7 | SUPPLEMENTARY MATERIAL

7.1 | The EFSA flowchart of Hardy et al. (2017)

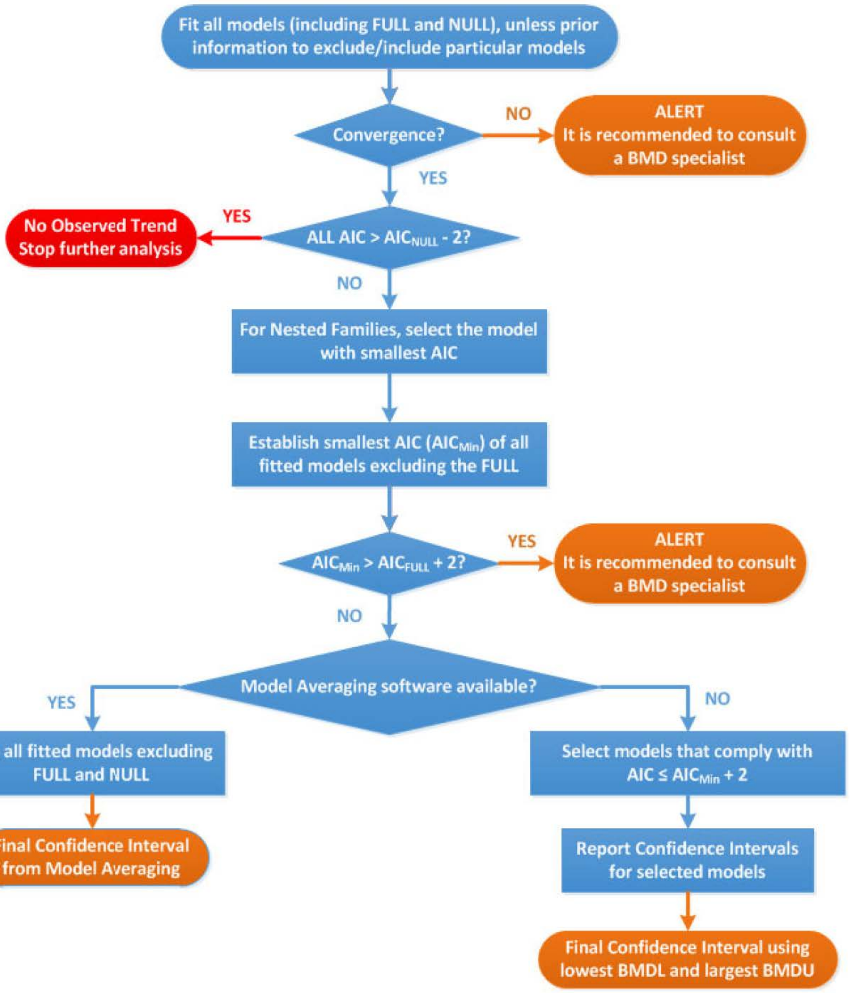

FIGURE 3 Flowchart to establish the BMD confidence interval and BMDL for dose-response data set of a specified endpoint. AIC: Akaike information criterion ; AIC_{NULL}: AIC value of the null model (no dose effect); AIC_{FULL}: AIC value of the full model (unconstrained ANOVA model); AIC_{MIN}: AIC value of the model with the lowest AIC value, the null and full models being excluded (Figure 8 from Hardy et al., 2017).

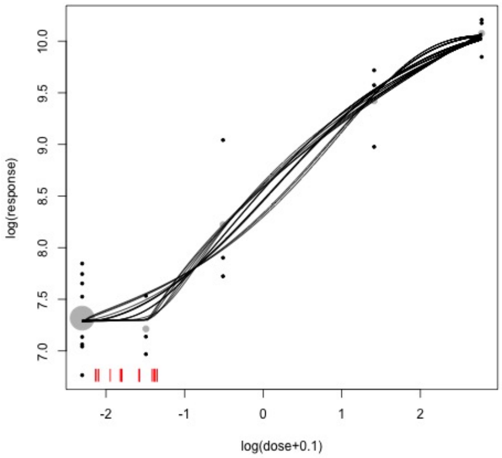

FIGURE 4 The cell proliferation data with reduced design: model specific dose response models and estimated BMDs (short red vertical lines along and above the horizontal axis).

7.2 | Cell proliferation data

Reduced design

Figure 4 shows the individual fitted models and corresponding BMD estimates (red vertical lines on the X-axis) to the CP data with the reduced design. Comparing this figure with the left panel of Figure 2, illustrates the flexibility of the candidate models, and the effect of the design on the fitted curves.

For the reduced model we get AIC_{FULL}=27.618 and AIC_{NULL}=76.877, so that again all models comply with the condition $\text{AIC} \leq \text{AIC}_{\text{NULL}}$-2. The same models were fitted, but, as the Lomax and the log-skew-normal resulted in a lower AIC than the corresponding simpler model, these were included as well (this was not the case for the inverse versions of these models). As compared to the full design, the flexible 4- and 5-parameter models show a quite different response behaviour in the range between the zero dose and the first active dose (see Figure 2). The weakest fitting model in the full design (the inverse exponential) fits best for the reduced design receiving weight 0.289, and likewise, the logistic and probit model, being the best ones for the full design, are now ranked as least good fitting models (with weights 0.075 and 0.069 respectively). The model specific BMD estimates vary considerably more in this case (range 0.02-0.15), likewise their BMDL values (range 0.001-0.08) and BMDU values (range 0.14-0.38). For the models selected and applied for both designs, the BMD estimates and BMDL and BMDU values are lower for the reduced design. The direct model averaging approach results in the averaged BMD estimate $\widehat{\text{BMD}}_{DMA}$=0.081 with Wald based limits BMDL=0.005 and BMDU=0.315 and bootstrap based limits BMDL=0.005 and BMDU=0.271. The indirect approach results in the averaged BMD estimate $\widehat{\text{BMD}}_{IMA}$=0.069 with bootstrap based limits BMDL=0.006 and BMDU=0.246. Although partly different models were selected for both designs and some models received quite different weights, and although the model specific BMD(L/U) values vary quite substantially, the model averaged (direct and indirect) estimates are quite similar.

TABLE 6 The cell proliferation data with reduced design. Estimates for all fitted models (with one representative for nested models), the model specific BMD estimates, 90% profile likelihood based BMDL and BMDU, corrected AIC and corresponding weight for averaging. Model averaged BMD estimates based on the direct approach with 90% Wald and percentile bootstrap BMDL and BMDU limits, and based on the indirect approach with 90% percentile bootstrap BMDL and BMDU limits. Estimates for the standard error are shown: using formula (23) and the bootstrap for the direct estimate and only the bootstrap for the indirect estimate. $B = 3000$ bootstrap samples were generated. Exp refers to the exponential, Inv Exp to the inverse exponential, LN to the log-normal and LSN to the log-skew-normal model.

Model	**a**	**b**	**c**	**d**	ζ	σ	**BMD**	**BMDL**	**BMDU**	**AIC**	**Weight**
Exp	7.281(0.101)	0.515(0.146)	1.384(0.040)	0.797(0.166)	-	0.365(0.053)	0.024(0.022)	0.004	0.147	29.744	0.083
Inv Exp	7.289(0.094)	0.823(0.340)	1.424(0.087)	0.681(0.282)	-	0.346(0.050)	0.108(0.060)	0.019	0.328	27.234	0.289
Hill	7.280(0.099)	1.338(0.727)	1.402(0.063)	1.077(0.332)	-	0.359(0.052)	0.043(0.036)	0.004	0.172	28.888	0.127
Lomax	7.297(0.089)	5e-06(2e-05)	1.652(0.502)	6.806(2.921)	0.028(0.031)	0.338(0.049)	0.149(0.062)	0.077	0.381	27.848	0.095
LN	7.284(0.098)	0.850(0.253)	1.396(0.058)	0.660(0.186)	-	0.354(0.051)	0.066(0.043)	0.009	0.200	28.292	0.171
LSN	7.298(0.088)	1.624(0.462)	1.499(0.224)	0.248(0.179)	32.124(92.764)	0.337(0.049)	0.154(0.060)	0.043	0.331	27.942	0.091
Logistic	0.958(0.104)	0.647(0.169)	10.075(0.253)	0.746(0.164)	-	0.366(0.053)	0.021(0.022)	0.001	0.144	29.923	0.075
Probit	0.593(0.058)	0.366(0.088)	10.065(0.230)	0.708(0.152)	-	0.368(0.053)	0.019(0.020)	0.001	0.150	30.097	0.069
The direct approach: standard errors estimate (23) and Wald type limits							0.081(0.067)	0.005	0.315		
The direct approach: bootstrap standard error and percentile limits							0.081(0.098)	0.005	0.271		
The indirect approach: bootstrap standard error and percentile limits							0.069(0.088)	0.006	0.246		