



3<sup>rd</sup> July 2019

Dear Ms Wood,

Thank you for the opportunity to provide additional clarity around the point highlighted in the transcript of the evidence given to the review by the Chair of the Association for Children Damaged by Hormone Pregnancy Tests (HPTs) on 20<sup>th</sup> May 2019.

The MHRA has advised me that the preliminary findings from Professor Vargesson's work in the zebrafish were initially discussed in October 2016, by the original HPT Expert Working Group (EWG) that was established by the Commission on Human Medicines (CHM). At that time there was some discussion around the observation of partial reversibility of some of the developmental parameters. This discussion is documented in the published minutes of the Group.

Professor Vargesson's team subsequently published its work in zebrafish in Scientific Reports<sup>[1]</sup> in February 2018 and the CHM established a new ad hoc Expert Group to consider these findings. The publication did not refer to reversibility of effect. During discussion of the work with the new Expert Group Professor Vargesson explained that reversibility of movement effects, but not developmental effects, was observed when embryos were transferred to water following drug exposure, with almost full recovery at 96 hours. This discussion is documented in the published minutes of the ad hoc Expert group.

The MHRA provided briefing to me on this matter that read: *'Vargesson's paper did not mention two preliminary findings that were raised when the work was originally presented to the Expert Working Group: that the effects were reversible in zebrafish and there was no effect when chick embryos were tested'*.

The MHRA has therefore apologised for inadvertently providing inaccurate briefing, on which my comments were based. It should be noted however that this has no bearing on the conclusions of the subsequent reviews of this study. A CHM Expert Group and the European Medicines Agency carefully examined it, and both agreed the conclusion of the original EWG on HPTs remained valid ie that the available scientific evidence does not support a causal association between the use of HPTs and adverse outcomes.

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[1] Brown S, Fraga LR, Cameron G, Erskine L, Vargesson N. The Primodos components Norethisterone acetate and Ethinyl estradiol induce developmental abnormalities in zebrafish embryos. Sci Rep. 2018; 8: 2917. <https://www.ncbi.nlm.nih.gov/pubmed/936986>

Yours sincerely,

A handwritten signature in black ink, appearing to read 'Sally C Davies'. The signature is fluid and cursive, with the first name 'Sally' written in a larger, more prominent script than the initials 'C Davies'.

**PROFESSOR DAME SALLY C DAVIES FRS FMedSci  
CHIEF MEDICAL OFFICER**