



**RE: Request by Clariant for opinion on proposed Repro2 classification with H361fd for Propylparaben**

I have been asked to provide my opinion on the appropriateness of the proposed Repro2 classification with H361fd for Propylparaben by the eMSCA.

I have 15 years of experience as Study Director Developmental and Reproductive Toxicology (DART) studies followed by 7 years of managing the group of Study Directors at  (a Contract Research Organization) in the Netherlands. I regularly consult our clients, the regulators and study directors on interpretation of General Toxicology and DART results. Moreover I have arranged education courses and workshops on this topic.

The CLH report concludes a H316 F classification based on sperm effects in the EOGRTS with propyl 4-hydroxybenzoate and the article "Effects of propyl paraben on the male reproductive system (Oishi S., 2002)".

When looking in more detail at the results obtained in the EOGRTS it can be concluded that the sperm changes were only marginal and were well within the normal range (when comparing individual values to the concurrent control and historical control values). Moreover, in the EOGRTS functional fertility (e.g. pregnancy rate and litter size) was not affected for two generations.

The Oishi paper has some flaws due to small group sizes (only 8 males per group), age of the animals at sperm assessment (seven week old Wistar rats would not have sperm production at adult levels [Campion et al, Comparative assessment of the timing of sexual maturation in male Wistar Han and Sprague-Dawley rats, Reproductive Toxicology 38 (2013) 16– 24], omission of individual sperm data and absence of historical control data. Moreover, a paper by Hoberman et al using correct group sizes and age at sperm assessment shows no effects on sperm for butylparaben and methylparaben [Lack of effect of butylparaben and methylparaben on the reproductive system in male rats, Birth Defects Res (Part B) 83:123–133, 2008].

The CLH report concludes a H316 D classification based on AGD and post-implantation loss modifications.

The report provides a summary table of the percentage of post-implantation loss (Table 49) in which four study reports are referred to. These average values are all within the normal range when comparing individual values to the concurrent control and historical control values. This can also be seen from the comparable average at a dose of 100 mg/kg in the first two studies. Post-implantation loss is a parameter that always shows a larger variability due to the way it is calculated [Marty et al, Inter-laboratory control data for reproductive endpoints required in the OPPTS 870.3800/OECD 416 reproduction and fertility test, Birth Defects Res (Part B) 86:470–489, 2009]. Moreover, there was no effect on post-implantation loss for the second generation in the EOGRTS. Important to mention is that the concurrent control value for Cohort 1B in the EOGRTS was 9,05% which is in line with the HD values of the four studies in Table 49.

The AGD values in male pups for all dose groups (i.e. treated and control) are comparable. The minor differences that are observed are not considered biologically relevant as all values are well within the normal range and the differences are slight. Moreover, the difference noted for female F1-pups are due to a slightly high concurrent control value as the values of all treated groups are similar (i.e. no dose response).



Taking together, the proposed Repro2 classification with H361fd for Propylparaben by the eMSCA is not appropriate as no adverse findings were noted on fertility and development.



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Section Head General Toxicology & DART

