Annex to: Re-evaluation of shellac (E 904) as a food additive and the new application on the extension of use of shellac (E 904) in dietary foods for special medical purposes. doi:10.2903/j.efsa.2024.8897

Annex A Benchmark Dose Modelling: Report

A.1. Data Description

The project intended to determine a reference point for chloroform (CAS No. 67-66-3), an impurity in the food additive shellac (E904), to perform risk assessment. Chloroform is classified as Carc Cat 2 (suspected to be carcinogenic) by the European Chemical Agency. Due to this fact, the existing TDI for chloroform in drinking water of 13 µ/kg bw per day, based on hepatotoxicity, seen in a chronic study in dogs (Heywood et al., 1979), derived by WHO (WHO, 1998), could not be used. Data from a chronic rat study (Jorgenson et al., 1985), in which carcinogenic endpoints have been evaluated were used to perform Benchmark dose modelling. In this publication, the only tumour rate which was statistically significantly increased was the sum of renal adenomas and renal carcinomas. The doses, given as mg/L, were converted into mg/kg bw per day using the converting factor of EFSA (EFSA, 2012).

The endpoint to be analysed is: response (number of tumours). Dose in mg/kg bw per day.

Data used for analysis:

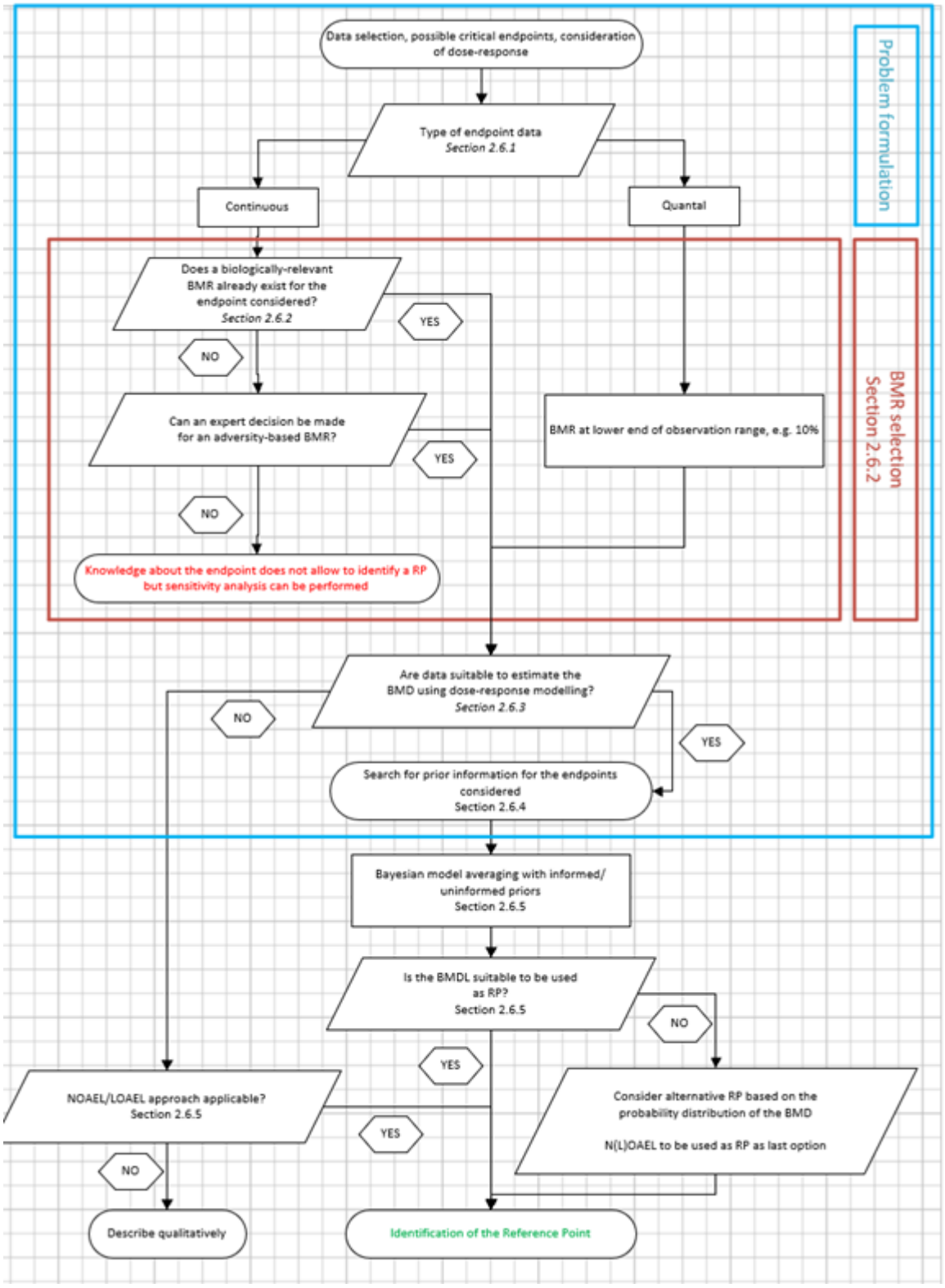
Dose	response	n
0.0	1	330
0.0	2	50
11.0	1	330
22.0	3	150
49.5	6	50
99.0	14	50

A.2. Software Used

Results are obtained using the EFSA web-tool for Bayesian BMD analysis, which uses the R-package [BMABMDR] version 0.0.0.9071 for the underlying calculations.

A.3. Justification of any deviation from the procedure and assumptions

No deviation from the procedure and assumptions



Flowchart to derive a Reference Point (RP) from a dose-response dataset of a specified endpoint, using BMD analysis.

A.4. Results

A.4.1. Goodness of Fit

Best fitting model fits sufficiently well (Bayes factor is 2.54e-03).

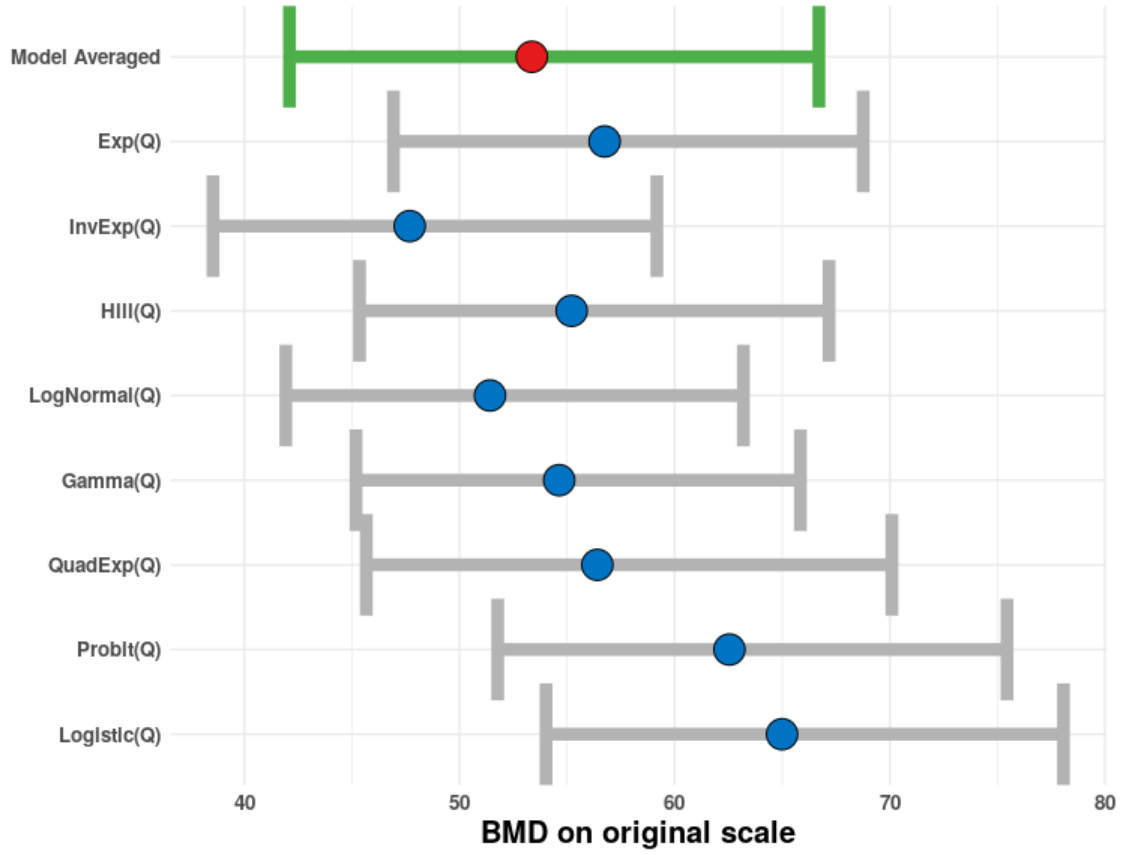
A.4.2. Model Averaged BMD

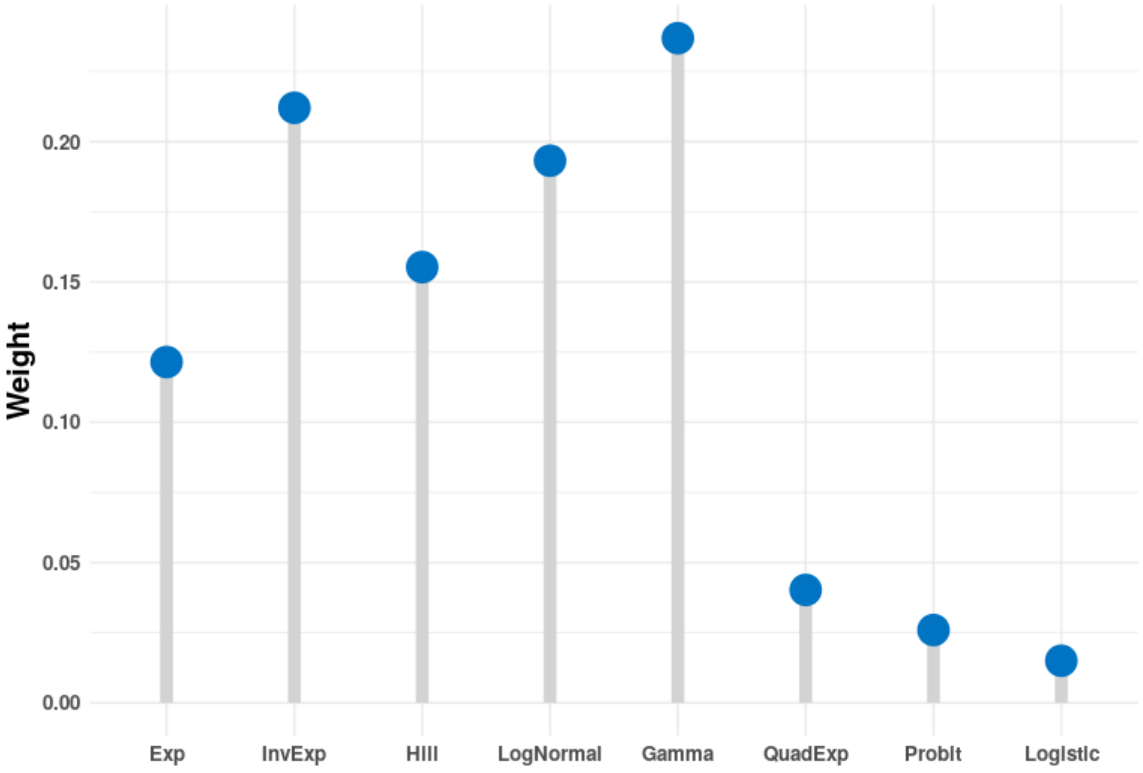
Model	Type	BMDL	BMD	BMDU
Model Averaged	LP	42.099	53.361	66.703

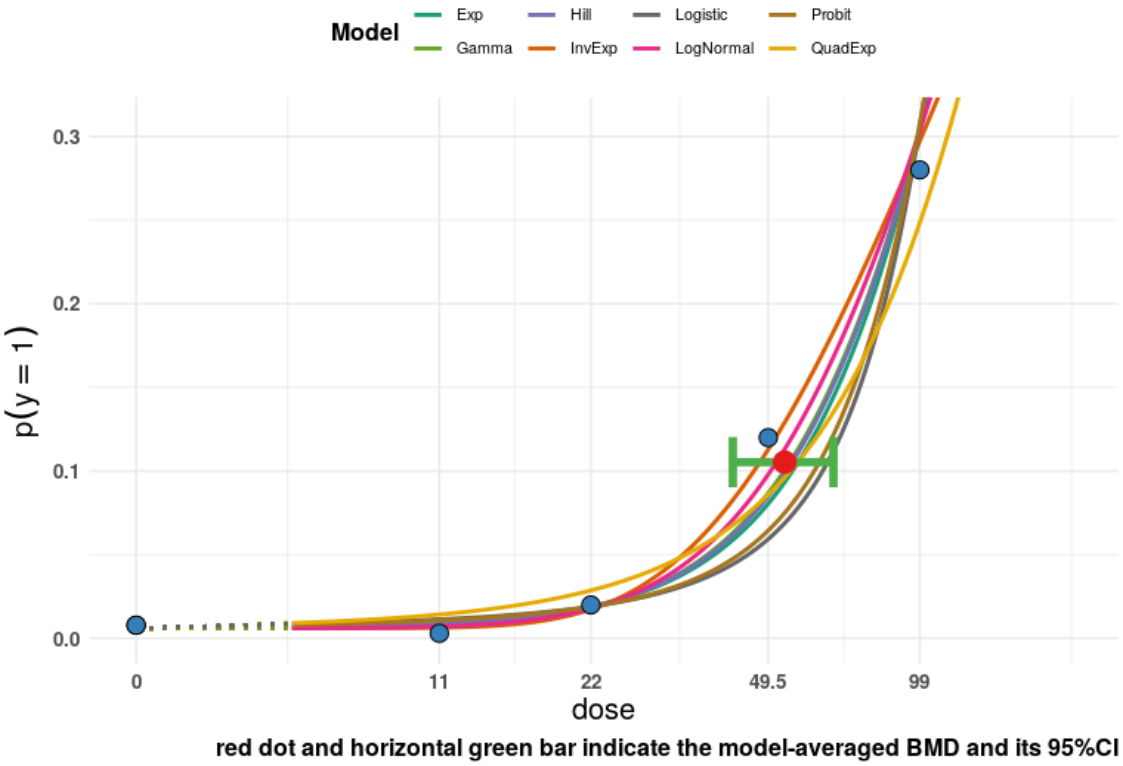
A.4.3. Estimated BMD per model

Model	BMDL	BMD	BMDU	Model Weights
E4_Q	46.930	56.744	68.762	0.121
IE4_Q	38.543	47.686	59.172	0.212
H4_Q	45.353	55.211	67.174	0.155
LN4_Q	41.927	51.419	63.193	0.193
G4_Q	45.191	54.632	65.843	0.237
QE4_Q	45.669	56.406	70.097	0.040
P4_Q	51.776	62.545	75.447	0.026
L4_Q	54.025	64.994	78.072	0.015

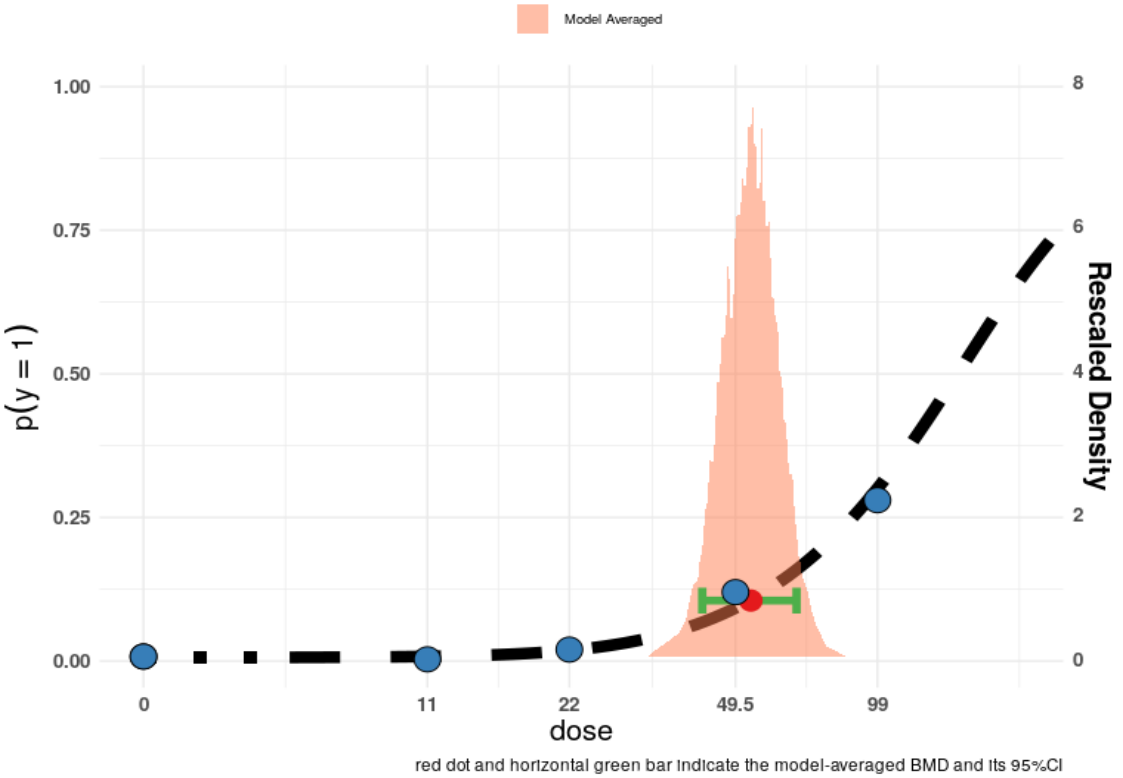
A.4.4. Plots of Fitted Models


Model Averaged
Exp(Q)
InvExp(Q)
HIll(Q)
LogNormal(Q)
Gamma(Q)
QuadExp(Q)
Probit(Q)
Logistic(Q)
40
50
60
70
80
BMD on original scale


Weight
0.20
0.15
0.10
0.05
0.00
Exp
InvExp
HIll
LogNormal
Gamma
QuadExp
Probit
Logistic



red dot and horizontal green bar indicate the model-averaged BMD and its 95%CI



red dot and horizontal green bar indicate the model-averaged BMD and its 95%CI

A.5. Conclusions

The resulting BMD confidence interval (42.099 to 667.702 mg/kg bw per day) is small indicating a small uncertainty which can also be deduced from the figure depicting the rescaled density for the results. The selection of the BMDL as the reference point for further assessment is justified. Because of the endpoint carcinogenicity an MOE approach is applied. The standard MOE for a genotoxic carcinogen would be > 10,000, for a risk not requiring immediate action (EFSA, 2012). However, in the case of chloroform with a non-genotoxic mode of action (non- genotoxic carcinogen) a reduced MOE of > 1000 would be considered appropriate resulting in an exposure of < 42 µg/kg bw per day which would not raise concern. Compared to this exposure the TDI for chloroform for the non-carcinogenic endpoint hepatotoxicity of 13 µg/kg bw per day for the non-carcinogenic endpoint hepatotoxicity would be already protective lower and should be used to assess the health effect of chloroform.

References

EFSA Scientific Committee; Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. EFSA Journal 2012;10(3):2579.

Jorgenson TA, Meierhenry EF, Rushbrook CJ, Bull RJ, Robinson M (1985) Carcinogenicity of chloroform in drinking water to male Osborne-Mendel rats and female B6C3F1 mice Fundam Appl Toxicol (4):760-9. doi: 10.1016/0272-0590(85)90200-3.

WHO, 1998. Guidelines for drinking-water quality, 2nd ed. Addendum to Vol. 2. Health criteria and other supporting information. Geneva, World Health Organization, 1998.