Fifth draft statement on the safety of Titanium Dioxide (E171) as a Food Additive- Summary of the EOGRT study (LPT, 2020)

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Methodology

112. The Extended One Generation Reproductive Toxicity (EOGRT) study was commissioned by interested business operators to address the data gaps identified in the EFSA 2016 Opinion. The protocol was later amended to include a satellite group per dose at the F0 generation to accommodate the investigation of additional parameters related to the occurrence and titanium dioxide-related induction of aberrant crypt foci (ACF) in the colon (preneoplastic lesions that had been reported by Bettini et al. (2017)). The study was carried out according to OECD TG 443 and good laboratory practice (GLP) compliance.

113. The test material: Titanium dioxide E171-E, Particle size (ECD); (number measurement, primary particle size) x10 = 0.070 µm x50 = 0.110 µm x90 = 0.180 µm via the diet. The doses used were: Group 1: 0 mg/kg b.w./day; Group 2: 100 mg/kg b.w./day; Group 3: 300 mg/kg b.w./day; 4: 1000 mg/kg b.w./day. Twenty male and 20 female rats from each dose group were evaluated. The concentration of the test item in the diet was adjusted based on the mean group food consumption per sex. The concentration was adjusted weekly using the food consumption values from the previous week.

114. The test item was administered at doses of 0, 100, 300 and 1,000 mg/kg bw/day to several groups of males and females from 10 weeks prior to mating, during mating and until weaning of the F1 and F2 generations. The F1 generation was dosed in the same way as the F0 generation after weaning. Until weaning, the exposure of the F1 Pups to the test item was indirectly through the breast

milk, however the pups additionally received the test item directly when commencing feeding by themselves during the last week of the lactation period. The duration of dosing depended on the requested endpoints for the different cohorts of the F1 generation. Cohort 1B animals were maintained on treatment beyond PND 90 and bred to obtain an F2 generation. Detailed examination of key developmental endpoints, such as offspring viability, neonatal health, developmental status at birth, and physical and functional development until adulthood, was performed to identify specific target organs in the offspring. Possible endocrine disruptor effects of the test item were also examined.

115. Table 3 describes the parameters considered in the EOGRT study with the corresponding generation, cohort and number of animals assessed for each.

Table 3. Parameters considered in the EOGRT study:

Generation	F0	F0 satellite	F1 pups	F1 1A	F1 1B	F1 2A	F1 2B	F1 3	F2
Number of animals /sex per group	20	30		20	20	10	10	10	
Mortality	X		X	X	X	X		X	
Clinical signs	X			X	X	X		X	
Body weight	X		X	X	X	X		X	X
Food consumption	X			X	X	X		X	
Water consumption	X				X				
Haematology	X			X					

Clinical biochemistry	X		X					
Lymphocyte typing (spleen)			X					
Urinalysis	X		X					
Sexual hormone levels	X		X	X	X	X		
Thyroid hormone levels	X	X	X					
Sexual maturation			X	X	X		X	
Oestrous cycle data			X					
Sperm parameters	X		X					
Necropsy	X	X	X	X	X		X	X
Histopathology	X		X		X	X		
Reproductive parameters	X	X		X				
Pre-postnatal development		X		X				X
Functional neurotoxicity observations					X			
Neurohistopathology					X	X		
Lymphocyte typing (spleen) after KLH immunistaion			X				X	

Anti-KLG IgM levels after KLH immunisation		X
Aberrant crypt foci (ACF) scoring	X	

EOGRT: extended one-generation reproductive toxicity; KLH: keyhole limpet haemocyanin; IgM: immunoglobulin M.

This table is taken from EFSA (2021).