Institution: University of Aberdeen

Unit of Assessment: UoA1: Clinical Medicine

Title of case study: Research on a hormone pregnancy test that sparked an international debate on drug safety

Period when the underpinning research was undertaken: 2009-2018

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Neil Vargesson	Professor in Developmental Biology	Aug 2007-present
Lynda Erskine	Professor in Neurobiology	Aug 2007-present

Period when the claimed impact occurred: 2017 onwards

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact (indicative maximum 100 words)

For decades people affected by Primodos and their families have sought recognition, an apology and compensation because of birth defects linked to this hormone pregnancy test, dispensed from 1959-1978. Research at the University of Aberdeen into the effects of components of Primodos - norethisterone acetate and ethinyl estradiol - on vertebrate embryos, described in several Sky produced documentaries, led to Professor Vargesson providing expert opinion throughout government debate on drug safety. Scientific opinion based on the research was presented to the UK Government's all-party parliamentary group of MPs, the German Government, the Medicines & Healthcare products Regulatory Agency and the European Medicine Agency. The research was at the centre of government discussions and parliamentary debate in questioning drug safety and helped contribute to an independent public inquiry in 2018 which concluded in July 2020 that systematic failures had let down the victims of Primodos. The inquiry called for survivors to receive a national apology, compensation and support, and advocated that existing regulations of patient and medicine safety should be overhauled.

2. Underpinning research (indicative maximum 500 words)

Primodos was a hormone pregnancy test (HPT) that was prescribed by GPs to 1.5 million women in the UK and Germany (and other countries) between 1958 and 1978, consisting of two pills (with norethisterone acetate and ethinyl estradiol as active ingredients) that were taken on consecutive days to force menstruation in non-pregnant women a few days later. The German manufacturer Schering (now Bayer) claimed that the drug would not affect existing pregnancies, but concerns about Primodos and its possible connection to birth defects were raised as early as 1967 (Gal, *Nature* 1967). Conflicting reports, largely from the 1970s and using different testing methodologies, attempting to address the safety of Primodos in pregnant animal studies proved unhelpful. Health warnings on Primodos packaging eventually appeared in 1975 and, three years later, Primodos was withdrawn from the British market. It is estimated that 800 people throughout the UK and a similar number in Germany (where the medicine was known as Duogynon) delivered babies with birth defects that were caused directly by Primodos, including limb malformations, facial anomalies, internal organ damage and spinal damage. In addition, miscarriages and still births were also alleged to have been caused by Primodos use. The components of Primodos are still used today in other medicines, including in the morning-after pill, albeit at lower concentrations.

The long-term campaign by the Association of Children Damaged by Hormone Pregnancy Tests (ACDHPT) asserted that Primodos is 'the forgotten thalidomide'. It led to the latest research by the Aberdeen team, who in 2009 had demonstrated the teratogenic mechanisms of another pregnancy-prescribed drug – thalidomide - on embryonic development [**R1**]. To address the question of drug safety of Primodos components using modern technologies, in 2018, the Aberdeen team led by Vargesson and Erskine published the effects of the components of the drug on zebrafish embryogenesis, in which teratogenic outcomes were identified [**R2**]. The research focused on applying a mixture of the two Primodos components in a ratio equivalent to that given to humans (10 mg norethisterone acetate and 2 µg ethinyl estradiol, i.e., 500:1) directly onto zebrafish embryos. The team demonstrated that this mixture acts in a time-dependent and dose-

dependent manner: the earlier in development the mixture was applied to the embryos and the higher the concentration, the more damage was seen – indeed, the team saw damage throughout the embryo including on blood vessels and nerves. For the first time, this demonstrated Primodos acts in a time-dependent manner in zebrafish embryos, just as thalidomide (and other known teratogens) did in zebrafish and other vertebrate embryos. This further indicated that in zebrafish, the drug directly affects the embryo. Mass spectroscopy was also used to show that the embryo and yolk-sac absorb the mixture and that the components persist for up to 48 hr post-treatment. In addition, the direct effects of the mixture on cell cultures of human endothelial cells and mouse nerve cells were assessed. A direct response was also observed, where endothelial cells failed to form blood vessels and nerve cell outgrowth was prevented. Together, this research indicated that Primodos has the potential to be harmful to embryos, and that the components have long half-lives. Shortly following publication of this research [**R2**], an Oxford team conducted a meta-analysis of case-control and cohort studies and found that hormone pregnancy tests taken by pregnant women were associated with birth defects. The Aberdeen research indicated that components of Primodos had potential to damage forming embryos, raising questions about the safety of the components of Primodos, which are still used today in other medicines.

3. References to the research (indicative maximum of six references)

The quality of the research is deemed to be at least of 2* quality as corroborated by the following peer-reviewed, international publications (with Google Scholar citations):

[**R1**] Thalidomide induces limb defects by preventing angiogenic outgrowth during early limb formation. Therapontos C, **Erskine L**, Gardner ER, Figg WD, **Vargesson N**. Proc Natl Acad Sci U S A. 2009 May 26;106(21):8573-8. doi: 10.1073/pnas.0901505106. Epub 2009 May 11 (235).
[**R2**] The Primodos components norethisterone acetate and ethinyl estradiol induce developmental abnormalities in zebrafish embryos. Brown S, Fraga LR, Cameron G, **Erskine L**, **Vargesson N**.Sci Rep. 2018 Feb 13;8(1):2917. doi: 10.1038/s41598-018-21318-9 (4) The Altmetric score is 620, and the paper has been in 78 news stories in 71 outlets, including national and international press.
Funding:
'Screening of thalidomide analogs for anti-inflammatory actions' - NIH Small Award – 2017-2019 - GBP19,368. Awarded to Professor Vargesson.
'Screening of thalidomide analogs for anti-angiogenesis activity' - NIH Small Award – 2018-2020 - GBP18,418. Awarded to Professor Vargesson.

4. Details of the impact (indicative maximum 750 words)

The underpinning research has given voice to the argument that the contribution of Primodos to deformities in babies born decades ago cannot be ruled out. From 2017 to 2020, evidence provided by Professor Vargesson on the causal effects of Primodos informed parliamentary debate leading to a major UK independent public inquiry into Primodos. Throughout, Vargesson presented scientific expert opinion based on the underpinning research to UK parliament; the UK Commission on Human Medicines (CHM) - Medicines & Healthcare products Regulatory Agency (MHRA); and the European Medicines Agency (EMA). He also advised German Parliament and their MPs on current scientific understanding based on his research.

Impact in the UK

In March 2017, Sky Atlantic and Sky News aired a documentary - *Primodos: The Secret Drug Scandal* - in which the story of the affected families (1.5 million women given the tablets and hundreds of families affected according to the ACDHPT) was, for the first time since the 1970s, brought to public attention [**S1i**] The documentary was subsequently nominated for a Royal Television Society Award - Best Documentary [**S1ii**]. Broadcast to over 35 million viewers in the UK, Europe, the Middle East, Africa, South Asia, Asia Pacific, Australia and the Americas, the documentary featured an interview with Professor Vargesson, who discussed findings from his research (at the time, unpublished) on the teratogenic effect of Primodos components on vertebrate embryos [**S1i** and **S1iii**]. The film sparked debate and Vargesson was invited to UK Parliament as an expert witness alongside a Sky news journalist, a historian of science, technology

and medicine; and Chair of the ACDHPT, on 21st March 2017 [**S1iii**]. Following a parliamentary screening, Professor Vargesson discussed the findings of his research and provided answers to questions from MPs and Lords, which led to calls from MPs, Lords and the ACDHPT for a new independent public inquiry into the actions of Schering/Bayer (the German manufacturer of Primodos/Duogynon) and the UK government about the safety of the drug [**S1iv**].

In November 2017, the CHM/MHRA Expert Working Group (EWG), published a controversial report [**S2i**] concluding that Primodos had no causal association with birth defects despite Professor Vargesson's evidence and expert opinion on drug action in embryos; this was primarily because the Aberdeen research had not yet been peer reviewed or published at that time. The report was criticised by journalists and MPs, including a Conservative MP, who condemned the report as failing to meet the terms of reference and remarking: "*The question of a causal link was not in its remit*" [**S2ii**]. The report had set out to determine: "*possible association between exposure in pregnancy to hormone pregnancy tests and adverse outcomes in pregnancy (in particular congenital anomalies, miscarriage and stillbirth*)" [**S2i**]. An EWG member also declared his disagreement with the committee's conclusions, describing the Aberdeen research as "*very, very compelling*" [**S2iii**]. On December 14, Professor Vargesson addressed an All-Party Parliamentary Group (APPG) of MPs at Westminster, ahead of a parliamentary debate, where he voiced concerns about the report's conclusions and presented suggestions for further work to be carried out [**S2iv**].

Then, on 13 February 2018, the Aberdeen team's research was published [**R2**], generating significant media interest - reported by 74 international news outlets [**S2v**]. A week later, Professor Vargesson advised the APPG about the research [**R2**], its implications and the need for further research, resulting in the then Prime Minister and Health Secretary, to announce a new, independent inquiry. It was discussed in Parliament by the Health Secretary and several other MPs that Professor Vargesson's newly published research was crucial to the new inquiry [**S2vi**].

Therefore, in March 2018 the Independent Medicines and Medical Devices Safety Review (IMMDSR) was established to focus on safety of Primodos, Valproate and Vaginal. Professor Vargesson was invited and presented his published data [**R2**] and also his group's more recent data on Primodos components [Ci; pp39-67]. Professor Vargesson was also invited to discuss his work with a Panel of the European Medicines Agency (EMA) that was specially formed to evaluate the clinical relevance of his findings in zebrafish [**S3i and S3ii**]. In October 2018, he also presented to the CHM/MHRA *ad hoc* group specially formed to discuss suitability of the zebrafish model for evaluating the effects of norethisterone and ethinylestradiol in human pregnancy. The ad hoc Group looked at the implications of the Aberdeen research for medicine safety, given that some of the components of Primodos are still used today in different medicines. The ad hoc Group concluding that "*further investigation could reveal additional effects*" [**S3iii**]. However, the ad hoc Group failed to consider the clinical dangers that Primodos components in use today may present. Professor Vargesson attended and spoke about his research and its implications at the IMMDSR oral hearing at King College London on 27 Nov 2018 [**S3iv**], and the following day, he unveiled his latest research to the APPG at the Houses of Parliament [**S3v**]. The House of Lords then discussed the Primodos scandal in February 2019 at a debate titled 'Safety of Medicines and Medical Devices', during which Professor Vargesson and Erskine's research was referenced as revealing "*anomalies that mirrored the adverse effects on victims of Primodos*" [**S3vi**].

In April 2019, an APPG on Hormone Pregnancy Tests convened in Westminster Hall to discuss the "no causal association" conclusions of the CHM/MHRA EWG in 2017 and how affected families were wronged, despite their decades-long campaign. They agreed that the Aberdeen research should not be ignored [**S4i**]. Gaining traction, the Primodos story took a new turn in August 2019 with the announcement of litigation between over 200 claimants and the UK Government and Primodos manufacturer Bayer (formerly Schering) [**S4ii**].

The IMMDSR report titled "First Do No Harm", was published in July 2020 [**S4iii**]; concluding that systematic health care failures had let down those affected by Primodos (alongside those harmed by Valproate and pelvic mesh). The report also reflected on the EWG's scrutiny of two pieces of scientific research on hormone pregnancy tests – one of which, was the key publication by Vargesson's group [**R2**] – and outlined procedural issues with EWGs, making recommendations for improved procedures of future EWGs [**S4iii**]. The report outlined recommendations including

a national apology and recompense for care and support for Primodos survivors [**S4iii**]. The inquiry outcome was accompanied by a public apology from the Health Secretary [**S4iv**]. The inquiry chair publicly said "*I and members of the Review team have conducted many reviews and we all agree – we have never encountered anything like this, the intensity of suffering, the fact that it has lasted for decades. And the sheer scale. This is not a story of a few isolated incidents. No one knows the exact numbers affected by mesh, Primodos and sodium valproate but it is in the thousands. Tens of thousands*" [**S4v**].

A new documentary entitled 'Bitter Pill: Primodos' – premiered on Sky Documentaries on 24 August 2020 and subsequently on Sky News (and repeated on both channels throughout the rest of 2020), and is also available on YouTube. It featured interviews with Professor Vargesson about his published work and his latest unpublished work about the dangers of Primodos components [**S4vi**], reaching viewing figures comparable to the first documentary [**S1iii**].

Impact in Germany

The German government contacted Professor Vargesson, who submitted an evidential document in March 2019 on the Primodos paper [**R2**] and new research ahead of the German Parliament convening to debate Duogynon (the German trade name of Primodos) and its link to birth defects [**S5i**]. His expert testimony helped contribute to the announcement in September 2020, that the German Government was establishing a far-reaching inquiry into Duogynon safety [**S5ii**].

5. Sources to corroborate the impact (indicative maximum of 10 references)

[**S1**] Impact of the UK Sky Atlantic/Sky News Documentary (2017)

i. *Primodos: The Secret Drug Scandal* documentary
ii. Royal Television Society Award (Best Documentary)
iii. Testimonial from Sky Home Editor (re: documentary screened in Parliament 21 March 2017)
iv. SkyNews article – calls for public inquiry, 22 March 2017

[**S2**] Impact of the Commission on Human Medicines (CHM) Expert Working Group Report (2017)

i. Report of the Commission on Human Medicines Expert Working Group on Hormone Pregnancy Tests (October 2017)
ii. Quote from MP https://www.penning4hemel.com/content/sir-mike-condemns-primodos-report-%E2%80%9Cwhitewash%E2%80%9D
iii. Quote – Aberdeen research is "very, very compelling" (SkyNews article, 13 Dec 2017)
iv. UK Parliament; Hansard Hormone Pregnancy Tests Volume 633; debated 14 Dec 2017
v. International news outlets (74)
vi. UK Parliament; Hansard Commons Chamber Volume 636: 21 Feb 2018

[**S3**] Impact of the Independent Medicines and Medical Devices Safety Review (IMMDSR) (2018)

i. Presentation to the IMMDSR; written evidence Dec 2018
ii. Presentation to the European Medicines Agency (EMA) (re: zeberafish model) Oct 18th 2018
iii. October 5th 2018; CHM/MHRA ad hoc group + EWG conclusions
iv. IMMDS Review Oral Hearing 27 Nov 2018, Kings College London (YouTube)
v. 28 Nov 2018 APPG at Houses of Parliament
vi. House of Lords 28 Feb 2019 debate: 'Safety of Medicines and Medical Devices'

[**S4**] Impact of the research to UK legislation and public health (2019-present)

i. 23 April 2019 APPG on Hormone Pregnancy Tests CHM/MHRA EWG
ii. Litigation between UK government and Bayer (SkyNews article, Aug 2019)
iii. IMMDSR published 8 July 2020 – 'First Do No Harm'
iv. Public apology from Health Secretary Matt Hancock
v. Inquiry Chair Speech
vi. New documentary – Bitter Pill: Primodos 24 August 2020

[**S5**] Impact of the research in Germany
i. Evidence support for German Parliament, March 2019
ii. UK campaign prompts German government investigation (SkyNews, Sep 2020)