division from **9.4.1973**, S. 2/3)

26.6.78 Schering Chemicals Limited UK Dr. Pitchford to Schering AG Dr. Amon[36]

We are concerned that the choice of a cut off point of **30%** of previous sales will be taken as an **admission** that for many years we have considered it **perfectly ethical** to maintain supplies in the face of a worldwide **misuse level of approximately 70% of turnover in this drug**.

"Changing the name of Duogynon/Primodos was proposed by, amongst others, Isabel Gal in **1975** and **1976** in the B.M.J and the **Committee on Safety of Medicines** asked for our comments on this suggestion. Schering replied that it did not consider a change in name represented "a **practical solution as far as misuse** is concerned". Dr. Pitchford wrote "it is a common practice for chemists to inform doctors when **older products** are no longer available and to **substitute accordingly**." We feel this practice must be particularly common in **third world** countries. The **correspondence** on this matter must be **disclosed in Court** proceedings in this country and will raise yet another **conflict** between Schering Chemicals Limited and Schering Berlin, which the media will be quick to seize upon

We feel it is legitimate to differentiate between England and the rest of the world, on the grounds that there was **no evidence of misuse** at the time in the UK. The sales figures alone indicated continued use as a H.P.T. from prescription data available."

"As we estimate that the sales figures of Cumorit will fall to 30 percent of PRIMDODOS we assume that **70** percent were for abuse = **abortion or pregnancy test** leading to abortion".

Schering Experiments with Duogynon simplex– from document dated 13.10.1978[37]

> *„Higher doses lead to death of the fruit in almost all implanted embryos. (Resorption rate of **100%** from the 1-times human dose*" Table: **1/10** human dose = 38% resorptions; **1/3** human dose 98% resorptions.

The same action (resorption or early abortions) was shown in **Rhesus Monkeys**
(Summary: Administered to three groups on 20th+21st, 27th + 28th, 34th+35th day) Only in the group with treatment on **20th and 21st** day p.c. did **one** foetus survive to caesarean.

ACTIONS OF GOVERNMENT HEALTH COMMITTEES - KEW & LANDESARCHIVE FILES

[36] Landesarchiv 13200 p. 194
[37]
Landesarchiv Berlin B058-13194 p 45
Landesarchiv Berlin B058-13194 p 56

1958: - Accepted an **untested** drug to the UK market, which had **no** therapeutic value when administered as a Pregnancy Test.

1958: - Failed to acknowledge the first warning from Dr. Edwards, who had noticed effects on the brain. The warning contained the statement "Hormone Pregnancy Tests could cause the type of insult, likely to cause foetal malformations.

1958-1967: - Ignored further written warnings from the medical profession, e.g. "This looks like it could be another **Thalidomide".**

1967: - Refused to acknowledge concerns by Dr. Isobel Gal, detailed in her extensive study and submitted to the BMJ, despite Dr. Inman's statement **"You have a prima facie case"**

1968 & 1969: - Letters written to **Schering Berlin** from **Schering Scientists in the UK**, stated **unequivocally "Primodos needs to be removed from the market". "There are growing** concerns *and **evidence*** regarding it's safety". Dr. Inman **refused** to support this request to Schering Berlin and instead wrote "In his opinion the **evidence is not sufficient** to take the drug off the market"

1969: - The study from the Royal College of General Practitioners was also available to Dr. Inman at this time, but his response was to write "the results are not conclusive". He also **dismissed** the Summary of the Report from the RCGP which stated "The results of this study can not be due to chance".

1967 - 1975: Dr. Inman had prevaricated for 8 years over growing evidence of miscarriages, stillbirths and abnormalities, presented to him as possible results of HPT's, by the medical community. His comment was **"we are defenceless in the 8 year delay"**

1974: - The Minutes of a meeting of the CSM and Sub Committee on Adverse Effects, documents "**there is a possibility that one result of our study may be the demonstration of a** t**eratogenic** hazard with **Hormone Pregnancy Tests**. In Table IV apparent excess of cases subjected to HPT's **is significant**. Other published data **supports** the same hypothesis. The Committee may wish to consider whether or not the Manufacturer should be put in the picture at this stage of the study. Most of the products are used for ***other*** purposes by pregnant and non pregnant women. 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 licence should be withdrawn** absolutely. Initialled by W.H.W.I. **(Dr. Inman)**

1975: - Dr. Inman contacted Schering Berlin to ***warn them*** he had found a **5:1** chance of malformations in his own study on Primodos. He stated he wanted to give them chance to **withdraw the drug discretely,** to avoid claims of medical negligence, **BEFORE** alerting the medical profession. He further asked them to **subpoena** him, to allow him to **discredit** his own study and advised them he had **destroyed**, or made **unidentifiable**, the entire material used in his study. **Schering** did subpoena Dr. Inman was and he did give evidence on behalf of Schering **AGAINST** the Association.

These are only a small example of the failures by the Government Medical agencies and in particular Dr. Inman, but there are many more.

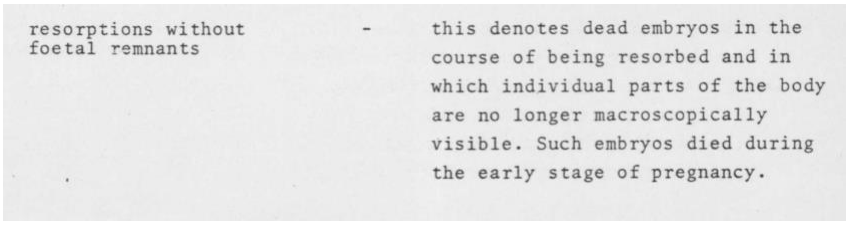
We have been advised that Files from Kew Archives have been removed and some files are sealed, or missing at transfer. We feel these documents may provide additional information, which has been withheld from the EWG.

REFERENCE DOCUMENTS

24. Review for meeting 8-10 - Tobias Arndt

Bullet Points:

1. Biased review of studies, e.g. Epidemiological studies are critically reviewed by using a bespoke evaluation system (Forest Plot) This resulted in discounting a majority of the studies in favour of an association. Animal studies conducted by Schering Scientists were included, despite obvious major design faults, which would impact on the ability to detect teratogenicity,e.g. In all studies, fetuses were examined too late. Dams were killed too late to provide fetal remnants, necessary to detect any malformations. Schering were aware of the design flaw as evidenced in their study documents, which states "Embryo's died during the early stage of pregnancy" Schering study No. 4042 p 7



resorptions without foetal remnants	-	this denotes dead embryos in the course of being resorbed and in which individual parts of the body are no longer macroscopically visible. Such embryos died during the early stage of pregnancy.

This indicates that fetuses which were completely resorped, died off in the early stage of pregnancy, possibly days 6 to 10. In almost all experiments dams were killed on day 19. The sample sizes in all studies were too small (less than 16 litters) to detect malformations. P.38 of report.

P 36

5.1.1 General toxicity

Sex hormones have been extensively studied in repeated dose studies in rodents, dogs and non-human primates, largely to support their use as combined hormonal contraceptives and hormone replacement therapy. The most prominent effects observed were related to exaggerated pharmacodynamic effects, in other words expected but amplified effects in steroidal sex hormone response in primary and secondary reproductive tissues, including suppression of body weight gain, decrease of white blood cells, proliferation of gland tissue, with lactation of mammary gland. Atrophy of sexual organs in males and females has also been observed.

Exaggerated pharma codynamic effects referenced. Serious effects include:

Suppression of body weight gain

Decrease of white blood cells

Proliferation of gland tissues

Atrophy of sexual organs in males and females

Admits expected effects, but state these were amplified.

P37

– Choice of species

Studies assessing the potential for reproductive toxicology are most often conducted in rodents and rabbits but an understanding of the mechanism of any observed effects and how drug exposure in animals relates to humans, is required in order to assess the relevance of any potential risk to humans. Studies of sex hormones in non-human primates are generally considered to offer advantages over rodents and rabbits because of the similarity of their reproductive systems to humans; however, their use poses ethical and practical limitations, particularly as they usually produce single offspring at a time, having a default litter size of one.

Drug-associated teratogenicity is dependent on many factors including the species, since different animal species can be more or less sensitive to the teratogen. These differences can relate to a number of factors including, differences in the pharmacokinetics of the drug, the stage of prenatal development when the exposure occurs, the dosage of drug administered and the mechanism of teratogenicity. These factors all need to be considered when interpreting the outcome of reproductive toxicity studies in animals.

Fails to acknowledge that the species with the highest sensitivity should be the one referenced, as an indication it may be harmful to humans. (Rabbit - Schering 2300 e.g.- 1976) Also states it is a requirement to understand the mechanism before relating the risk to humans. Incorrect. (Asprin)

P38

– Timing

The time of greatest sensitivity to teratogens is during organogenesis. Table 7 below provides the major developmental milestones for a variety of species during organogenesis, presented in gestational days (starting from the formation of the primitive streak to the closure of the hard palate).

This section fails to disclose how the study should be designed, to detect exposure time related effects. e.g. Typical day 7 damage , dams should have been killed on day 8 or 9 to examine the fetus. In most of Schering studies, the dams were killed on day 19(in some as late as day 28), when the fetus were fully resorped, therefore no fetal remnants were available. Not one study examined the fetuses shortly after administration of the drug.

No fetal remnants available as fetus's died off very early. This was known to Schering as evidenced below from Study 4042.(p 7) This indicates that Schering would have been aware that their studies were designed NOT to detect malformations. This information should have been discussed within the EWG review, to ensure the Group were aware of the shortfalls in all studies. . Considering the emphasis placed on the appropriate design of epidemiological publications, it is astonishing that this evident design fault was not highlighted within the report also.

Dying off during early stage of pregnancy has a great likelihood of malformations being the cause of death.

Schering study No. 4042 p 7

resorptions without foetal remnants	-	this denotes dead embryos in the course of being resorbed and in which individual parts of the body are no longer macroscopically visible. Such embryos died during the early stage of pregnancy.

– Sample size

Animal reproductive toxicity studies usually lack the statistical power to detect subtle increases in rare events. Currently, for all but the rarest events, evaluation of 16 to 20 litters for rodents and rabbits is considered necessary to provide a degree of consistency between studies. For this reason, reproductive toxicity studies include high doses of test substance so as to induce some maternal toxicity and maximise the possibility of detecting a response. Studies conducted a long time ago, including those on NETA and EE were mostly based on the evaluation of fewer than 16 litters per group and so lack the power of studies conducted today.

The litter sizes used by Schering in their studies, were far less than the 16 to 20 required, yet this is not taken into consideration when study results (from Schering) declaring no malformations, were presented. This is a study design fault, which impedes the detection of malformations.

For this reason, any rare events found should not be excluded, but should be taken as evidence for teratogenicity. (anophthalmia - 2 eyes missing, erronous brain development oedeomatic bodies, Schering study EE/Neta - 27.04.1970 Primodos.) Rats 4 HED

The EWG accepts the data of studies which use higher doses, to counter the lack of sample size, therefore adverse effects, particularly malformations, at those doses, can not be discounted

P39

In the absence of data on drug levels in the blood in animal studies, a dose equivalence has to be estimated. A dose comparison based on an assumption that doses scale 1:1 between species when normalised to body surface area (mg/m^2) is currently considered more appropriate, though in many older studies dose equivalence of the administered substance in mg/kg body weight to that used in humans was used.

This information was provided to the MHRA by me, at the last EWG meeting in April, 2017. The previous calculation (mg. per kg body weight) had been used until that time. This calculation undermined the true significance of animal study findings. eg for Rats the correct dose is 6 times higher than previously referenced. (body surface area not weight)

P40

teleconference was held on the 25th August 2017 between Dr Vargesson, an EWG non-clinical expert and the secretariat. Dr Vargesson reported that this additional work had confirmed and extended the results presented to the EWG in October 2016 for dose dependent developmental effects in the zebrafish embryo; that the NA/EE mixture acts on the embryo in a time sensitive manner; that the drug accumulated in the embryo and that damage was observed rapidly. Dr Vargesson confirmed that his aim was to continue this

Although Neil [Vargesson]'s Study was referenced, due to the fact is has not been published it was excluded, however one unpublished study by Wiseman&Dodds was submitted for review by the EWG.

P41

The majority of studies with NETA (and related progestogens) showed genital malformations of the fetus with doses generally higher than those used in HPTs. This finding was observed in mice, rats, guinea pigs, rabbits and non-human primates. The induction of genital abnormalities is related to the known androgenic activity of NET and structurally related hormones.

P72-3

6.2.1.1 Effect of norethisterone

Embryo-lethality was observed in studies in which NETA (and related progestogens) was given to mice, rats, rabbits and non-human primates during organogenesis. Embryo-lethal doses of NETA were generally higher than those used in Primodos. The lowest doses of NETA that had no effect on embryo-fetal survival in these studies are shown in Table 18.

Table 18. NO(A)EL doses for embryo-fetal survival of NETA; X-fold difference to Primodos.

Species	NO(A)EL	X-fold difference vs Primodos*
Rats Schering studies #2330 (1976) and #5303 (1978); Suzuki, 1978	10 mg/kg/day by mouth	9
Mice Schering study #5304	≥48 mg/kg/day by mouth	≥32
Rabbits Schering study #2300 (1976)	<0.1 mg/kg/day by mouth	<0.1
Rhesus macaques Wharton, 1964	<25 mg/animal intramuscular 5 days/week	<25
Baboon Beck, 1982	<2.5 mg implant throughout pregnancy	–

* based on human equivalent dose calculated on a mg/m^2 basis: assume Primodos daily dose of 10 mg norethisterone acetate, 0.002 mg ethinylestradiol for a 60kg women. Based on 1 mg/kg = 4.3 mg/m^2 for a rat; 1 mg/kg = 11.8 mg/m^2 for a rabbit; 1 mg/kg = 38.8 mg/m^2 for a human.

"Embryolethal dose of NETA were generally higher than those used in Primodos". This statement is misleading as in rabbits an embryolethal effect was already established in a 1/3rd human equivalent dose. (3rd study in table above)

Schering study 2300 (NETA – rabbits) - 13227 p76

"*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.*"

0,1 mg/kg = 1/3 HED, 1mg/kg = 3 HED, 10 mg/kg 30 HED

In study 2300 – foetuses were examined on day 28 after dams killed, even though the substances were given on days 7-18 – Why were the dams not examined earlier? The study is from 1976, when the problem of non existent foetal remnants should have been known (reference study design faults).

P41 on NETA

- equivocal increase in malformations in one rabbit study (Schering #2300, 1976 – two fetuses with umbilical hernia) at doses higher than those used in HPTs.

From table on page 89 -13227- in group 3 – 1mg/kg - 3 times HED –
The report does not point out that in the entire study this was 2 malformations in 3 resorptions with fetal remnants . All other resorptions were without fetal remnants. Again, this questions the study design which examined the foetuses only on day 28 and not shortly after administration of NETA in the sensitive period.

983 EE rats

P 41 MHRA Report:

- equivocal increase in malformations in one study in the rat (Schering study #983, 1973) which was not repeated in a larger study (Schering study #4136, 1980)

983 in 1973 EE rats Translated document **13226 page 129** plus
"A **teratogenic effect** after 0.3 mg / kg **cannot be ruled out**, since foetuses with externally visible anomalies were observed in this group (one each of the following anomalies: agnathy of the lower jaw, pig tail, a rudimentary tail and oedematous swelling of the whole body). No other divergences from the control group were found"

P 41 MHRA Report continued :

These studies do not support an increase in malformations in non-reproductive tissue following EE exposure.

Contradictory in view of the above results.!!

Fails to reference p 131 (p167 13226 german)
"The issue whether ZK 4.944 at doses exceeding 0.03 mg / kg, in which case embryolethal effects occur in part (in rats up to 1.0 mg / kg), also **has teratogenic effects, should be settled through additional trials** to be conducted at some future time.

At the present time, we do not consider such experiments necessary, since in its intended use for discontinuing pregnancy, (p.c. "emergency medication") in which the instructions on use should

state that in case of failure an abortion must be performed. (See minutes of the 46th meeting of the Sex Subject Matter Group on 9.4.1973, pp. 2-3)"

From study 4136, shows massive amount of early resorption. e.g resorptions without fetal remnants therefore malformations could not be ascertained.

		Group 1	Group 2
Dead fetuses			
total number		1	6
number per group	(M/SD)	0 /0.1	0.1/0.4
% of implantations per group		0.2	1.4+
% of implantations per animal	(M/SD)	0.1/1.0	1.0/3.2
Resorptions			
total number		39	233
number per animal	(M/SD)	0.7/1.1	4.3/4.5
% of implantations per group		5.8	35.8+
% of implantations per animal	(M/SD)	5.7/9.1	36.4/39.8
Type of resorptions			
early	(number/%)	38/97.4	219/94.0
late	(number/%)	1/ 2.6	14/ 6.0
Postimplantation loss			
total number		40	239
number per animal	(M/SD)	0.7/1.1	4.4/ 4.5
% of implantations per group		6.0	36.8+
% of implantations per animal	(M/SD)	5.8/9.1	38.6/38.8

P 172 study
Resorptions mostly without fetal remnants

P 178 study
Administration of substance between days 6-15 – killing of dams on 19th day

Tables pager 183-184
Groups 1-3 no fetal remants(Control 0, Group 2 . 0.03mg. Group 3. 0.1 and Group 4. 0.3mg.)
Group 4 – 10.5% fetal remnants, malformations as detailed above.
Groups 2 and 3 may have had malformations, but no fetal remnants to study.

Once again, no discussion regarding the study design or the late killing of the dams. Could – not ascertain any malformations as there were practically no fetal remnants

P41 report

> Consistent findings were shown in studies with NETA and EE (or structurally related synthetic progestogens) across mice, rats, guinea pigs and rabbits. In accordance with their hormonal actions, genital organ malformations were observed at high doses in some of these studies.

P42

Schering study 3579

CAVEAT

This document was prepared in contemplation of litigation and is confidential. Its contents may not be disclosed to any third party without the consent in writing of the Company.

Medical Department, Schering Chemicals Limited. July, 1979.

Schering study 3578 – Provided by Bayer

CAVEAT

This document was prepared in contemplation of litigation and is confidential. Its contents may not be disclosed to any third party without the consent in writing of the Company.

Medical Department, Schering Chemicals Limited. July, 1979.

Study 3579 - early resorptions – This indicates no fetal remnants, which will be due to continued design flaw, e.g. administration days 6-15 days, killing and examination only on day 19

EWG Report P42/3 on study 3578 Inaccuracy/Misrepresentation in EWG report.

malformations were observed. Microscopic analysis of the thorax was conducted and, with the exception of subcutaneous oedema, there was no increase in thoracic anomalies (**Table**

Contradictory statement re: study 3578 actual statement is below:

of foetal development. Teratogenic effects were not observed. However, histological examination of the thorax of half the foetuses for heart and blood vessel abnormalities is still in progress.

4284

The subcutaneous oedema in two of the only three fetuses available for examination in group 5 might be a result of treatment, However, the number of examinable fetuses was too low for any relevant interpretation. The slight increase in incidence of subcutaneous oedema in three fetuses only from group 4 was considered to be equivocal when compared with a similar observation in one control fetus

Again lack of foetal remnants not referenced in the Report, but acknowledges findings of subcutaneous oedema might be the result of treatment.

P43 EWG report

delayed or non-ossification of the fetal skeleton and wavy ribs. Developmental variations also occurred in the control animals. An increase in skeletal variations was also observed in two Schering studies (study #2221 and #1631) in which rats were given the natural forms of estrogen and progesterone.

This 2221 study is excellent.

1/10th human dose of Duogynon had been found to be the dose that does not kill all embryos any more, 1/3rd human dose caused 98% of embryo loss (Report No. 2221)

When measured against HED the actual dose is 1.66% of the human dose. This dose does not kill off all embryos. 5% of the HED kills 98%

Massive embryo lethality at low doses. Once again the dams should have been examined much earlier to find foetal remnants.

This study should be referenced in section 6 of the EWG report. "Evidence for an abortifacient effect of HPT's in early pregnancy" This section should have included a subsection detailing combinations of gestegen and estrogen, e.g. NETA & EE

P43

Standard embryo-fetal development studies by necessity are generally designed to dose a pregnant animal throughout the period of major organogenesis. The production of malformations however often requires a specific set of conditions, and dosing a pregnant animal on one or two days of gestation can be an efficient means of eliciting malformations. In a series of studies conducted by Schering in rats and rabbits the hypothesis was tested that after treatment with a combination of NETA and EE spanning different periods of organogenesis, teratogenic effects might occur, which otherwise might have been masked by a more markedly embryo-lethal effect observed after treatment throughout organogenesis.

However, the dams were only killed on or after day 19 of any of these studies. Thereby in all studies the vast majority of resorptions did not leave any fetal remnants. Obviously, it is impossible to ascertain malformations on a completely resorbed fetus – or in other words on nothing. The study design has to be criticised here.

P 43/44

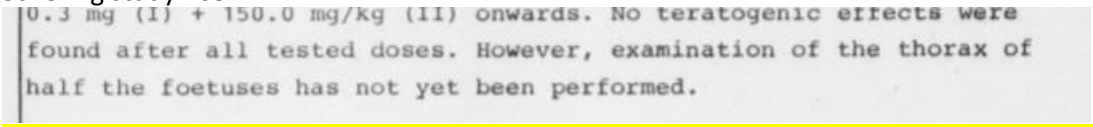
Table 11

Table 11. Distribution of external, skeletal and visceral malformations in rats dosed with NETA and EE; studies #4037 [1979]; #4042 [1979]; 4044 [1979]; #4045 [1979]; #4046 [1979]) (number of malformations/number of fetuses examined).

Gestation Day	Vehicle control	Low 50 + 0.01 mg/kg	Mid 150 + 0.03 mg/kg	High 500 + 1.0 mg/kg	Very high 1500 + 3.0 mg/kg
6–7	0/172	0/152	0/128	0/22	–
8–9	1/225 (0.4%)[a]	1/177 (0.6%)[a]	0/109	0/14	–
10–11	0/247	0/191	0/157	0/62	–
12–13	0/264	1/206 (0.5%)[b]	0/203	1/228 (0.4%)[c]	–
14–15	0/284	–	0/250	0/151	0/230

[a] Umbilical hernia (external)
[b] Malformation of the tail and atresia ani (external)
[c] Malformation of the tail (external)

Line 1
Schering study 4037


0.3 mg (I) + 150.0 mg/kg (II) onwards. No teratogenic effects were found after all tested doses. However, examination of the thorax of half the foetuses has not yet been performed.

Only half of the "viable foetuses" were studied for visceral and the remaining half for skeletal abnormalities (p 9 study) detailed in table 8 and table 10 of the study.
This is not mentioned in the report neither in the table nor text.
Almost all resorptions were without fetal remnants (table 4 of study)
Administration of drugs on days 6 and 7, dams only killed on day 19 (p 8 study)

Line 2 administration days 8-9
Schering study 4046
"However, examination of the thorax of half of the foetuses has not yet been performed"
All "viable foetuses" were studied for external malformations but only half for visceral and the remaining half for skeletal abnormalities (p 9 study) detailed in table 9 and table 11 of the study.
Almost all resorptions were without fetal remnants (table 4 of study)
Administration of drugs on days 8 and 9, dams only killed after day 19 (p 8 study indirectly as last weighing was on day 19)

Line 3 administration days 10-11
Schering study 4042
"However, examination of the thorax of half of the foetuses has not yet been performed"
All "viable foetuses" were studied for external malformations but only half for visceral and the remaining half for skeletal abnormalities (p 9 study) detailed in table 8 and table 10 of the study.
Almost all resorptions were without fetal remnants (table 4 of study)
Administration of drugs on days 10 and 11, dams only killed after day 19 (p 8 study indirectly as last weighing was on day 19)
Line 4 administration days 12-13
Schering study 4045
"However, examination of the thorax of half of the foetuses has not yet been performed"
All "viable foetuses" were studied for external malformations but only half for visceral and the remaining half for skeletal abnormalities (p 9 study) detailed in table 8 and table 10 of the study.
Clear majority of resorptions were without fetal remnants (table 4 of study)
Administration of drugs on days 12 and 13, dams only killed after day 19 (p 8 study indirectly as last measuring of bodyweight was on day 19)

Line 5 administration days 14-15
Schering study 4042
"However, examination of the thorax of half of the foetuses has not yet been performed"
All "viable foetuses" were studied for external malformations but only half for visceral and the remaining half for skeletal abnormalities (p 10 study) detailed in table 8 and table 11 of the study.
Almost all resorptions were without fetal remnants (table 4 of study)
Administration of drugs on days 14 and 15, dams only killed after day 19 (p 9 study indirectly as last weighing was on day 19)

Anyway this late administration is far less toxic and malformations less likely. However, the almost 50% presence of foetuses with fetal remnants supports the hypothesis that the later after administration the less remnants is correct.

Also this study clearly ascertains a dose dependent rise of skeletal variations (table 8) – Control: 6.4%, 0.3 EE +150 NETA mg: 16.5%, 1 EE+500 NETA mg/kg: 37.3%, 3 NN+500 NETA mg/kg 42.4%

(Table 12).

Table 12. Distribution of external skeletal and visceral malformations in rabbit studies dosed with NETA and EE; studies #3581 [1978]; #4036 [1978]; #4038 [1978]; #4039 [1978]; #4040 [1978]; #4041 [1978]; #4043 [1978] (number of malformations/number of fetuses examined).

Gestation Day	Vehicle control	Very low 0.15 + 0.0003 mg/kg	Low 0.50 + 0.001 mg/kg	Intermediate 1.5 + 0.003 mg/kg	Medium 5.0 0.01 mg/kg	High 15 + 0.03 mg/kg
6–7	0/103	–	0/90	–	0/65	0/13
8–9	0/64	–	0/52	–	0/54	0/1
10–11	0/67 1/34[a] (2.9%)	–	0/48	–	0/74	0/2
12–13	1/71[b] (1.4%)	1/89[c] (1.1%)	1/72[d] (1.4%)	–	0/30	–
14–15	0/64	0/74	0/79	0/59	–	–
16–17	1/67[b] (1.9%) 1/35[e] (2.9%)	0/55	0/56	0/54	–	–

[a] Fusion of the 7th and 8th rib on the left side;
[b] Umbilical hernia;
[c] Exencephaly;
[d] Severe malformation;
[e] Anophthalmia on the right side

Schering 3581 Pages 43 in the Report NETA/EE rabbits
Again prepared for the litigation. - major bias.
Dams killed on day 28

Line 1, 4043,
Line 2, 4041
Line 3: 4040
Line 4: 4038
Line 5: 4036
Line 6: 4039

All “viable foetuses” were studied for external malformations but only half for visceral and the remaining half for skeletal abnormalities.
Dams killed after day 28 (last measuring of body weight)
Table 4 almost no foetal remnants
Table 8 (9 in 4039) skeletal variations 4043 IV 100%, 4041 IV no survivors, 4038 II Encephalocele (71 survivors), III severe malformation (30 survivors)

- All dose related increase

Table 10 (11 in 4039) visceral malformations

Conclusions

7.5 times HD (1.5mg NETA + 0.03 mg EE /kg) in rabbits is 2.5HED and is partial embryo lethal (51%) at that dose.

Page 75 of the EWG report on this same Schering 3581 fails to point out that the highest dose was just equivalent to the 2.5 HED.

A further experiment was therefore performed (Schering study #3581, 1978) to explore the effect of NETA and EE at the lower end of the dose range. In this study, pregnant rabbits received vehicle control or NETA and EE at doses of 1.5 + 0.03 mg/kg/day, 0.5 + 0.001 mg/kg/day, or 0.1 + 0.0002 mg/kg/day between gestation days 6 to 18. There was clear embryo-fetal loss (51%) in the high dose group although a potential trend to embryo-fetal loss in the mid and low doses was observed.

In view of this the conclusions of the section on abortifacient effects of NETA and EE combinations on page of the EWG report is misleading:

6.2.1.4 Key observations

- Depending on the species studied, embryo-lethal effects with NETA and EE separately or in combination were seen, most often at daily doses and durations much higher than those used in HPTs.

On Page 45

- *Virilisation*

Genital tract abnormalities / malformations including virilisation of female fetuses were reported in rodents and non-human primates exposed to these hormones during the period of sexual differentiation. The effects on male and female reproductive tissue reflect the known hormonal action of these compounds.

Consolidates the known effect of these hormones, but attempts to trivialise the serious and indisputable finding. Also highlights these findings have implications on other anomalies caused by hormones.

Vascular disruption

P XIV

Death of the developing embryo with high doses of estrogens has been consistently observed in animal studies and is now considered to be a well-established effect. A similar effect has been observed in studies with norethisterone (or related progestogens). As may be expected, the combination of norethisterone and ethinylestradiol also shown consistent embryo-lethality in different animal species. This effect was higher with increased doses and varied according to when during pregnancy it was given.

There was no vascular disruption identified by the EWG.

p.49 - 5.1.5 - Overall conclusions on vascular disruption
"No evidence that NET and/or EE could disrupt the pregnancy by vascular disruption at the doses used in Primodos was identified"
Does not mean it does not exist, just not identified and may be at a higher dose.

5137 report
Fails to stipulate malformations identified by Schering in connection with drug. Fails to acknowledge the studies are for an abortifacient use.

P52

BioMedical Computing Ltd re-categorised the anonymised HPT-exposed ADR data, based on a Microsoft Excel database provided by MHRA. EUROCAT categorisation displays only 'major anomalies' or 'major + minor' anomalies; minor anomalies alone are not captured unless associated with a major anomaly within the same case report.173 cases were categorised as having a major congenital anomaly according to the EUROCAT method of which five reports were identified as reliably having a genetic cause:

- Cornelia de Lange syndrome
- DiGeorge syndrome
- Chromosomal abnormality unspecified (x2)
- Angelman syndrome

Not many genetic causes in 173 cases, but would like to know how they identified the 5 cases. Check how many members have undergone a genetic test. All were cleared

Anecdotal evidence[38]

P 71-72

This section does not include the most important case reports, Schering documents and publications of the German equivalent of the BMJ, which discusses the abortifacient use of Duogynon.

The section does not acknowledge the vital importance of anecdotal evidence with respect to case reports on adverse events. The tone of the report is to dismiss the information forwarded to the Health authorities as unreliable and somehow exaggerated.

In science, definitions of anecdotal evidence include:

- "casual observations or indications rather than rigorous or scientific analysis"[6]
- "information passed along by word-of-mouth but not documented scientifically"

Anecdotal evidence can have varying degrees of formality. For instance, in medicine, published anecdotal evidence by a trained observer (a doctor) is called a case report, and is subjected to formal peer review.[7] Although such evidence is not seen as conclusive, it is sometimes regarded as an invitation to more rigorous scientific study of the phenomenon in question.[8] For instance, one

[38] **Scientific context**
In science, definitions of anecdotal evidence include:
- "casual observations or indications rather than rigorous or scientific analysis"[6]
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Anecdotal evidence is considered the least certain type of scientific information.[10] Researchers may use anecdotal evidence for suggesting new hypotheses, but never as validating evidence.

study found that 35 of 47 anecdotal reports of drug side-effects were later sustained as "clearly correct."[9]

Contergan Trial - Scientific proof not required because it comes too late, only a suspicion and has to be withdrawn.

Epidemiology

MHRA paper epidemiology March 2017

The paper dismisses all categories of congenital damages in association with HPT excepting *a small increased risk of congenital heart defects associated with HPTs cannot be excluded* on basis of what could be summarized as insufficient quality assessment score of the studies.

However, when measuring the findings of the studies for the various damage groups a majority and in most cases a clear majority of studies favor an association of birth defects and HPTs as presented in the forest graphs.

MHRA paper epidemiology March 2017[39]

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[39] MHRA paper epidemiology March 2017

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However, when measuring the findings of the studies for the various damage groups a majority and in most cases a clear majority of studies favor an association of birth defects and HPTs as presented in the forest graphs.

Nervous system defects
Page 9: "*Our conclusion is that overall the results from these studies do not suggest an association betwieen HPTs and neural tube defects*."
Forest plot on page 10: Overall 15 Studies, 10 favor an association, 3 do not favor an association, 2 neutral

Congenital heart defects
Page 12: "*Our conclusion is that a small increased risk of congenital heart defects associated with HPTs cannot be excluded."*
The forest plot on page 13: Overall 15 Studies, 12 favor an association, 3 do not favor an association

Orofacial clefts
Page 14: "*Our conclusion is that the studies assessed do not provide robust evidence for an association between HPTs and any orofacial clefts*."
The forest plot on page 15: Overall 5 Studies, 4 favor an association, 1 does not favor an association

Digestive system and abdominal wall defects
Page 15: "*The results for abdominal wall defects are conflicting between the two studies and in our opinion do not support an association with HPTs."*
The forest plot on page 16: Overall 9 Studies, 6 favor an association, 3 do not favor an association

Urinary system defects
Page 18: "Overall two studies investigating three different urinary system defects consistently found significantly increased risks of varying magnitude. Both studies are judged to be of poor quality and our

The paper dismisses all categories of congenital damages in association with HPT excepting *a small increased risk of congenital heart defects associated with HPTs cannot be excluded* on basis of what could be summarized as insufficient quality assessment score of the studies.

However, when measuring the findings of the studies for the various damage groups a majority and in most cases a clear majority of studies favor an association of birth defects and HPTs as presented in the forest graphs.

Nervous system defects
Overall 15 Studies, 10 favor an association, 3 do not favor an association,
2 neutral
Congenital heart defects
Overall 15 Studies, 12 favor an association, 3 do not favor an association
Orofacial clefts
Overall 5 Studies, 4 favor an association, 1 does not favor an association
Digestive system and abdominal wall defects
Overall 9 Studies, 6 favor an association, 3 do not favor an association
Urinary system defects
Overall 3 Studies, all 3 favor an association.
Genital defects
Overall 2 Studies, all 2 favor an association
Musculoskeletal defects
Overall 8 Studies, 7 favor an association, one does not favor an association
VACTERL
Overall 5 Studies, 3 favor an association, two are neutral.
All Congenital anomalies
Overall 12 Studies, 8 favor an association, four are not in favor for an association.

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conclusion is that the strength of any association between HPTs and urinary system defects remains uncertain."
The forest plot on page 19: Overall 3 Studies, all 3 favor an association.

Genital defects
Page 20: "*The studies reported non-significant increased risks of different genital defect outcomes and it is unclear what outcomes are included in the study by Torfs 1981. Both studies have limitations and in our opinion the strength of any association with HPTs is unclear.*"
The forest plot on page 21: Overall 2 Studies, all 2 favor an association

Musculoskeletal defects
Page 23: "*Our conclusion is that the results of the studies assessed do not support an association between HPTs and other skeletal defects."*
The forest plot on page 21: Overall 8 Studies, 7 favor an association, one does not favor an association

VACTERL
Page 26: "*The reason for the conflicting results between these studies is unclear but our view is that these do not provide robust evidence for an association between HPTs and VACTERL."*
The forest plot on page 27: Overall 5 Studies, 3 favor an association, two are neutral.

All Congenital anomalies
Page 29: "The majority report a small increased risk but this is non-significant increase despite being adequately powered to detect an increase if one exists."
The forest plot on page 30: Overall 12 Studies, 8 favor an association, four are not in favor for an association.

P48/9

- Two studies in which 25 women were given NETA 40 mg and EE 0.04 mg or 11 women were given NETA 20 mg and EE 0.04 mg at weeks six to seven of gestation, found no effect on endogenous progesterone or estradiol levels, and did not identify any macroscopic or microscopic differences indicative of placental damage, (eg thrombosis

or in degenerative changes and leucocytosis in the termination products) compared with similar numbers of untreated women (Pulkkinen, 1984).

P78

6.2.2 Clinical data

A possible pathological effect of Primodos on early human pregnancy involving necrosis and subsequent bleeding in the developing placenta or a reduction in the high maternal levels of circulating progesterone necessary to support early pregnancy was investigated in a series of two studies in women seeking legal termination of pregnancy in Finland (Pulkkinen, 1984).

The first study was double-blind in design. Women who were eight to nine weeks pregnant were randomly assigned to receive NETA 20 mg and EE 0.04 mg (equivalent to two tablets of Primodos taken together) or placebo (n=25 women per group). Primodos or placebo were taken at time 0, with ultrasound scans at 0, 24, 48 and 96 hours before dilatation and curettage at 96 hours. The termination of pregnancy products were examined for any pathology indicative of placental damage. The second study was an open label (unblinded) study in which endogenous hormone levels in ten untreated women (at 8.5 ± 0.5 weeks of pregnancy) were compared to the levels in 11 women who were given NETA 20 mg and EE 0.04 mg (at 6.8 ± 0.4 weeks of pregnancy). Limited plasma samples were taken during the first 6 hours following treatment.

None of the women who received Primodos miscarried during the observation period. The details of the pathology findings can be found in section 5.1.4.2.

Pulkkinen

For me, this is very interesting as it demonstrates actual plasma levels of NOR and EE after a single administration – and shows the levels are raised and present in the plasma for 48hrs.

The data we have in the fish embryo is the drug accumulates in the embryo – so if doing so in the human embryo – the amount of drug will be much higher than plasma concentration.

There is no evidence that they looked at the embryo – the focus was on saying NOR/EE doesn't cause placental bleeding. The presumption must be there was no damage – but they don't actually state this.

The studies did not go on long enough to see if there was outward (or internal physiological) damage. The study really seems focused on saying the NOR/EE combinations doesn't cause maternal bleeding.

I am amazed pregnant women were happy to do this. There is no detail on Ethics.

Page 83 of the EWG report:

7.2.1.3 Requirements for studies in humans

Randomised controlled trials in humans are required to establish the efficacy and safety of a new medicine before it can receive a product licence.

For many years, no women (of any reproductive status) were included in clinical trials of medicines, a decision based on the experience with thalidomide. Clinical research was conducted mostly in men until 1997 when the ICH E8 European guideline "General Considerations for Clinical Trials" allowed for women to participate as long as those of childbearing potential used highly effective contraception. While it is recognised that there may be advantages in including women who are pregnant in trials, there have been no initiatives to encourage their recruitment because of the potential dangers. If, however, the product is intended specifically for use during pregnancy, a trial in pregnant women is required with those taking part being provided with information on the potential risks before giving consent and with subsequent follow-up of the pregnancy, fetus, and child.

For products that are not specifically indicated in pregnancy but are expected to be used by pregnant women, a randomised controlled trial is not required but safety data would be collected after licensing through a post authorisation safety study.

25. Boko et al (2017) Interroger au Bénin les usages populaires d'un medicament abortif, le misoprostol

Boko, I., Baxerres, C., Ouattara, F., Guillaume, A. (2017) Interroger au Bénin les usages populaires d'un medicament abortif, le misoprostol. Revue de médecine périnatale 9(1): 20-24 https://doi.org/10.1007/s12611-016-0388-2