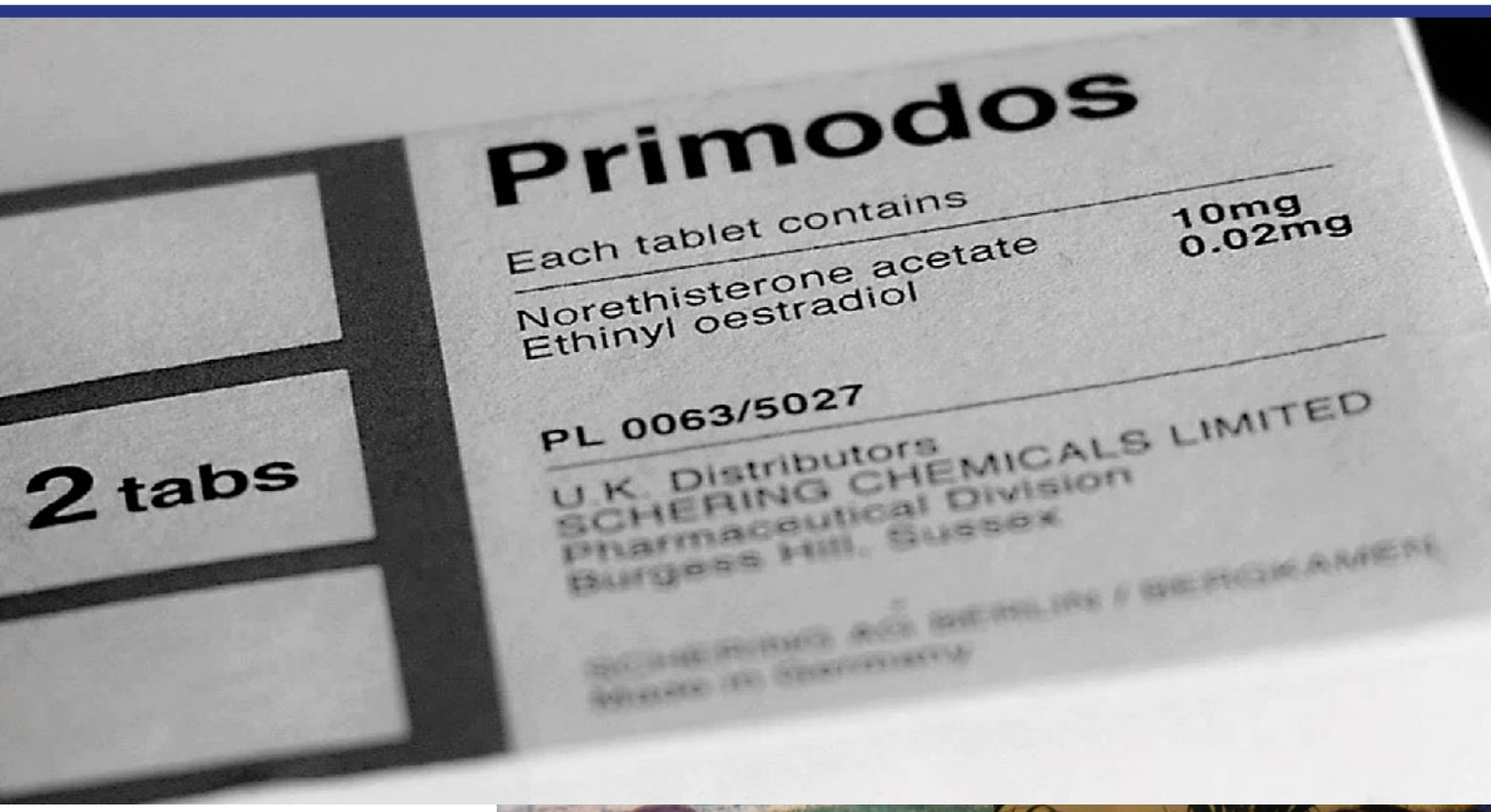
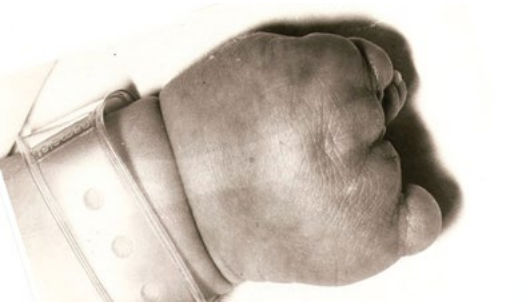
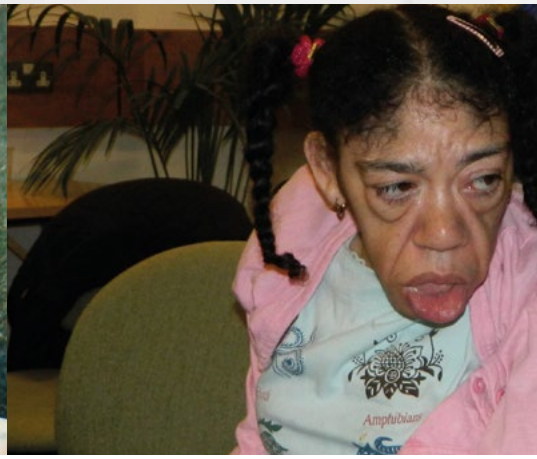
All-Party Parliamentary Group
Hormone Pregnancy Tests

A Bitter Pill: Primodos
The Forgotten Thalidomide







February 2024

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Who we are

The All-Party Parliamentary Group (APPG) on Hormone Pregnancy Tests is one of the largest cross-party groups and includes over 133 MPs and Peers, who share an interest in the drug Primodos, many of whom have constituents affected.

The purpose of the group is to raise awareness of families affected by the use of the drug Primodos.

The group has been set up and led by Chair, Yasmin Qureshi MP since 2012.

The secretariat of the APPG is provided by the Association of Children Damaged by Hormone Pregnancy Tests (ACDHPT).

The group meets regularly to receive updates on developments in the campaign on the historic use of Primodos. It seeks to represent the interests and needs of families affected by Primodos. Since the group was formed, it has coordinated five parliamentary debates, Early Day Motions, Parliamentary Questions, and regular engagement with Ministers, academics, and legal experts.

Acknowledgements

First and foremost, the APPG wishes to thank the families whose lives have been so terribly impacted by the drug Primodos. It has been vital for the APPG to hear their stories and understand their concerns, hopes and fears. Without them this report would not be possible. We also pay tribute to those who have sadly died during this campaign and offer our heartfelt condolences to their loved ones.

We pay special tribute to the gallant efforts of Mrs. Marie Lyon, Chair of the 'Association of Children Damaged by Hormone Pregnancy Tests'; she and her husband Mike have dedicated their lives to seeking justice for these families. Her courage and tenacity is an inspirational to us all.

We also wish to thank Jason Farrell, Liz Lane and the Sky News team for their outstanding journalism and long-term commitment to exposing the truth.

We appreciate the time and expertise of all those who have provided support to the APPG, particularly Barrister Charles Feeny, Professor Carl Heneghan of Oxford University, Professor Neil Vargesson of Aberdeen University and Professor Bengt Danielsson. Their work has been truly exceptional, and we owe them a great debt of gratitude.

The report has been written by Sadia Ali on behalf of the APPG, with research support from Marie Lyon, Charles Feeny, and Liz Lane.

Foreword

Successive governments of differing political persuasions have sheltered behind the assertion that there is no proven link between the drug Primodos and babies born with malformations. This is both factually and morally wrong.

It is now over five decades since the first alarm bells on Primodos were raised by Paediatrician Dr. Isabel Gal; forty years since the late Jack Ashley MP, raised concerns in the House of Commons; twelve years since this APPG began meeting Ministers; six years since the former Prime Minister, Theresa May felt dissatisfied with the findings of the Expert Working Group and announced that an Independent Medicines and Medical Devices Safety (IMMDS) review would investigate historic failures; three years since the Health Secretary apologised on behalf of the Government after its review found Primodos had caused 'avoidable harm'; and almost three weeks since the 'Patient Safety Commissioner' announced to a packed room in Parliament that the Government had specifically directed her to exclude Primodos from a review on redress.

This report presents an opportunity for the government to turn a corner; fairly and reasonably. It asks for an evaluation of compelling new scientific evidence and an 'independent' review of the Expert Working Group report. Any such review must be independent of the Medicines and Healthcare products Regulatory Agency (MHRA) which has long taken a defensive approach to this issue.

Families have been sidelined and stonewalled at every turn in their pursuit of answers. A conscious lack of government action has shattered their hopes. We understand that it is never comfortable for governments to acknowledge such injustices, but the state has a moral duty to these families. It's time for the Government to face up to its responsibilities; just as it eventually did to victims of the thalidomide scandal. Primodos families too have been badly failed, not only by the pharmaceutical and medical establishments, but also the political one. We must not fail them again. Justice has been delayed, and denied, for too long.

Yasmin Qureshi MP
Chair

Hannah Bardell MP
Vice Chair

Sir. Ed Davey MP
Vice Chair

Sir. Jacob Rees-Mogg MP
Vice Chair

Executive Summary

The question of whether Hormone Pregnancy Tests caused damage to babies in the womb has been the subject of contentious debate for over five decades. The APPG believes there is evidence to suggest that they did, and it was covered-up. We believe it is possible to piece together a case that could reveal one of the biggest medical frauds of the 20th century.

Since the APPG was formed in 2011, it has heard from a wide range of experts who have demonstrated that, at best, the government, medical experts, and drug company Schering were reckless and incompetent. At worst, they treated patients as unwitting guinea pigs and for the past 50 years have continued to cover it up.

Approximately 1.5 million expectant women were prescribed 'Primodos', a hormone-based pregnancy test drug used in the 1960s and 1970s. Its ingredients were similar to oral contraceptives but 40 times the strength.

Some members of the APPG have seen files that revealed in 1967 that a paediatrician at Queen Mary's Hospital in London, Dr. Isabel Gal, had found a link between the use of hormone pregnancy test drug 'Primodos' and bodily malformations in new-born babies. Dr. Gal wasn't the only one. The Royal College of General Practitioners also produced a report showing the drug was causing higher rates of miscarriages and infant deaths. The author of the report concluded "the drug should be withdrawn". Similarly, a letter to the Medical Research Council stated: "It looks like this could be another thalidomide story."

The warnings could not have been clearer. Germany, USA, Australia, Ireland, Sweden, Finland, and the Netherlands issued warnings and took decisive action to withdraw the drug as early as 1970. The UK government failed to take those steps until 1978, despite the Committee on Safety of Medicines being the first medical authority in the world to know of its dangers.

Files from the Berlin National Archives show that in January 1975, Dr. William Inman, Principal Medical Officer for the UK Government, had found that women who took a hormone pregnancy test "had a five-to-one risk of giving birth to a child with malformations".

Instead of withdrawing the drug, UK Government adviser, Dr. Inman called drug manufacturer Schering to warn it to "take measures to avoid medico-legal problems". Other documents show that Dr. Inman destroyed the materials on which his findings were based, "to prevent individual claims being based on his material".

In 2021, the Independent Medicines and Medical Devices Safety ('IMMDS') review led by Baroness Cumberlege conducted a comprehensive review of historic documents and found that Hormone Pregnancy Tests had caused "avoidable harm", that they should have been withdrawn by the regulator after the first warnings in 1967 and that this "failure to act meant that women were exposed unnecessarily to a potential risk".

This is not just a historic issue. The APPG has worked with affected families for over a decade, seeing up-close their daily struggles and psychological suffering. Colleagues have met affected families in their constituency offices and surgeries and heard countless stories of sorrow and anger after a lifetime spent needlessly and irreparably damaged both physically and mentally. Mothers continue to be burdened by the guilt of having taken the tablets. Parents of the affected children, now in their 70s and 80s, are deeply anxious about what will happen to their adult children when they are no longer there for them. A small selection of their stories has been shared in this report.

Campaigners in the Association of Children Damaged by Hormone Pregnancy Tests have spent decades fighting for justice. In 2017, after sustained pressure from the APPG, the government announced that an Expert Working Group supported by the MHRA would review the scientific evidence to seek an answer to the question of possible causation. The news was met with suspicion given the conflict of interest (how could the MHRA participate in investigating its predecessor the 'Committee on Safety in Medicine'?). Nevertheless, the government reassured us that the review would be independent, transparent, and thorough.

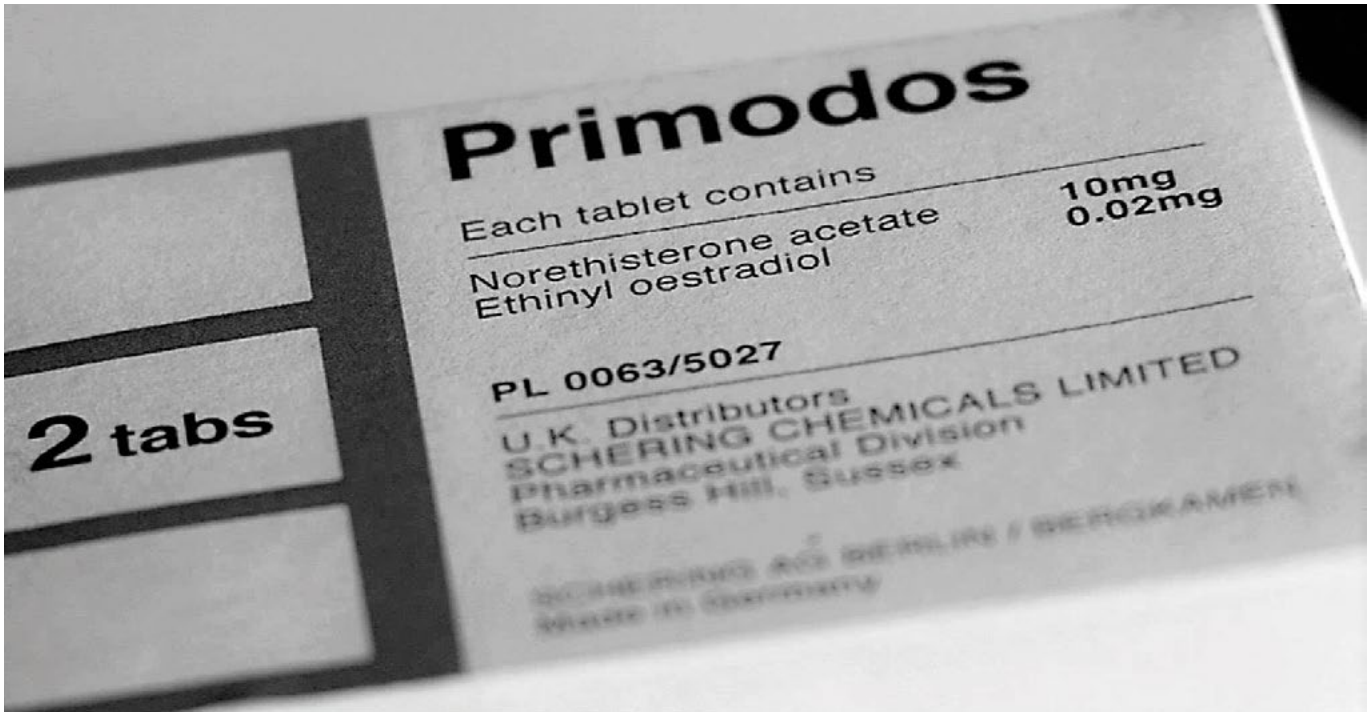
Our report will seek to dismantle and highlight the flaws in the 'Expert Working Group Report', and the process it followed.

Recently, the former Prime Minister, Theresa May, both in the House of Commons and in a Sky News interview, explained that her dissatisfaction with the report's findings led her to commission the IMMDS review. The Expert Working Group changed its terms of reference from a "possible association" to a "causal association" and disregarded the question of using meta-analysis to review the evidence.

In December 2023, a Swedish Professor of Pharmacology and Toxicology, Bengt Danielsson, published a study that identifies a causal mechanism for birth defects associated with HPTs. This conclusion is achieved by following a rigorous scientific approach. The study uses a rigorous approach to analyse data from studies on HPTs, concluding that the drug had the potential to cause a range of congenital problems such as shortened limbs, skeletal malformation, and a range of other defects. We call on the government to review this study urgently.

The government must set up an independent review of the 'Expert Working Group' review. As was recommended in the IMMDS review, this must be independent of the MHRA (and the Department of Health). The appointment of experts must be done so in collaboration with the families affected by Primodos to ensure that any future review has the trust and confidence of those most impacted by its decisions.

1. Introduction: what was the Hormone Pregnancy Test 'Primodos'?



Primodos was the mostly widely used hormone pregnancy test (HPT) prescribed by doctors to women in the UK between 1958 and 1978. It was produced by the German company Schering AG which was later taken over by Bayer in 2006.

The pill was composed of a similar compound to oral contraceptives containing Norethisterone Acetate and Ethinyloestradiol. These are two synthetic hormones prescribed to prevent conception. The dosage contained in these tablets was '40 times' the strength of an oral contraceptive prescribed today.

The test involved taking two pills on consecutive days. If a woman was not pregnant, the pills would induce a period, meaning no bleeding indicated pregnancy. If a woman was pregnant, the large doses of hormones would simply be absorbed into the body. Unlike Thalidomide, Primodos was an unnecessary test with no therapeutic value.

The number of women who used HPTs as pregnancy tests is uncertain. A compounding factor was the use of free samples of HPTs. These tablets were given, often from a doctor's desk drawer, without a prescription and often with no record-keeping.

Research at the time suggested there might be an association between the drug, miscarriages, babies born with shortened limbs, abnormalities in their internal organs, brain damage and heart defects. Many children died at birth or before reaching adulthood. Some of those who survived are blind, deaf, brain damaged and severely disabled.

Between 1958 and 1970, Primodos was marketed as a hormone pregnancy test and for the treatment of secondary amenorrhea. However, this was changed to the treatment of just secondary amenorrhea from 1970 to 1978, at which stage Primodos was withdrawn from the UK market.

When Primodos was placed on the UK market in 1958, there was no centralised structured pharmaceutical regulation. In other words, no licence was required, no specific safety test was needed and there was no general consumer protection legislation.

2. The Human Cost of Primodos

In a call for evidence, the APPG asked some of the families affected by Primodos to share with us the impact that Primodos had taken on their lives.

We saw evidence of the continuing psychological suffering caused by its use; the sorrow and anger that naturally arises from lives that have been needlessly and often irreparably damaged both physically and mentally.

The APPG has worked with these families for over a decade; some have travelled across the country to attend meetings and parliamentary debates, some with visible malformations, heart defects and brain damage. We note with great concern that the impact of carrying a relentless sense of burning injustice for decades without resolution has taken its toll on these families.

The now elderly parents of the affected children are deeply anxious about what will happen to their adult child when they are no longer there for them. Mothers continue to be burdened by guilt at having taken the tablets.

The extent of the suffering, endured over decades, cannot be underestimated.

"I had endured five miscarriages in trying to have a family. My husband and I were desperate to become parents.

"After so many disappointments, when our baby son was born, we were ecstatic and the staff at the hospital, many of whom I knew personally, celebrated his birth with us.

"When he suddenly died, we were in shock. We thought we had done everything we could to ensure our son would have the best chance of survival, unaware that the two tablets I had taken would have such a devastating effect on our unborn baby."

"I can honestly say that my heart is broken at the outcome of those two tablets given to me by my doctor."

"My doctor gave me a prescription for 2 tablets and told me to take them. I have a copy of the prescription. I had a bleed very early in my pregnancy and although the pregnancy continued, I was very sick all the time.

"When my daughter died, we organised a funeral for her and we laid her to rest with a little bunch of forget me nots in her hand. Those forget me nots are a reminder of the tablets Primodos which I believe were responsible for the death of my special little Angel. We will never forget her.

"For 52 years every Christmas and every Easter we visit her grave together with our families to remember her short, but much wanted life."

"The doctor opened his drawer and gave me two pills to take and explained it was called a Hormone Pregnancy Test, he said if you bleed that means you are not pregnant.

"My pregnancy went very well without any complications and the delivery was straightforward. It was later that we noticed that my daughter wasn't reaching a certain milestone. A Consultant eventually told us that the communication part of my daughter's brain has been cut off.

"As her parents we give Vanessa the best care that we possibly can. We are ageing and it's taking its toll on us to care for her 24 hours every day and it's having a massive impact on our lives. Vanessa has been diagnosed with digestive problems. She cannot describe how she feels both explain mentally or physically. She lives on painkillers, most nights she is having difficulty sleeping and crying through the night. On occasions, in the middle of the night the pain and crying is unbearable, and we have to take her to the hospital.

"I have to relive every day the memory of when I ingested the two pills that I believe caused my daughter's brain injuries. I cannot take the clock back. My daughter's life has been destroyed."

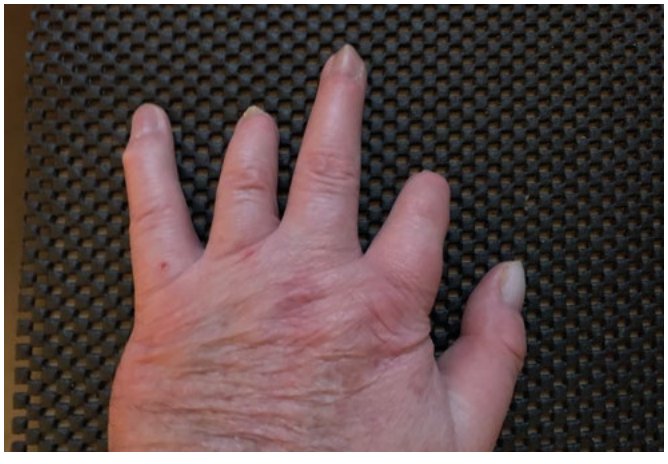
"I was born with Spina Bifida…I was born with 'Pulmonary Stenosis'. I was born without a back passage. I have no control over my bowel or bladder and as a consequence I have both a Colostomy and a Urostomy since I was five years old. I have one kidney. My right kidney hadn't developed properly. My thumb on my right hand and my elbow did not develop properly which affects my grip. I was born with two cervixes instead of one. I am deaf in my right ear. I have developed Osteoporosis. I struggle to sleep.

"So many memories of my childhood relate to being in hospital.

"I feel desperately disappointed that my Mum was used as a guinea pig in a medical/drug experiment. I feel sad and very angry for my Mum and Dad that they had to go through what they did when they were both very young.

"If these 2 tablets had not been taken from the doctor's drawer, my life, plus my family's life would have taken me down a completely different path and who knows where I might have ended up and who I may have become.

"My dreams and aspirations have had limitations due to the way I have had to live my life and my Mum would not be living with the feeling of guilt for taking the 2 tablets. In my eyes my Mum is guilty of nothing except showing unconditional love and care which knows no boundaries."



2. The Human Cost of Primodos continued

"My right arm only goes as far as the wrist and left arm, well I have an elbow and that's it. My feet when I was born were folded inwards. I only have four toes on each foot. One foot is considerably larger than the other foot. I have had many dental procedures because my jaws don't fit together properly. I have one eye that doesn't really work at all. I have a shortened tongue; part of my gum is missing.

"I find the energy required to do very many basic tasks considerable, as my manual dexterity is limited. This also means I become physically tired sooner than most people.

"I had a sense of otherness from a very early age, which has often been manifested by people staring at me openly, asking questions on why I didn't have hands."

"It's lonely. I am on my own. I have never met anybody.

"I never married; I will never have children. It's almost like I am not there."

"Mum was given Primodos by her GP in the early weeks of her pregnancy with my brother Steven… he was born in 1967 with severe brain damage. In many ways he had a difficult life. He had profound learning disabilities and was unable to speak, feed or wash himself. He was incontinent and wheelchair bound. He suffered violent seizures daily, due to a form of epilepsy that medicine was unable to control and that kept him awake at night. He needed twenty-four-hour care and my incredible parents cared for him with great difficulty, but with absolute devotion, at home full-time, from the day he was born until the day he died aged 53 years.

"I am in no doubt of the love for Steven, but the daily grind of looking after someone with such profound disabilities was awful to witness.

"Steven's epilepsy kept him awake at night; my parents had a round-the-clock watch. Mum, in her 80s, sat up overnight, only sleeping when dad woke up in the early morning to take over the watch."

– Steven died in December 2020.

"I was given a Primodos pregnancy test in the late 1960s, completely unaware of the risks. My son Raymond was born apparently healthy and happy, but I soon became worried when he failed to put on weight. Three months into his life, and after numerous visits to different doctors it was discovered that his heart had failed to develop properly in the womb. Raymond underwent six surgical procedures during his childhood, and there were many points at which I was worried that he would not survive.

"He did survive, but his whole life has been impacted. His growth and education, and he continues to struggle with his mental health, as well as having to take a huge number of pills every day. He receives no financial assistance whatsoever, not even to help pay for the prescriptions that he needs to deal with the effects of the drug."

"The future for me involves a heart transplant (if I live long enough). I feel so very angry that this drug was given to my mother. It has caused many years of heartache and still continues to do so to this day, and my family have to watch my continued deterioration. It has robbed me of a normal life, a successful career, and also possibly my future."

– Jamie died in July 2023.

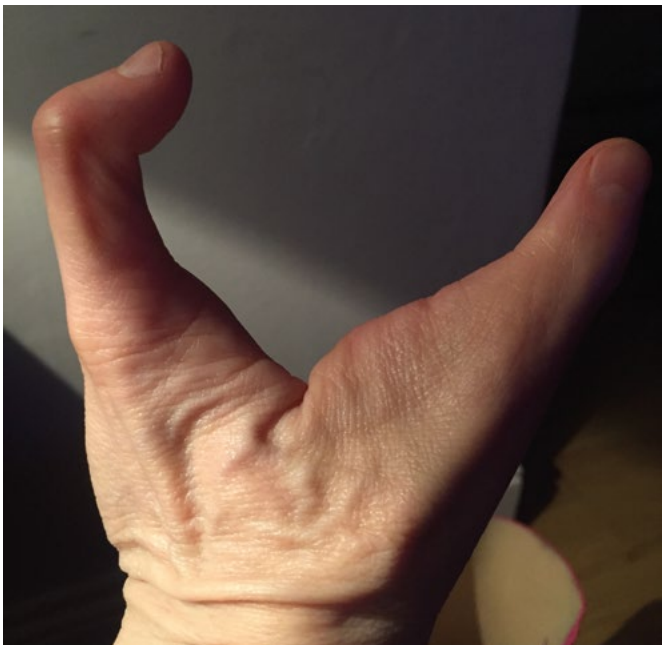
"Beccy has never walked and has always been wheelchair dependent. She has curvature of the spine and some deformation of her hands and feet. She has had many diagnoses including cerebral palsy and autism, and this leads to very complex and challenging behaviours. She will often go days without food and refuse to co-operate with her carers.

"She has very limited speech. This can be very frustrating, and she is often reduced to very distressing screaming sessions. Beccy has been subjected to innumerable tests and procedures, including full genetic screening. There has been no explanation or cause for her impairments. Primodos is the only common denominator."

"Beccy lives in a residential home with 24-hour care. She can do virtually nothing without help.

"She does stay at home with us family regularly, which is very important to her and our family; when she is at home, she relies on us family for all her needs, but that is becoming more and more difficult with age.

"I am terrified about what will happen to Beccy when I am not around."



2. The Human Cost of Primodos continued

"Over the course of my lifetime I have taken over 30 different medications. The financial burden has been immense, over £9,000 spent on medication and an estimated £8,000 in travel towards a lifetime of medical appointments".

"The report had said '1960: Population Genetic Research: Congenital malformation rates have remained constant for 30 year, BUT Monstrosity and Ancephalic Rates have recently shown an increase'

"And I began to wonder whether this was why my baby had 'Monster Child' written on his death certificate".

"We were told she needed a new liver, but it was not a possibility. We would be lucky to have her for 3 months.

"Liver failure causes abdomen to fill with fluid, which had to be drained. Painfully and slowly.

"The last time I held her, she was taken out of my arms by a nurse. Visiting time was over and we had to go. She screamed "Mummy, Mummy, Mummy…" That haunts me to this day.

"The next day she deteriorated and was unconscious. The day after she was in a coma, her organs were shutting down. When visiting hours ended, we were sent away. Her time of death was minutes after we left her.

"My husband blamed me.

"But it wasn't my fault, was it? I only took two little white pills.

"My heart was ripped out leaving a huge empty space…"

3. Regulatory Failures

Early Warnings

The first major warning came in 1967. Dr. Isobel Gal alerted the Committee on Safety of Medicines (CSM) to disturbing results found in her study on Hormone Pregnancy Tests (HPTs) which looked to her 'as if it could be another thalidomide story.' The study compared HPT use in 100 mothers of babies with neural tube defects and 100 mothers of healthy babies. This was the first statistically significant association between HPT use and malformations.

The Committee dismissed these concerns and disputed her methodology in obtaining the study result.

The Government's Principal Medical Officer, Dr. Inman, later wrote in his autobiography:

> *"Had we been convinced by Dr. Gal's study the Committee would have banned HPTs immediately in 1967."*

As noted in the IMMDS, 2021 review:

> *"Given the concerns raised, the non-essential nature of HPTs and the provision of risk-free alternative tests, we consider that the CSD focus should not have been whether or not to issue a warning. They should have recommended the withdrawal of the indication for use as a pregnancy test in 1967. This was the same year that DHSS had recommended that hospitals accepted pregnancy tests from GPs, so there was an alternative means of pregnancy testing."*

The APPG has examined some alarming exchanges between Dr. Gal and Dr. Inman:

Dr. Inman wrote to Dr. Gal:

> *"My personal view about the value of pregnancy tests is identical to yours, I frankly do not think that they are sufficiently useful when compared with other biological methods to justify even the slightest risk of teratogenicity."*

In his autobiography he went on to explain the reluctance to act:

> *"…but there was another aspect that had to be absolutely taboo. Most of the hormones that could be used for the pregnancy test also had important applications in the treatment of various gynaecological disturbances. Even more important, the HPT hormones were also very similar to the hormone mixtures used for contraception. A thalidomide-type scare in the media could easily cause panic among women using oral contraceptives."*

Even more alarming is that in 1967 Schering UK commissioned expert statistical analysis from Dr. Denis Cooke on HPTs and malformation rates:

'…he compared the increase in the sales with the number of recorded deformities in newborns, which, he says, *"show a rather alarming direct and strong correlation."* He recommended Schering conduct further studies.

In 1969, Schering UK wrote to Schering Germany and recommended removing the pregnancy testing indication due to concerns about its safety Despite these concerns, we note that Primodos continued to be marketed in the UK and was not altered.

It is clear to us, that action should have been taken

The APPG has examined at length the mounting evidence setting out events from the first warnings until the eventual delayed withdrawal of Primodos in 1978.

- **May 1966:** The Hormone Pregnancy Test, Amenorone Forte, was deleted from the Proprietary Index at the request of the manufacturer.
- **4 November 1966:** the Consultant Pathologist A.J.N. Warrack wrote *"The test is unreliable; it may well be dangerous and could possibly precipitate abortion in a not well established pregnancy."* In December 1966, this was reinforced in a letter from Dr. Duckworth, Dr. Wright and Dr. Hedgecock.
- **10 January 1967:** extracts from minutes noted that Dr. Thompson had obtained expert advice that Hormone Pregnancy Tests substantiated the previous warnings.
- **2 June 1967:** Dr. Inman, of the Committee on Safety of Medicines wrote *"clearly there can be no doubt about the statistical evidence of your data"*, in reference to the Dr. Isabel Gal study.
- **23 June 1967:** a letter from the Medical Research Council stated *"there is an apparent connection between congenital malformations and the Hormone Pregnancy Test. It looks like it could be another Thalidomide story."*
- **26 June 1967:** a letter from Dr. Inman of the Committee on Safety of Medicine to Professor Jeffcott states *"in spite of these objections, I do believe that they have a prime facie case against the hormone pregnancy test. I do not think we can lightly dismiss this work simply on the grounds of selection."*
- **13 November 1967:** in a letter from Dr. M. Briggs, the lead scientist of Schering UK (now Bayer), stated: "The results look rather alarming, we are dealing with a product that may be capable of altering the chemical environment of the foetus and we will have to be ultra-cautious in this matter."
- **8 January 1968:** a letter to Dr. Inman of the Committee on Safety of Medicines stated *"there is quite a lot of evidence that some women imagine the tablets can be used as an abortifacient. I have a feeling they may sometimes be right. Finally, in view of the unreliability of Hormone Pregnancy Tests and doubts about their safety and the dubious profitability I would not be too surprised if the manufacturers ceased to promote them."*
- **17 May 1968:** the Royal College of General Practitioners wrote to the Committee on Safety of Medicines. N.M.B. Dean, a lead scientist involved in the study, was disturbed by the indisputable statistic of 10% abortions after taking Primodos. He wrote: " There is no sound medical reason for the use of Hormone Pregnancy Tests. Primodos should be withdrawn from use."
- **30 June 1969:** an extract from the preliminary draft on the Safety of Hormone Pregnancy Tests concluded: "There is an urgent need for further investigation into their safety. Until their safety is established the use of hormones for such purposes presents an unnecessary risk."

- **3 September 1969:** In an extract from a letter to Dr. Inman from the then pharmaceutical company Rousell: *"As can be expected the study was somewhat difficult to carry out. In view of the undeniable interference with the ovum implantation. I am sure you will want to know that we ceased promoting Amenorone Forte several years ago and have now removed its use as a pregnancy test as an indication"*
- **7 November 1969:** In a letter from Dr. Inman to the then pharmaceutical company, Rousell states: *"From what you say, these did not really produce any concrete results and it is somewhat difficult to summon up enough enthusiasm to place a high priority on this, when so much other and possibly more important work is pressing."*
- **1 February 1970:** the Standing Joint Committee for proprietary medicines wrote to the pharmaceutical company Schering to inform them that, unless the indication for pregnancy was removed from Primodos immediately, the drug would be withdrawn from the UK Market. Dr. William Inman, Committee on Safety of Medicine, the Government Health Agency, authorised the 'discrete' withdrawal of the indication for pregnancy, but deliberately suppressed the information and failed to inform doctors or the medical profession that the indication for pregnancy had been removed.

The timeline of failures

- **11 July 1967:** The Government Health Agencies ignored the advice of the 'Adverse Reaction Committee' which contacted them to advise that it felt a case had been made for further investigation and also then failed to advise doctors of adverse reaction concerns.
- **13 November 1967:** a letter from Dr. Inman stated that *"we are somewhat concerned about sporadic reports from other sources linking congenital abnormalities with progestogens used for diagnostic purposes."* The Committee failed to advise doctors of concerns and, instead misled the Paediatrician Dr. Isabel Gal by stating *"there has been very little in the way of enquiries about the possible teratogenic effect of progestogen".*
- **12 January 1968:** Chief Government Scientist Dr. Inman wrote *"it does raise nasty suspicions which can only be resolved by further work".* Again, there was another failure to warn or advise doctors of concerns.
- **17 February 1969:** in a letter from Dr. NMB Dean of the Royal College of General Practitioners, he stated *"Primodos should be withdrawn from use."*

  Dr. Inman refused to support Dr. Dean's request but instead wrote to the manufacturer of the drug Schering AG to state:

  "the opinion expressed by Dr. Dean that Primodos should be withdrawn should not be taken into account. You are actively pursuing the question of whether or not Primodos should be withdrawn. Personally, my view is that the data you have so far is quite unhelpful in making this decision. Some women deliberately use excessive doses of Primodos with the intention of ridding themselves of an unwanted pregnancy."

  Again, warnings were ignored and there was a failure to issue any warning to doctors.

3. Regulatory Failures continued

In 1970, Norway and Sweden banned the use of Hormone Pregnancy Tests

- **28 May 1971:** An article appeared in the World Times, Norwegian National Newspaper stating:

  "A much-used pregnancy test is blacklisted in Norway after evidence was submitted last year that the test can cause fetal malformations. It was shown that in 20 cases it was felt there was proof of deformities because of this preparation, says Consultant Per. A. Nilsen at Aker hospital."

  Again the British Committee on Safety of Medicines took no action and failed in its duty of care.

Also reported in Stockholm:

"Withdrawn as it is probable that the deformity hypospadias can be caused by these hormones if administered early in pregnancy. Dr. Ake Liljestrand State Pharmaceutical Laboratory."

Again the British Committee on Safety of Medicines took no action.

- **February 1971:** Finland banned the use of Hormone Pregnancy Test products.

  Again, the British Committee on Safety of Medicines took no action.

- **17 November 1971:** a report by Dr. Inman on congenital abnormalities marked *'not for publication'* contained the information that 11 abnormalities were recorded after Primodos and Amenerone Forte had been used. It is notable that at least four were limb reductions."

  Again the British Committee on Safety of Medicines took no action.

  Warning Notices were also issued in Germany in 1972, U.S.A 1973, January to May 1975 Australia, Ireland, Netherlands.

- **10 October 1973:** a notice from the Federal Drugs Agency called for the withdrawal of the approval of progestin – steroid hormones that have the effect of progesterone during early pregnancy.

  The occurrence of congenital malformations and potential risk of teratogenic effects were considered high enough to warrant removal of pregnancy-related indications.

  Still no further warnings were issued

- **2 January 1974:** in a letter from PGT Bye (Schering UK) to Schering AG, it was written:

  "please note that after discussion with the Committee on Safety of Medicines we agreed some time ago not to recommend for the use of pregnancy diagnosis. It is not recommended for early pregnancy since the possibility of virilisation (abnormality) of the female foetus cannot be excluded with certainty."

  Still no warnings were issued by the Committee on Safety of Medicines.

- **22 January 1974:** in further letters from Schering, it was stated that *"side effects cannot be reliably excluded"* and that *"Primodos should no longer be recommended for the diagnosis of pregnancy. Primodos possesses an androgenic effect even though extremely slight. The Federal Drug Agency issued theoretical restrictions since there exist immunological pregnancy tests possessing adequate reliability."*

  Again, no further warnings were issued to doctors.

- **20 November 1974:** in the minutes of a meeting of the Sub-Committee on Adverse Reactions, it is stated:

  "A study into congenital abnormalities has been going on since 1968. One result may be the demonstration of an association between teratogenic hazard and Hormone Pregnancy Tests. Preliminary publication of the work is not justified although an early approach to manufacturers may be made to invite them to consider voluntarily deleting the indication for pregnancy."

This was followed by the statement:

"If this finding is confirmed the actual number of babies affected could be quite large. In table IV apparent cases subjected to Hormone Pregnancy Tests is significant."

The Committee on Safety of Medicines still did not send out warning letters to doctors.

Instead, Dr. Inman of the Committee endorsed that no approach should be made to Schering as the study was due for completion in the next six months.

- **22 January 1975:** Dr. Inman from the Committee on Safety of Medicines contacted Schering AG to warn of a *'5:1 chance of abnormalities'* for women who had used Primodos. He advised that he was contacting them to ensure they could avoid medico-legal challenges, by being prepared before the results were published.

  The Committee still did not instruct warning letters to be sent to doctors.

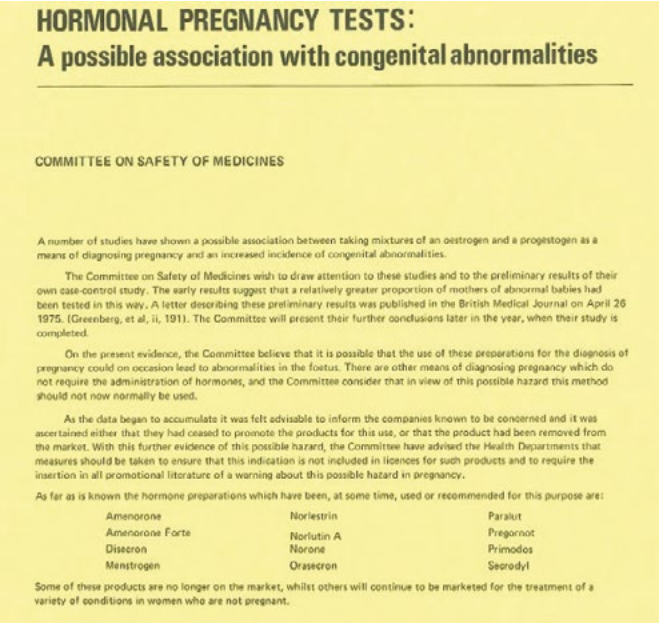
- **4 June 1975:** the Committee on Safety of Medicines issued the first warning stating:

  "A number of studies have shown a possible association between Hormone Pregnancy Tests and an increased incidence of congenital abnormalities.

  "The Committee on Safety of Medicines have sent to all doctors in the United Kingdom a letter informing them of a possible association between hormonal pregnancy tests and an increased incidence of congenital abnormalities. They recommend that, in view of the possible hazard, doctors should not normally prescribe certain hormonal preparations for pregnancy tests."

- **4 August 1975:** Dr. Gal sent a critique of the decision to the CSM highlighting sentiments that the APPG strongly endorses.

  *"...the Committee's responsibility is not averted from allowing the 8 years use of an unnecessary diagnostic test tablet, whose serious irreversible adverse effects were well known to them. It is also of interest that the warning on the hormonal pregnancy test was introduced earlier in the United States, Australia and Ireland than here, despite the fact that the concept originated in this country, and the Committee was in the favourable position of having first-hand knowledge of it in 1967. Although the Committee's own study confirmed my observation (**BMJ – 28 Apr. 1975**), active steps were only taken on 5th June, due to pressure of the public press." (**Sunday Times – 25 May**).*



HORMONAL PREGNANCY TESTS:
A possible association with congenital abnormalities

COMMITTEE ON SAFETY OF MEDICINES

A number of studies have shown a possible association between taking mixtures of an oestrogen and a progestogen as a means of diagnosing pregnancy and an increased incidence of congenital abnormalities.

The Committee on Safety of Medicines wish to draw attention to these studies and to the preliminary results of their own case-control study. The early results suggest that a relatively greater proportion of mothers of abnormal babies had been tested in this way. A letter describing these preliminary results was published in the British Medical Journal on April 26 1975. (Greenberg, et al, ii, 191). The Committee will present their further conclusions later in the year, when their study is completed.

On the present evidence, the Committee believe that it is possible that the use of these preparations for the diagnosis of pregnancy could on occasion lead to abnormalities in the foetus. There are other means of diagnosing pregnancy which do not require the administration of hormones, and the Committee consider that in view of this possible hazard this method should not now normally be used.

As the data began to accumulate it was felt advisable to inform the companies known to be concerned and it was ascertained either that they had ceased to promote the products for this use, or that the product had been removed from the market. With this further evidence of this possible hazard, the Committee have advised the Health Departments that measures should be taken to ensure that this indication is not included in licences for such products and to require the insertion in all promotional literature of a warning about this possible hazard in pregnancy.

As far as is known the hormone preparations which have been, at some time, used or recommended for this purpose are:

Amenorone	Norlestrin	Paralut
Amenorone Forte	Norlutin A	Pregornot
Diseoron	Norone	Primodos
Menstrogen	Orasecron	Seorodyl

Some of these products are no longer on the market, whilst others will continue to be marketed for the treatment of a variety of conditions in women who are not pregnant.

We agree with Dr. Gal's statement that HPTs were unnecessary. They should have been stopped in 1967 when the first warnings suggested an increase of risk. Further opportunities to act were missed in 1970, 1973 and 1974. We are also concerned that further opportunities for action were missed in 1970, 1973 and 1974 when it became known that the preliminary results indicated an association between HPT use and malformations.

Dr. Inman acknowledged these shortcomings in an internal memo:

> *"The Department would be vulnerable if Dr. Gal launched an attack on the Committee by drawing attention to the eight years that elapsed from the time she published her observations to the time we were in a position to publish a preliminary communication based on our own work. She is aware that the pilot stage of our study commenced in 1969 and it must be obvious to her, from the small number of cases assembled in our preliminary communication, that progress has been extremely slow. It may not have escaped her notice that, if the relative risk suggested by our publication turned out to be true, a large number of congenitally abnormal babies have been born as a result of hormonal pregnancy tests carried out after publication of her paper."*

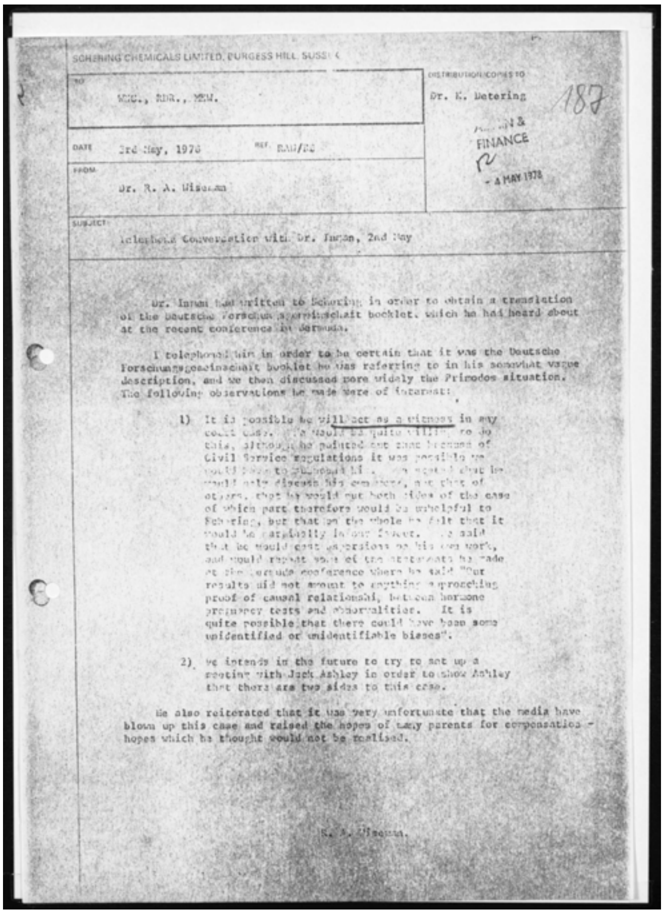
- **15 October 1975:** Dr. Inman wrote *"We are defenceless in the matter of the eight-year delay."*

The APPG has noted that in the two years following the 1975 CSM warning, HPTs continued to be used because the warning had not been effective.

- **17 November 1977:** A CSM second warning: 'Hormonal Pregnancy Tests and Congenital Abnormalities: A further statement' was sent to all doctors, hospital, and retail pharmacists.

> *"In June 1975 the Committee on Safety of Medicines published a warning about a possible association between Hormonal Pregnancy Tests and Congenital abnormalities (Adverse Reactions Series No. 13).*
>
> *The publication was based on preliminary evidence: further results have now been published (Greenberg, et al British Medical Journal 1977, 2, 853-856) and the association is confirmed. The Committee therefore reiterate their view, expressed in their earlier warning (which is attached) that hormonal tests for pregnancy should not be used. Alternative methods are available which are free from this risk."*

- **25 January 1978:** Schering ended its HPT licences due to falling sales. On 14 February Schering withdrew the pregnancy test indication worldwide.


SCHERING CHEMICALS LIMITED, BURGESS HILL, SUSSEX

TO: [illegible]

DISTRIBUTION COPIES TO: Dr. K. Detering

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FINANCE

4 MAY 1978

DATE: 3rd May, 1978 REF. RAW/[illegible]

FROM: Dr. R. A. Wiseman

SUBJECT: Telephone Conversation with Dr. Inman, 2nd May

Dr. Inman had written to Schering in order to obtain a translation of the Deutsche Forschungsgemeinschaft booklet, which he had heard about at the recent conference in Bermuda.

I telephoned him in order to be certain that it was the Deutsche Forschungsgemeinschaft booklet he was referring to in his somewhat vague description, and we then discussed more widely the Primodos situation. The following observations he made were of interest:

1) It is possible he will act as a witness in any court case. [illegible] this, although he pointed out that because of Civil Service regulations it was possible [illegible] to subpoena him. [illegible] that he would only discuss his own [illegible], not that of others, that he would put both sides of the case of which part therefore would be unhelpful to Schering, but that on the whole he felt that it would be [illegible] in our favour. [illegible] said that he would cast aspersions on his own work, and would repeat some of the statements he made at the Bermuda conference where he said "Our results did not amount to anything approaching proof of causal relationship between hormone pregnancy tests and abnormalities. It is quite possible that there could have been some unidentified or unidentifiable biases".

2) He intends in the future to try to set up a meeting with Jack Ashley in order to show Ashley that there are two sides to this case.

He also reiterated that it was very unfortunate that the media have blown up this case and raised the hopes of many parents for compensation - hopes which he thought would not be realised.

R. A. Wiseman.

4. The Expert Working Group (EWG) Report

In October 2014, the then Minister for Life Sciences, George Freeman, responding to a parliamentary debate, confirmed that there would be an independent review of the evidence relating to Primodos.

The Commission on Human Medicines set up an Expert Working Group (EWG) to investigate whether there was an association between the use of Hormone Pregnancy Tests (HPTs) and congenital malformation. Dr. Ailsa Gebbie was appointed Chair of the EWG and committed to an independent and transparent review process.

After the initial call for evidence was published in March 2015, families and those affected were invited to give evidence to the Expert Working Group. The Chair of the 'Association of Children Damaged by Hormone Pregnancy Tests' (ACDHPTs), Mrs. Marie Lyon, was invited to be an observer to the review panel.

In her evidence to the IMMDS review we note that Mrs. Marie Lyon, Chair of the ACDHPTs, raised the issue of her observer status, stating as follows:

> *"The statement again from the Expert Working Group from Dr. Gebbie [Chair of the EWG] was that I was invited to comment after every Expert Working Group meeting. This is untrue. I was publicly admonished by the Chair at the first – at the very first – meeting, when I attempted to question a statement from the MHRA. I was told I should not have attempted to speak as I had observer status only and would not be allowed to contribute unless invited by the chair."*

Families giving evidence to the panel reported feeling intimidated and mistreated by members of the secretariat and review panel. A Minister later apologised on behalf of the MHRA for its conduct.

In addition to this, Mrs. Lyon was 'gagged' by a confidentiality agreement and prevented from speaking about issues she had identified during the review of evidence.

The APPG recognises that reviews need to be carried out with an appropriate degree of confidentiality, however this should have been balanced with the right of observers to hold the EWG to account.

The MHRA provided the secretariat to the EWG. In their role as the secretariat, some MHRA staff were present during EWG decision-making. Serious concerns were raised with the APPG about the potential of interference in the decision-making process.

After the review was complete and Mrs. Lyon was able to speak to the APPG she informed us:

> *"As an observer to the workings of the EWG, I had serious reservations about the process and approach of the group. The members of the group were nominated by the MHRA. A number of them had a background in medical regulation and awareness of the issues surrounding HPTs. Members and advisers were only excluded from the group if there was evidence that they had expressed strongly held views about the issues in public. Members and advisers were not excluded on the basis that they had a clear established view as to HPTs and abortifacient drugs known to cause birth defects. It was apparent to me from the conduct of the group that a number of the members and advisers were intent on discounting any link between HPTs and birth defects. Put simply, they did not approach the assessment with an open mind."*

4. The Expert Working Group (EWG) Report continued

Ministers had reassured MPs on numerous occasions that the review and its conclusions would be conducted by 'independent experts' who were instructed to declare any conflicts of interest. Yet evidence obtained by Sky News revealed numerous email exchanges that suggested involvement from several others outside of the expert panel were involved in the deliberations on the report's conclusion.

The review concluded that the evidence was insufficient, mixed, and too heterogeneous to support an association between Primodos and congenital malformations.

(a) A 'possible association' or a 'causal association'?

The terms of reference for the EWG were agreed in the first meeting. Its first term of reference was:

> *"To consider all available evidence on the possible association between exposure in pregnancy to hormone pregnancy tests (HPTs) and adverse outcomes in pregnancy (in particular congenital anomalies, miscarriage and stillbirth) including consideration of any potential mechanism of action."*

The report went on to conclude that there was insufficient evidence to find a "causal association". The terms of reference do not mention a causal association.

A 'possible association' means that HPTs might have caused malformations, a causal association confirms that HPTs did cause malformations. Like Thalidomide, it is not possible to establish a 'causal association' unless the drug is tested on pregnant women.

(b) Why were significant historical studies disregarded by the review panel?

The review looked at the historical data of those who used Primodos and found that of the 15 studies into heart defects, 11 favoured a link. Of the studies that looked at limb reduction, all five favoured a link. Also:

(i) An American study by 'Heinonen', considered to be the most robust, showed a statistically significant two-fold increased risk of cardio-vascular anomalies. A British study in the same year by 'Greenburg', looking at the overall defects, observed a statistically significant risk and is considered to be amongst one of the better-quality studies at the time.

(ii) One 1979 study examined by the Expert Working Group – released by the pharma-ceutical manufacturer Schering (now owned by Bayer) – found that mice were deformed by compounds within the drug. It reported "visceral malformations, including the heart, lung and thorax wall" and said …"the increase in these malformations in this study should be considered drug related".

(iii) Another test on rabbits indicated skeletal problems and 'wavy ribs' caused by the drug. A number of studies into rats even found embryos were killed by high doses of it.

But the Expert Working Group concluded that the animal studies provided "insufficient evidence" for a connection between Primodos and deformity.

The Expert Working group has also examined human studies. The majority favoured an association, but the Expert Working Group still felt the evidence was not strong enough.

(c) Academic Scrutiny of the Expert Working Group Report

In November 2018, a team of academics at Oxford University led by Professor of Evidence-Based Medicine, Carl Heneghan, conducted a review into the Expert Working Group (EWG) Report.

Professor Heneghan obtained results from a Freedom of Information (FOI) request to obtain the raw data that was used by the MHRA in its Expert Working Group (EWG) Report. Using this data, he carried out a 'random-effects meta-analysis' that concluded there was an association between Primodos and malformations. The study found that the EWG had failed to follow the correct approach for systematic reviews in that it did not pool all the data together or properly collate it to show an overall effect.

At an APPG meeting in December 2019, Professor Heneghan explained he was not convinced by the methodology of the EWG report which had used Randomised Controlled Trials (RCTS) to judge the strength of the evidence. He argued that the best available evidence comes from case-control and cohort studies and then meta-analysing them in a systematic review.

The EWG did not perform a meta-analysis, instead citing concerns about combining data because:

> *"the studies were not sufficiently robust, were too heterogeneous in design and because the weighting system is usually based on study size which, given the extensive limitations of many of the studies would not have been appropriate."*

The APPG believes that these are not legitimate reasons to refuse conducting a meta-analysis. As Professor Heneghan argued:

> *"…the way to assess heterogeneity is statistically by performing a meta-analysis. In our analysis, there was no heterogeneity in the effect estimates. If you are concerned that study methods may influence the results, you can also deal with this by removing all but the best-designed studies. As we did and showed no relation between effect size and quality of the study".*

When the treatment effect is consistent from one study to the next, as it is in the case of Primodos, then it is wholly appropriate, and evidence-based, to use meta-analysis to determine the common effect.

Pharmaceutical companies use meta-analysis to approve new drugs; the US Food and Drug Administration (FDA), and The European Medicines Agency (EMA) use it as part of the approval process; clinicians and researchers in medicine, education and in the criminal justice system amongst a host of other fields use it to determine whether a treatment works or not.

Julie and her brother Michael enjoying July sunshine – one of the last photos taken. Julie died suddenly of heart failure on the 21st September 1976.

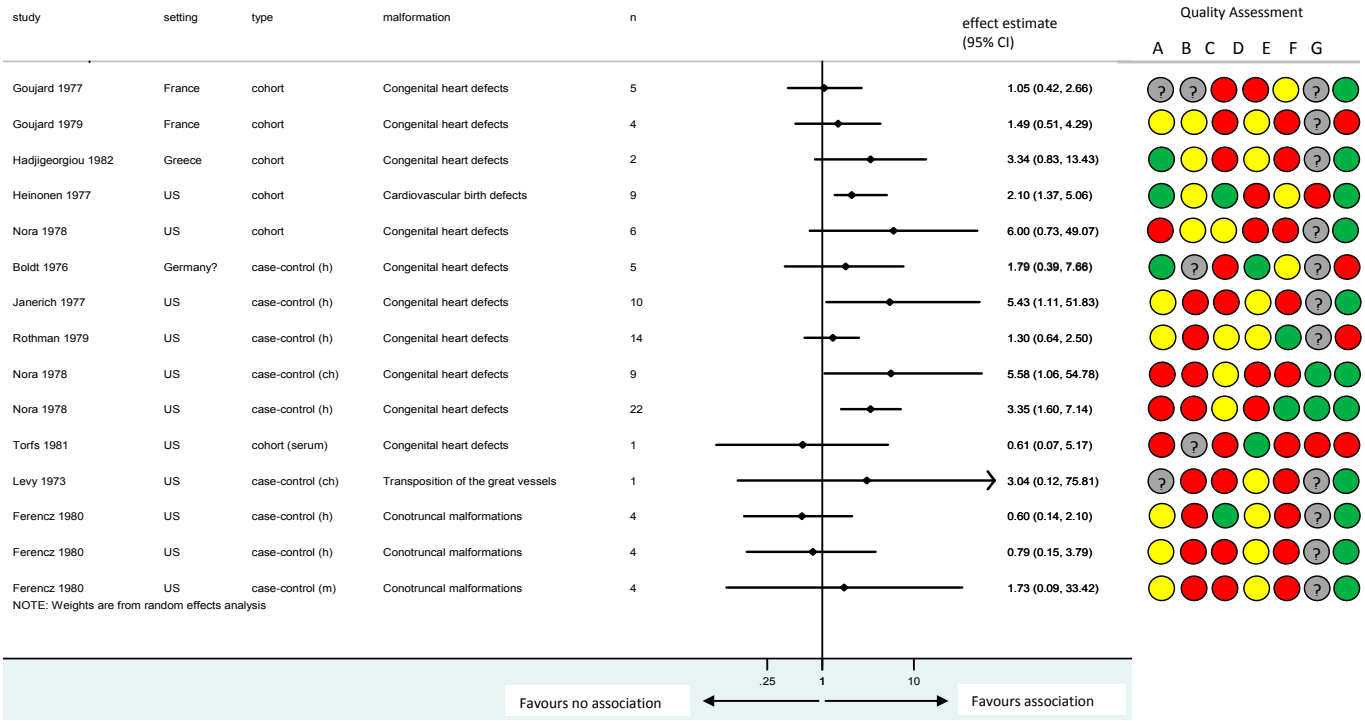
4. The Expert Working Group (EWG) Report continued

We also note that, in its report, the EWG presented the forest plot graphs used in a meta-analysis. However, we are deeply concerned that it chose to omit the summary estimate.

The reasons for this are highly questionable and while we know that one study does provide a definitive conclusion, the power of meta-analysis is its ability to summarise evidence, to provide an estimate of the association based on all the evidence that is more valuable than any single study. In the draft version of the EWG report, the forest plot graphs showed that many historical studies found that there is an association between Primodos and malformations.

This was removed from the published report.

Figure 2. Forest plot and quality assessment of epidemiological studies of HPTs and heart defects



* study reports multiple outcomes, + study sponsored by industry, n = number of exposed cases, case-control (h) = healthy controls, case-control (m) = malformed controls, case-control (ch) = controls with chromosomal defects, A = selection of controls/comparator group, B = exposure ascertainment, C = confounding factors, D = definition of exposure, E = sample size, F = biological plausibility, G = multiplicity

In this crucial graph from EWG report, Professor Heneghan points to the summary estimate being missing; however, the weights were generated by random effects (see the bottom left of the figure). He argues this suggests that someone did, at some point, do a meta-analysis; however, it was not included in the final report. *"You cannot automatically apply a random effects analysis (a type of statistical gizmo) without the system producing a summary estimate (another stats gizmo, which adds up all the effects at the end of the plot you see in the figure)."*

Using the 'eyeball' test of the figure to estimate and assess the graph, Professor Heneghan argues that the "confidence intervals overlap" suggesting they are homogenous, opposite to what the EWG had reported; 12 of the 15 estimates favour an association, and one trial is statistically significant. The eyeball test suggests the effect favours the association. The correct approach with such data is to perform a meta-analysis. Therefore, the reasons given on why one was not performed are implausible.

Professor Heneghan demonstrates that the sample sizes had strengthened the result of his review, which were sufficiently large to suggest that any small unpublished studies would have little effect on the estimates. Since the studies were homogenous, they all showed similar significant results in the same direction showing an association of Primodos with congenital malformations.

(d) Changes to the report

The Commission on Human Medicine (CHM) commissioned the EWG to provide an independent, expert viewpoint. The APPG notes with concern that a draft version of the EWG report was sent to the CHM for 'review' rather than being sent to an independent panel of experts.

Any risk of undue influence was confirmed by Freedom of Information (FOI) requests obtained by Sky News and the ACDHPTs that revealed a significant number of changes made to the draft version of the report.

The APPG examined the FOIs and notes with alarm that there have been hundreds of alterations, and some amount to changing the meaning of the report. This raises serious concerns that the final copy of the report seeks to mislead. The IMMDS Review also raised questions about the changes made between the draft and final copy of the report.

When the APPG sought clarification on this from the Chair of the Expert Working Group, Dr. Ailsa Gebbie, at a meeting on 22 November 2017 she responded:

> *"The report went to the Commission on Human Medicines, who had tasked us with developing the report... They felt we should strengthen the wording and offer greater clarity based on the findings."*

This was an extraordinary admission which undermines the independence of the review, leading to questions about why the findings of the report were influenced by others.

The original report had been ambiguous about its findings and said in its final summary:

> *"The limitations of the methodology of the time and relative scarcity of evidence means it's not possible to reach a definitive conclusion."*

This line was also removed from the final copy – giving more certainty to the EWG's assertion that evidence suggested there was no causal association between Primodos and birth defects.

4. The Expert Working Group (EWG) Report continued

A sample of changes and comments made to the draft of the report by non-members of the EWG and the CHM this highlights the extent of undue influence:

Original text (Before publication)	Final published text
From: *"there is limited evidence for no association between the use of Hormone Pregnancy Tests."*	**To:** *"the data suggests no association between the use of Hormone Pregnancy Tests".*
From: *"The evidence is insufficient to draw any conclusions about a possible association between the use of hormone pregnancy tests."*	**To:** *"from the evidence available it was not possible to draw any conclusions about a possible association between the use of hormone pregnancy tests* *adds in 'causal': "With respect to evidence from animal studies being supportive of a causal association."*
From: *"There is insufficient evidence to determine whether taking NET and EE, at the doses found in Primodos tablets, for two days during the first trimester of pregnancy could have had an effect on the developing foetus".*	**To:** "From the evidence available it was not possible to determine."
From: *"and determine the nature of the association between HPTs and adverse pregnancy outcomes. A number of studies have found an association between HPTs and various congenital anomalies and so the Group's objective was to determine whether the evidence was sufficient to support the association being causal.*	The Lay Summary addition in red below does not accurately or fairly reflect the remit detailed in the body of the document. and to determine the nature of the association between HPTs and adverse pregnancy outcomes that had been observed in some studies. Therefore, the EWG's objective was to determine whether the available evidence was sufficient to conclude that the congenital anomalies were caused by taking HPTs during early pregnancy (a causal association), or whether they could have occurred by chance alone or were due to other factors." *"My concern is that the 'association' and other interested parties may see this as a blatant attempt to rewrite the remit in particular, because this is a substantive addition and not a 'tweak'. Might it be safer just to paste this into the above paragraph?"*
Report changed from: *"there is limited evidence for no association."*	**To:** *"the data did not support an association"*
From: *"the limitations of the methodology of the time and the relative scarcity of data means it is not possible to scientifically rule out an association with certainty.*	**To:** *"based on an extensive and thorough review the EWG's overall finding is that even with its limitations, the available scientific evidence does not, on balance, support a causal association between the use of HPTs, such as Primodos, during early pregnancy and adverse effects."*

The terms of reference of the Expert Working Group (EWG) were finalised and agreed at its second meeting on 4 December 2015, as follows:

"To consider all available evidence on the possible association between exposure in pregnancy to hormonal pregnancy tests (HPTs) and adverse outcomes in pregnancy potential mechanism

Feedback from an invited expert on 9 October 2015

"I was not sure whether, as an invited expert and therefore not having been part of the process of drawing the final conclusions. I am only sending my comments now because there are a few issues I feel quite strongly about and I thought I would raise, although I appreciate it may now be too late.

"My overall feeling is that there is a contradiction between the scientific conclusions, which I think are stated too negatively, and the assessment of the regulatory process which is said to have been slow and inconsistent in the face of mounting global evidence (even though today the committee says there is no evidence).

"An example of the negative conclusions is "Nevertheless, based on an extensive and thorough review, the Group has found no scientific evidence for an association between the use of HPTs and adverse outcomes of pregnancy". This is preceded in the main body of text by very careful use of terms such as limited and insufficient which are the more appropriate wording and should in my opinion appear in the overall conclusion."

"If the Committee is saying that there is no scientific evidence, why would the evidence have been any more convincing at the time, indicating the need for immediate action, even on a precautionary basis. From my memory of the historical material, the crucial aspect was that in the face of scientific uncertainty, there was no need to run any risk when the benefit of using Hormone Pregnancy Tests was no longer there. I don't think this comes across in my reading, and contributes to the apparently contradictory approach.

"I think it would be useful to include the evidence provided by the mothers themselves when they came to speak to the Committee – they confirmed that the HPTs had been taken within the critical period for foetal development, and that in many cases a test was recommended by the doctor rather than requested.

"That pills were given even to first time mothers who were not in any high risk category, and that the doctor in several cases had taken what appeared to be free samples from his/her drawer, rather than making out a prescription. One of the contentious areas for the Committee was whether the exposed women were high risk women. I think the Report needs to be careful to clearly acknowledge that certainly this was not always the case. It is also not factually correct that half of CA are completely of genetic origin"

4. The Expert Working Group (EWG) Report continued

Report text	Group members comment
Report: *"In the 1950s and 60s testing for pregnancy was not common, and usually reserved for women who were thought to be more at risk of having a difficult pregnancy."*	**Comment:** *"this was not borne out by the evidence, nor the figures."*
Report: *"However, very little evidence in support of a possible disruptive effect of the components of Primodos on placental blood vessels was identified."*	**Comment:** *"This seems odd given the effect of the drug in early pregnancy?"*
Report: *"there was no single anomaly or set of anomalies that were reported more than would have been expected in the general population."*	**Comment:** *"This is not strictly true of limb reduction defects."*
Report: *"The search identified 4,390 potentially relevant publications of which 4,227 were excluded according to pre-set exclusion criteria."*	**Comment:** *"Might be helpful to say what the most frequent exclusion criteria was, since it looks as if most evidence thrown out!"*
Report says: *"A key bias is in comparing those who had a pregnancy test compared with those who did not seek them."*	**Comment:** *"This wording is very contentious – the women attest to not seeking the pregnancy test but being given it."*
Report says: *"In general, the studies were judged to have important limitations in their design and were of poor quality, which made it difficult to draw any robust conclusions.* *"With the publication of more safety studies and mounting global concern over the safety of these products…"* *"In 1975 CSM issued a warning to all prescribers advising them not to use hormonal tests for diagnosing pregnancy because of the possible risk."*	**Report said:** *"Nevertheless, based on an extensive and thorough review the Group has found no scientific evidence for an association between the use of HPTs and adverse outcomes of pregnancy."*
Final Report says: *"There was no single or set of anomalies that were reported at a higher rate than would have been expected in the general population."*	**Comment:** *"Limb reduction defects were reported at a higher rate."*

Report text	Group members comment
Original Draft Report: *"That the totality of the available data from studies in mice, rats, rabbits, and non-human primates are inadequate to support a causal association between administering Primodos and the development of malformations in non-sexual tissues of the offspring."*	**Final Report:** *"The totality of the available data from studies in mice, rats, rabbits, and non-human primates does not provide evidence to suggest there is a causal association between administering Norethisterone."*
Original Draft Report: *"The data suggest no association between the use of HPTs by the mother (other than limb reduction defects) or overall congenital anomalies in the baby but evidence is limited."*	**Final Report:** *"The data do not support an association, but the quality of the evidence is limited."* **Comment says:** *"On the first change I definitely prefer "are inadequate".* The second suggestion is not correct as there is clearly some evidence from mice of teratogenicity at high doses.

Notes/comments obtained via Freedom of Information Act (FOI) requests

"I attach a report that has been updated to address comments made by CHM (and Mrs. Lyon) and Professor [redacted]

"As you are aware, the report was considered by CHM at their meeting on 6th October [redacted] and Mrs. Lyon was invited to give a statement. Mrs. Lyon referred primarily to i) [redacted] perceived misalignment between the terms of reference, which refer to a 'possible association' and the conclusions of the Group, which refer to a 'causal association', ii) an apparent inconsistency in the Group's overall conclusion which states both that "a definitive conclusion cannot be reached" but then goes on to state that "the data do not support a causal association" and iii) to the conclusion that the data do not support a causal association despite the report highlighting throughout, the scarcity of the evidence and limitations of the available data. Mrs. Lyon's script is attached for ease of reference.

"The CHM considered the report and Mrs. Lyon's statement. CHM endorsed the Group's conclusions and recommendations and had the following additional comments and suggestions:

Comments are included against the most substantive changes and your comments on the following are particularly requested:

Mrs. Lyon's comment at CHM about the terms of reference referring to a possible rather than a causal link

"There was no single anomaly or set of anomalies that were reported more than would have been expected in the general population" has been deleted with the comment: it is not factually accurate."

In other places, we say at the ends of sections that there is insufficient evidence to conclude causation and then at the end that there is no evidence. Can I suggest that these are harmonised and support [redacted]s suggestion that some of the conclusions that there is no evidence should read insufficient:

"I am slightly reluctant to change another conclusion at this late stage but see your point. I have added the following to the lay summary and to Chapter 5 and hope that this goes at least some way to addressing it."

"Time is now running out as the report needs to go to CHM tomorrow for discussion next week and it would be nice to at least have more views on the conclusions. Ideally, we want the members to agree with the conclusions of the review."

The Expert Working Group's overall finding is that the available scientific evidence does not, on balance, support a causal association between the use of HPTs, such as Primodos, during early pregnancy. That said, the limitations of the methodology of the time and the relative scarcity of data mean it is not possible scientifically to rule out any association.

Comment: *"I've reworded this the other way round to present the lack of causal association first which has to be the relevant finding."*

Comment: *"…about the whole above paragraph, which had been inserted by the CHM: I think this section is just not very relevant, it wasn't discussed by the group and [redacted] is not that happy about it."*

Comment: *"It was my decision to set out the conclusion like this in the first place and was not based on an EWG proposal."*

"Re drafted the overall conclusion, saying it is important to have the actual conclusion first. This is more or less how we had it previously but thought having the text on uncertainty at the end making the overall conclusion less robust."

"The reason for it: Based on the comment by Mrs. Lyon at CHM about the terms of reference referring to a possible rather than a causal link."

The EWG's overall finding is that the available scientific evidence, taking all aspects into consideration, does not support a causal association between the use of HPTs, such as **Comment**: I suppose that higher levels with HPT would support an association.

Suggests adding in the line (re the above): *"making identification of possible associations challenging"* EWG member comments :(I've added this) – not sure if true but just a thought…

Overall conclusions. **Comment:** Put the other way round, *"Say that there was no evidence, but it wasn't possible to exclude a (weak) association".*

The findings of the review for Primodos do not have implications for any currently licensed medicines.

Comment: What about the pill? It says later that the pill could deliver a similar dose of E2 and P during early pregnancy (if for example a woman continued to take it when she was pregnant).

"Regarding the suggestion to adjust the results for multiple comparisons I wouldn't advise this. We didn't do formal statistical testing as conducting these on spontaneous data I think gives the impression the data are more robust that they are…"

"I am really loath to change conclusions that have gone through umpteen rounds of comments already to get to this stage."

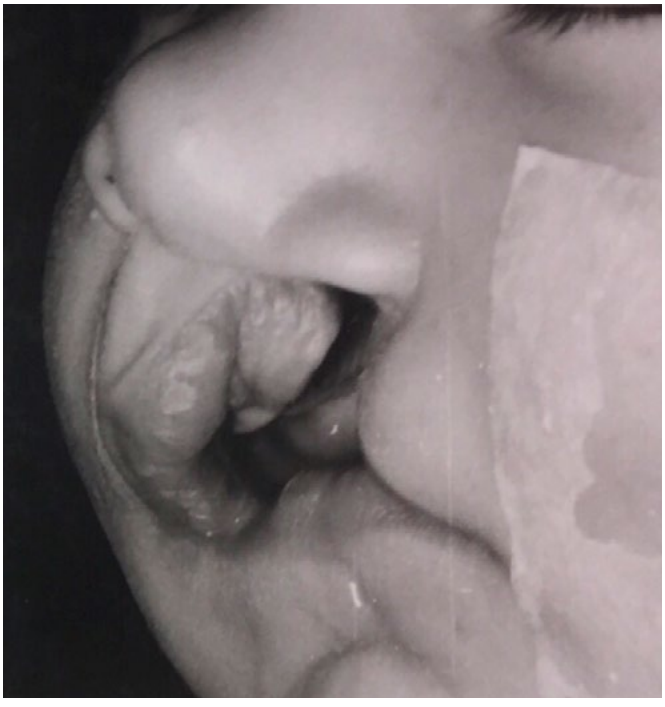
Report says: The findings of the review for HPTs, including Primodos, do not have implications for any currently licensed medicines. They are in fact reassuring for women who may inadvertently become pregnant whilst taking these hormones for contraception or gynaecological indications.

It is impossible to compare potency and dose as too complex but most of us think the HPT was a drop in the ocean. I've tried to imply this.

Comment: *"Yes agree as below if we can possibly add the negative hits as well – strengthens our position of being able to exclude any association rather than just say we couldn't find one."*

Comment: *"I'm just a bit worried that this is quite different to "it was not possible to determine" because of the huge limitations of the data. Do you think the members would be OK with the change?"*

"Please could you send my thanks to the Commission for their valuable comments and suggestions."



The other thing the Government has done is hide behind the Expert Working Group Report. Many issues have been related to the Expert Working Group Report, which of course found in its overall conclusion that:

> *"the available scientific evidence, taking all aspects into consideration, does not support a causal association between the use of HPTs, such as Primodos, during early pregnancy and adverse outcomes, either with regard to miscarriage, stillbirth or congenital anomalies."*

Given that conclusion, it might seem rather strange to the Minister and the House that it was that very report that led to my setting up the Cumberlege review. The reason I did so was that earlier in the report it says:

> *"The totality of the available evidence from pharmacology, non-clinical, epidemiological and adverse event reporting data was very limited and did not, on balance, support a causal association between the use of HPTs, such as Primodos, by the mother during early pregnancy and congenital anomalies in the child."*

To me, 'on balance' means that there was an argument against a causal link and, on the other side, an argument for a causal link, so the strength of the absolute decision that the Expert Working Group came out with was, I think, a misrepresentation of what they had put earlier in the report. It was that sense of a balanced argument that led me to call for the Cumberlege review.

My final point is… Women who took Primodos, and who saw their children suffer, often feel guilty; they feel somehow that it was them and their fault. It was not. They have no reason to feel guilty at all. The drug was given to them by their GPs. I hope that the Minister will stand up and say very clearly that women who took Primodos and whose children suffered were not in any way at fault and should not feel guilty at all. The fault lay with the NHS".

– Former Prime Minister, Theresa May speaking in a House of Commons debate on 7 September 2023

5. Independent Medicines and Medical Devices Safety (IMMDS) Review

In 2019, Prime Minister Theresa May commissioned Baroness Cumberlege to carry out an Independent Review on medicines and medical device safety. The review was instructed to look at the use of Primodos, anti-epileptic drug Sodium Valproate in pregnancy, and vaginal mesh.

In an interview with Sky News in April 2020, Mrs. May explained that her decision had been, in part, informed by her reading of the conclusions of the Expert Working Group Report.

> *"Certainly, when I looked at the report, I felt that it wasn't the slam dunk answer that people said it was."*

The review sought to examine the UK's decision-making around HPTs by the healthcare system, including the regulators and manufacturers. The report was published in July 2020 and its main findings in relation to Hormone Pregnancy Tests were as follows:

- Hormone Pregnancy Tests (HPTs) should no longer have been available from 1967. An alternative to HPTs was available, and the expression of any concern about risk should have led to action by the regulator. In failing to act for 11 years, women were exposed unnecessarily to a potential risk.
- The Government health regulators had failed patients and that Primodos was responsible for "avoidable harm."
- Both the state and the manufacturer had "an ethical responsibility" to fund a financial scheme for "those harmed" to help them with the cost of care.

The APPG welcomed the findings of the IMMDS Review and thanked Baroness Cumberlege for conducting the review collegiality, with thoroughness and transparency.

We also welcome the apology issued by the then Health Secretary, Matt Hancock, who said:

> *"I want to issue a full apology on behalf of the NHS and the whole health care system to those who have suffered and their families, for the frustration and the time they have taken to have their voices heard."*

As per the recommendations in the review, a Patient Safety Commissioner (PSC) was appointed in July 2022. The PSC was commissioned by the government to undertake to look at the options around redress as set out in IMMDS review.

In February 2024 the PSC published a report that explored options for redress for those harmed by mesh and Sodium Valproate but not Primodos.

The APPG is deeply disappointed that those harmed by Primodos have been whitewashed out of the IMMDS recommendations on redress. When the PSC, Dr Henrietta Hughes, was questioned about this, she said she had wanted to include Primodos in her redress proposals, ***but the government had told her not to*** and that if she had tried to insist it might have jeopardised the whole report. Campaigners have been left feeling betrayed by this latest disappointment.

6. New Scientific Evidence on Hormone Pregnancy Tests

Reproductive Toxicology 122 (2023) 108488

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

Teratogenicity and Reactive Oxygen Species after transient embryonic hypoxia: Experimental and clinical evidence with focus on drugs causing failed abortion in humans

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In December 2023, a new scientific report led by Swedish professor of Pharmacology and Toxicology, Bengt Danielsson, was published in the *Reproductive Toxicology* journal. Professor Danielsson has worked in the field of drug safety and teratology for over 40 years, whilst also working in academia, industry, and regulatory governmental agencies. His paper is the product of two years of rigorous research into the mechanisms of vascular disruption causing birth defects.

During an APPG meeting in December 2023, members were briefed on the findings of the study, which revealed that HPTs could cause damage to the foetus in similar ways to abortion drugs. Professor Danielsson's analysis is both rigorous and thorough with 165 citations in the paper, several of which have been published after the EWG report was first published in 2017.

In seeking to understand the significance of the paper to identify a clear mechanism for the causation of birth defects by embryo hypoxia it is important to appreciate the context:

(a) When a pregnant woman used HPTs, she would generally have high levels of pregnancy-induced progesterone. This maintains pregnancy normally and there is no bleed – and this is how the woman knows she is pregnant.

(b) Professor Danielsson's study found that the hormone spike from HPTs would cause women with low progesterone levels to have uterine contractions, resulting in the womb attempting to expel the uterine lining with the living embryo. In other words, it has the potential to initiate a failed abortion process, causing bleeding in some women particularly those who have naturally lower progesterone levels when pregnant.

Crucially the study presents convincing evidence that this decreases the blood flow to the embryo, starving tissues of oxygen ('hypoxia'). When the oxygen returns it impacts newly formed blood vessels within the embryo ('vascular disruption') and potentially damaging anything that maybe developing at the time. For example, damage to organs such as the heart and brain, or shortened limbs and hand defects.

The study convincingly demonstrates that ‘vascular disruption’ is the same mechanism that can occur with the morning-after pill, ‘Misoprostol’, should it fail to abort the embryo.

He cites support for this hypothesis with numerous factors including a human clinical trial in Australia. During the trial, women who had used HPTs had ‘spotting’ and symptoms of an early threatened miscarriage.

Professor Danielsson notes that the types of malformations seen in HPT victims are near identical to those associated with Misoprostol. More specifically, the time when the ‘hypoxia’ or oxygen deficiency takes place, will determine the type of malformation.

If taken early, the malformation could be severe such as a partially formed arm, and if taken later it might be the branches of the latest developed vessels such as the fingers.

The data presented in the study is convincing evidence that ‘Misoprostol’ and HPTs are human teratogens, due to failed abortions in some pregnant women and hypoxia-related damage in the embryo.

The study demonstrates by clear and comprehensive analysis of the evidence, why the same mechanism accounts for the increased incidence of birth defects resulting from the use of Hormone-based Pregnancy Testing drugs (HPT’s) established by epidemiological evidence.

The APPG believes the study has identified compelling evidence showing that vascular disruption is a plausible mechanism.

We call on the Government to urgently review this new evidence.

7. Conclusion and Recommendations

After almost five decades of campaigning, 'The Independent Medicine and Medical Devices Safety Review (IMMDS)' was a milestone moment that concluded that the failure to regulate Primodos had caused 'avoidable harm' and that it should have been withdrawn eleven years before the drug was taken off the market; the report even referred to it as a 'scandal'.

The words 'avoidable harm' are a shuddering reminder of how much suffering, struggle and heartbreak could have been 'avoided' had the government of the day acted responsibly. A subsequent apology from the then Health Secretary, Matt Hancock, was an extraordinary moment of recognition for the thousands of families who had been wronged.

It is now four years since that apology, twenty-two more victims of Primodos have died and many survivors do not have the luxury of time. Whilst we cannot undo what has happened, we have a moral duty to act and to do so with the utmost of urgency.

A prominent factor often cited in the government's justification for its inaction, is the question of a causal link. It is widely accepted that causation is notoriously difficult to prove just as it was for thalidomide, indeed it would be unethical to test the drug on a pregnant woman. The Expert Working Group was commissioned to seek out an answer on whether there was a "possible association" and instead it retreated to the unfounded question of causal association. The APPG was amongst the first to express disquiet about the working and remit of the group. The former Prime Minister, Theresa May, was also unconvinced and set up the Cumberlege Review.

Fundamental to the question of association is a need to evaluate the EWG's approach on meta-analysis, which it believed would be of little value. However, it is apparent that the software it used would have produced a meta-analysis which it appears to have deliberately ignored. Subsequently, a meta analysis carried out by Professor Carl Heneghan and his team at Oxford University showed a clear association between HPTs and defects. The MHRA sought to discount Professor Heneghan's study by challenging his scientific methodology. This has mystified Professor Heneghan and his team. They have undertaken over 100 meta-analyses and have never had such challenge before. Yet their work particularly in relation to Sodium Valproate and vaginal mesh has been accepted, indeed welcomed, by the Government.

When the families recently had to resort to litigation the MHRA, conducting the litigation on behalf of the Secretary of State, joined with the manufacturers, Bayer, in seeking to strike out the claims. In doing so, the MHRA was prepared to rely upon expert evidence which can be shown to be clearly inaccurate. Particularly, in relation to vascular disruption, Professor Anthony Scialli expressed the view that abortifacient drugs do not cause limb reduction defects. Professor Friedman stated that abortifacient drugs only produced a distinct pattern of multiple defects. It has been seen from considering Professor Danielsson's paper (Chapter 6) that both these statements are emphatically untrue. If it is accepted that the MHRA relied upon this evidence in good faith, then that it did so only serves to confirm Professor Danielsson's view that there was a distinct lack of understanding and awareness in relation to current knowledge of vascular disruption.

The APPG was deeply dismayed when affected families were not able to proceed with the litigation. The lawyers who launched the claim abandoned the claimants at a critical stage in what appeared to be dubious circumstances. Even though there were grounds for appeal, the families could not realistically finance such an appeal. They were also understandably concerned about their costs liability which was said to be running to a potential of £10m at this stage.

There are obvious parallels between the position of these families and recent publicity surrounding the Sub-Post Masters. It is very difficult for isolated and vulnerable individuals to obtain a level playing field when faced with large and well-financed organisations.

Recommendations

We call on the Secretary of State to implement the following recommendations:

(a) To set up an independent review to examine the findings of the 'Expert Working Group':

  (i) Appointed scientists must have a background in, and detailed understanding of this technical area.

  (ii) Any selection and appointment of experts must be independent and in consultation with the families affected by Primodos to ensure they have trust and confidence in the process.

  (iii) As set out in the IMMDS review, this must be independent of the MHRA which has taken a defensive approach to this issue.

  (iv) Where it is necessary to peer-review the draft report, this should be reviewed by an independent panel of experts to avoid the potential of undue influence.

(b) To review the compelling new evidence published in the 'Reproductive Toxicology' journal as set out in chapter 6.

All-Party Parliamentary Group
Hormone Pregnancy Tests