Summary - Review of EFSA Opinion

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This is a paper for discussion.

This does not represent the views of the Committee and should not be cited.

Reproductive and Developmental Toxicity

255. Developmental toxicity – EOGRT study - No treatment-related pre- or postnatal loss was observed in the F0 and F1 generations. The average litter size at birth in all dose groups was comparable or higher than in the control group. The sex ratio was unaffected. No external or internal abnormalities were detected in F1 and F2 pups at termination. No effects of E 171 on pre- and postnatal development were observed. Uncertainties included missing data on puberty in

males (i.e., an appropriate assessment of the timing of the balanopreputial separation) however, given the lack of any other treatment-related effects, the EFSA Panel did not consider this to be critical.

256. Sexual function and fertility - EOGRT study - No statistically significant or dose-related effects on sperm motility, total spermatids/gram testis, percentage of abnormal spermatozoa and male mating index were observed in the F0 generation and no effects on any of the sperm endpoints in F0 or F1 generations in males. It was also noted that there were no effects on mean oestrus cycle in F0 and F1 and all F0 females in the control, 100, 300 and 1,000 mg/kg bw per day groups mated. The pregnancy rate was slightly lower in the F0 generation at 300 and 1,000 mg/kg bw per day but was not confirmed in the F1 generation. The Panel considered it as incidental and not treatment related. No effects were noted on pregnancy duration, number of implantation sites and post-implantation loss. No effects of E 171 on sexual function and fertility were observed.

Literature Search (See Annex B for data summaries)

257. The EFSA Panel agreed with the author conclusions that there were no significant toxicological or developmental effects in females or fetuses at any of the dose levels or compounds tested and considered the NOAEL for each compound to be 1,000 mg/kg bw per day, the highest dose tested (Warheit et. al, score: 4). An additional study (score 2) showed an impairment of female fertility at a dose of 100 mg TiO_2 Nanoparticles (10–25 nm)/kg bw per day.

258. For the literature review papers scored 2, The Panel considered that TiO_2 Nanoparticles (size unknown) at 100 mg/kg bw per day had an effect on testis weight, testicular toxicity was observed with TiO_2 Nanoparticles (20–30 nm) at a dose of 300 mg/kg bw per day, the only dose tested, and a further two studies showed 50 mg TiO_2 Nanoparticles (< 30 nm)/kg bw per day resulted in adverse effects on the testis, and TiO_2 Nanoparticles (7 nm), at 50 or 100 mg/kg bw per day, resulted in a dose-related reduction of sperm motility and increased sperm malformations, accompanied by histological observations in the testis, changes in BTB-related protein levels, changes in MAPK-related mRNA levels and reduced circulating testosterone concentrations.

259. One study with a score of 3 showed that no adverse effects were reported with TiO_2 Nanoparticles (21 nm) up to 1,000 mg/kg bw per day, the highest dose tested.

Developmental Immunotoxicity

260. EOGRT Study - It was noted that the assay conditions may have not been optimal resulting in an apparent low antibody response when compared to the literature. The study authors considered that all tested animals in the study had a weak immunogenic response that was insufficient to identify a T-cell-dependent immunotoxic effects of E 171. The study authors therefore considered that no conclusion can be drawn on the effect of E 171 on the developing immune system and the EFSA Panel agreed.

Literature Search (See Annex B for data summaries)

261. For studies scored 1, The Panel considered that the results of one study suggest that while E 171 (5 mg/kg bw per day) alone administered for 10 weeks had no effect on tumour formation, it can potentiate intestinal tumour formation in mice. A second study analysis, which were limited to few animals, showed some evidence for modest inflammation which cannot be clearly identified as adverse.

262. A further study demonstrated that particles in E 171 administered via the diet are taken up by basal cells of intestinal lymphoid follicles, however, the parameters investigated did not show an effect on the immune system or inflammation.

263. Another study (several test materials containing different percentages of Nanoparticles) indicated that E 171 has pro-inflammatory potential at the systemic level, paralleled by the development of an inflammatory microenvironment in the intestinal mucosa and that E 171 alone at a dose of 10 mg/kg bw per day may induce development of ACF in male rats. The Panel also noted that E 171 at a dose of 10 mg/kg bw per day increased the number of ACF initiated by a genotoxic carcinogen.

264. For NP studies scored 2, the EFSA Panel noted several conclusions including changes for inflammatory markers at doses starting from 100 mg TiO_2 Nanoparticles (5–12 nm)/kg bw per day, histopathologically, reduced numbers of goblet cells were found as a result of exposure, as well as inflammatory infiltration, data to indicate an effect of TiO_2 Nanoparticles (5–6 nm) exposure at all dose levels tested, as evidenced by histopathological lesions, corroborated by intermediate endpoints indicating disturbance of intracellular ion homeostasis that were adrenergic receptors in the heart.