Comparison between 3-MCPD and its palmitic esters
in a 90-day toxicological study

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The final report covers the whole 90-day study with either 3-MCPD (respectively 29.5, 7.37, and 1.84 mg/kg b.w. per day) or 3-MCPD dipalmitate (respectively 156.75, 39.19, and 9.78 mg/kg b.w. per day). The results can be summarized as follows: (i) urinary excretion of 3-MCPD and 3-MCPD mercapturate can be used to monitor exposure to both 3-MCPD and its dipalmitate, whereas only trace amounts of \( \beta \)-chloro-lactic acid were recovered in urine samples from treated animals; (ii) dipalmitate exposure was associated with urinary excretion rates of both 3-MCPD and 3-MCPD mercapturate about 30\% lower as compared to the same urinary biomarkers observed after exposure to equimolar doses of 3-MCPD; (iii) after daily treatment with high doses of 3-MCPD dissolved in corn oil, five female rats (50\%) died from acute renal failure after weeks (1-5) since the beginning of exposure, whereas only one out of ten female rats died towards the end of the 90-d treatment with the intermediate dose. In a subsequent animal loading phase with the same dose (29.5 mg/kg b.w. per day), only two out of 10 animals died from acute renal failure, the difference from the first load was not statistically significant; (iv) 100\% survival was observed in the remaining treatment groups; (v) surviving females receiving 3-MCPD and the other treatment groups showed changes in nephrotoxicity biomarkers: the overall picture was consistent with mild tubulotoxicity and hyperfiltration, consistent with the observed increase in kidney weight and histopathological changes; (vi) mild and dose-related normochromic anemia was another finding common to all experimental groups; (vii) histopathological examination confirmed that in male rats the testes are critical organs: indeed, extensive testicular toxicity was observed in males treated with the high dose of 3-MCPD and 3-MCPD dipalmitate, with impressive cell depletion. Moderate testicular damage was observed with the intermediate dose, with consistent increases in the activity of caspase 3, without any concomitant increase in markers of oxidative stress (TBARS and carbonyl groups) which suggests apoptotic mechanisms requiring further investigation; (viii) changes observed after treatment with dipalmitate were similar, but milder and proportional to the urinary excretion of metabolites, which was lower by about one third as compared to the groups treated with equimolar doses of 3-MCPD; (ix) Benchmark doses (BMD\(_{10}\)) for severe damage to renal and testicular structures in male rats were 5.6 and 8.4 mg/kg b.w. per day, respectively for 3-MCPD. The corresponding BMDL\(_{10}\) were 2.5 and 6.0 mg/kg b.w. per day, respectively; (x) in parallel with the low dose experiment, the high dose load was repeated for female rats: although the mortality was somehow lower (20\%), it was not significantly different from the 50\% mortality observed in the first experiment. BMD\(_{10}\) and BMDL\(_{10}\) for mortality in female rats were 7.4 and 2.3 mg/kg b.w. per day, respectively. Different BMDs were obtained for 3-MCPD dipalmitate, depending on the contribution of the 3-MCPD moiety to the molecule and probably a slower and/or lower excretion rate. In male rats, BMD\(_{10}\) for severe renal and testicular damage induced by 3-MCPD dipalmitate were 41.1 and 64.4 mg/kg per day, respectively. The corresponding BMDL\(_{10}\) were 17.4 and 44.3 mg/kg per day.