Assessment of toxicological data

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Genotoxicity

39. Genotoxicity testing was performed with the epoxy resin (ER) of TMBPF-DGE, not TMBPF-DGE itself.

40. While TMBPF-DGE ERwas clearly positive for clastogenicity and gene mutation in vitro, the in vivo bone marrow micronucleus (MN) test, a follow-up for clastogenicity, was negative. All three Committees agreed that the available (although limited) toxicokinetic data supported adequate exposure of the bone marrow under the test conditions. TMFPF-DGE, mostly as its hydrolysis product, was present in the blood and hence was assumed to have reached the bone marrow, which is a well perfused tissue.

41. An in vivo spermatogonial chromosomal aberration test was considered negative for chromosomal aberrations; however, the data did show an increase in polyploidy. While the Committees considered this unlikely to be a biologically relevant effect, given the polyploidy occurred at high concentrations (2 g/kg bodyweight (bw)) at 48 hours only and that the bone marrow assay did not show an increase in MN, uncertainty over the data and significance of the potential polyploidy remained.

42. There was no evidence from the available data for positive results in the in vivo Comet data, as a follow up to the in vitro gene mutation findings. However, there were uncertainties over the data as the studies and results were of varying quality. While liver Comet data were negative, the duodenum data showed a statistically significant decrease in % tail intensity (TI). Decreases in %TI are widely acknowledged to occur if there are DNA-DNA or DNA-protein crosslinks. However, clouds (also known as ghosts or hedgehogs) were present across all groups, especially the vehicle control group. Clouds indicate heavily damaged cells and show extensive DNA migration that cannot be reliably quantified by the software used to measure the comets. The aetiology of clouds is unknown but is indicative of poor quality cell suspensions and slide quality, especially when levels of clouds above 20 – 30% are recorded in the vehicle controls. Hence, all three Committees regarded the duodenum data as uninterpretable. While the effect detected was most likely the result of processing issues, Members could not entirely exclude cross-linking based on the data provided.

43. Given the large number of in vivo studies (and data available) all three Committees did not consider a transgenic assay necessary at this stage of the assessment, and it would be in contradiction of the principles of the 3Rs (Replacement, Reduction, Refinement).

44. While some uncertainties remain, specifically around the significance of the potential polyploidy, the data provided a large margin of safety and overall, the Committees agreed that it is unlikely that there would be a risk to human health from any mutagenic effect of TMBPF-DGE.

General toxicity

45. Given the above conclusion on genotoxicity, the FCMJEG and COT considered whether the risk assessment should be based on the general toxicity data.

46. Chronic toxicity/carcinogenicity and reproduction/developmental toxicity studies were not available. However, a combined short-term repeated dose toxicity study with reproductive/developmental toxicity screening was provided with the submitted documentation. Males were exposed for 29 days, i.e. 2 weeks prior to mating, during mating, and up to the day prior to scheduled necropsy. Females were exposed for 38 - 56 days, i.e. 2 weeks prior to mating, during mating, during post-coitum, and during at least four days of lactation (up to the day prior to scheduled necropsy). Pups were not treated and terminated on postnatal day (PND) 5 - 7.

47. At 100 and 300 mg/kg, all animals survived the full study duration, animals in the 1000 mg/kg dosing group were terminated before mating commenced due to signs of toxicity/ill health. There were parental effects on the liver and kidney at doses of ≥ 300 mg/kg bw per day. However, the authors of the submitted documentation considered the effects of equivocal toxicological significance as they were not accompanied by histopathological signs of adversity and the only change in clinical chemistry was a less than 2-fold increase in serum enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) at 300 mg/kg bw per day in females only. The study report identified a parental no observed adverse effect level (NOAEL) of 100 mg/kg bw per day and reproductive and developmental NOAELs of at least 300 mg/kg bw per day based on the reported effects.

48. Members of the FCMJEG and COT concluded that the available data did not indicate any reproductive or developmental effects at a dose of 300 mg/kg bw per day or raise any concerns with a parental NOAEL of 100 mg/kg bw per day.

49. The endocrine data available for TMBPF-DGE ER, while not a requirement for the assessment, were of good quality and largely negative. Weak positive results were reported in an in vitro assay for induction of estradiol synthesis, an assay which the Committees noted, tended to be overly sensitive and hence can produce positive results that are not biologically relevant. The results were just above that required for a positive “call” in the OECD test guideline where a 1.5-fold change is considered positive. No comparable activity was observed in an appropriate in vivo follow-up assay.