Annex to:

EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), Schrenk D, Bignami M, Bodin L, Chipman JK, del Mazo J, Grasl-Kraupp B, Hogstrand C, Hoogenboom LR, Leblanc J-C, Nebbia CS, Ntzani E, Petersen A, Sand S, Schwerdtle T, Vleminckx C, Wallace H, Guérin T, Massanyi P, Van Loveren H, Baert K, Gergelova P and Nielsen E, 2010. Scientific opinion on the update of the risk assessment of nickel in food and drinking water. EFSA Journal 2020;18:6268, doi:10.2903/j.efsa.2020.6268

Annex A – Benchmark dose analysis

A.1. Post-implantation loss 2GEN F1F2 study

A.1.1. Data description

The incidence of post-implantation loss as reported for the F1/F2 generation in the 2-generation study (SLI, 2000b) was used and the individual data are included in Section A.1.6. of this Annex. The incidence of post-implantation loss was calculated as follows: implantation scar count minus the number of live pups at delivery. The litter effect was taken into account.

A.1.2. Selection of the benchmark response

A default benchmark response (BMR) of 10% (extra risk) and a 90% confidence interval around the benchmark dose (BMD) were selected as recommended by the EFSA Scientific Committee (2017).

A.1.3. Software used

Results are obtained using the EFSA web tool for BMD analysis, which uses the R-package PROAST, version 67.0, for the underlying calculations.

A.1.4. Specification of deviations from default assumptions

General assumptions

No deviation from the recommended defaults (e.g. gamma distributional assumption instead of log-normal, heteroscedasticity instead of homoscedasticity) was made.

Dose–response models

No deviation from the recommended defaults. Default set of fitted models:

Model	Number of parameters	Formula
Null	1	$y = a$
Full	no. of groups	$y = \text{group mean}$
Logistic	2	$y = \frac{1}{1 + \exp(-a - bx)}$
Probit	2	$y = pnorm((x - a) \cdot b)$
Log-logistic	3	$y = a + \frac{1 - a}{1 + \exp\left(c \cdot \log\left(\frac{b}{x}\right)\right)}$
Log-probit	3	$y = a + (1 - a) \cdot pnorm\left(c \cdot \log\left(\frac{x}{b}\right)\right)$

Weibull	3	$y = a + (1-a)\left(1 - \exp\left(-\left(\frac{x}{b}\right)^c\right)\right)$
Gamma	3	$y = pgamma(bx; c)$
Two-stage	3	$y = a + (1-a)\left(1 - \exp\left(-\frac{x}{b} - c\left(\frac{x}{b}\right)^2\right)\right)$
Exp model 3	3	$y = a \cdot \exp(bx^d)$
Exp model 5	4	$y = a \cdot (c - (c-1)\exp(-bx^d))$
Hill model 3	3	$y = a \cdot \left(1 - \frac{x^d}{b^d + x^d}\right)$
Hill model 5	4	$y = a \cdot \left(1 + (c-1)\frac{x^d}{b^d + x^d}\right)$

For the Exp and Hill family, we fit models with 3 and 4 parameters as listed in the table. The 3-parameter model is selected if the difference in AIC is smaller than 5, otherwise the 4-parameter model is selected.

Procedure for selection of the BMDL

There was no deviation from the procedure described in the flow chart to obtain the final BMD confidence interval.

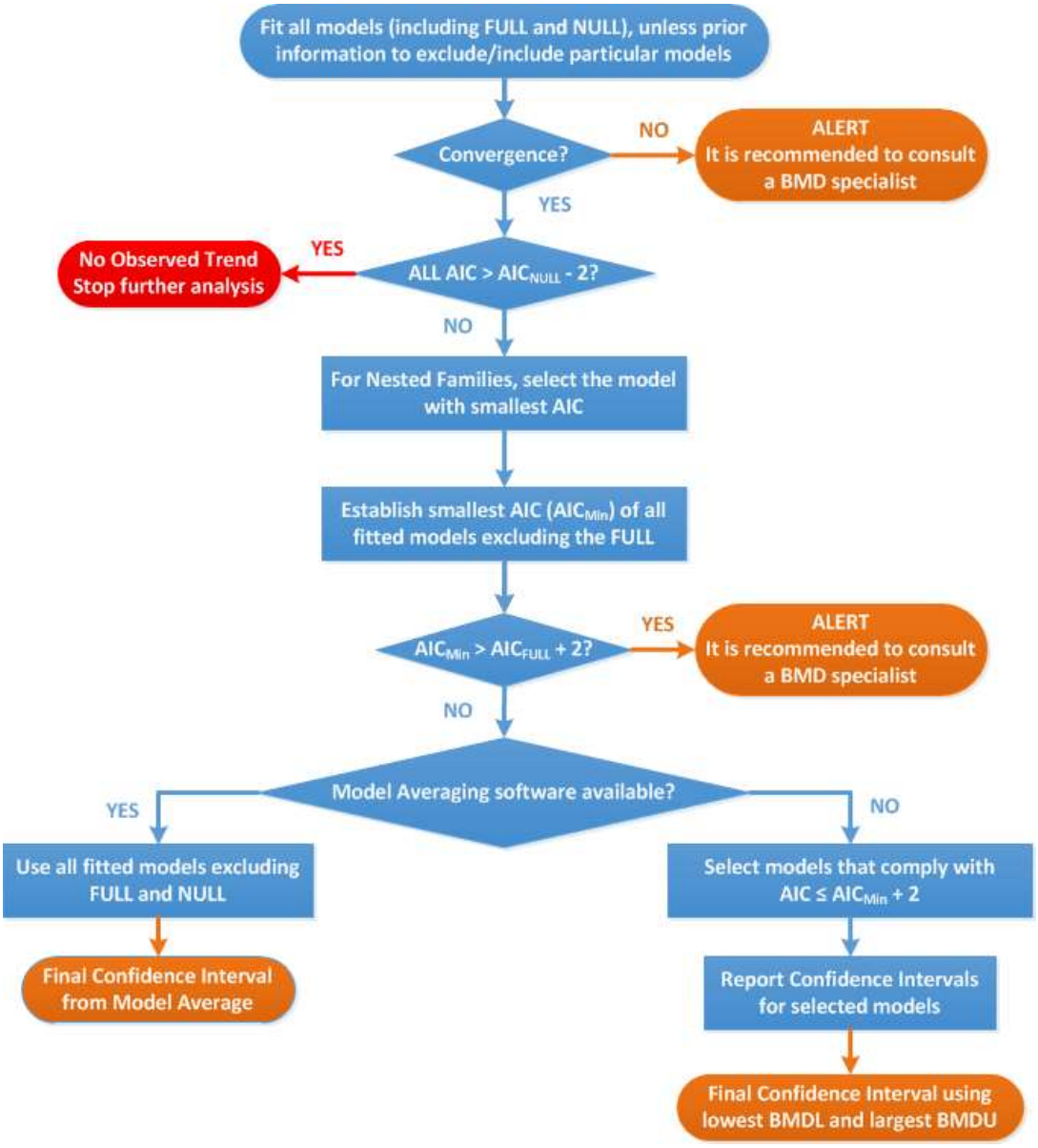


Figure A.1. Flowchart for selection of BMDL

A.1.5. Results

Table A.1: Results for the incidence of post-implantation loss in rats studied in the F1/F2 generation of the two-generation study

model	No.par	loglik	AIC	accepted	BMDL	BMDU	BMD	conv
null	2	-503.87	1011.74		NA	NA	NA	NA
full	6	-502.76	1017.52		NA	NA	NA	NA
two.stage	4	-503.50	1015.00	no	NA	NA	NA	yes
log.logist	4	-502.87	1013.74	no	NA	NA	NA	yes
Weibull	4	-502.87	1013.74	no	NA	NA	NA	yes
log.prob	4	-502.87	1013.74	no	NA	NA	NA	yes

model	No.par	loglik	AIC	accepted	BMDL	BMDU	BMD	conv
gamma	4	-502.87	1013.74	no	NA	NA	NA	no
logistic	3	-503.53	1013.06	no	NA	NA	NA	yes
probit	3	-503.52	1013.04	no	NA	NA	NA	yes
LVM: Expon. m3-	4	-502.94	1013.88	no	NA	NA	NA	yes
LVM: Hill m3-	4	-502.93	1013.86	no	NA	NA	NA	yes

None of the fitted models is better than the null model: All fitted models' AIC values are larger than null model's AIC – 2.

Estimated model parameters

two.stage

estimate for alfa- : 4.73
estimate for a- : 0.07186
estimate for BMD- : 11.72
estimate for c : 1e-06

log.logist

estimate for alfa- : 4.936
estimate for a- : 0.05952
estimate for BMD- : 58090
estimate for c : 0.1302

Weibull

estimate for alfa- : 4.936
estimate for a- : 0.05952
estimate for BMD- : 49710
estimate for c : 0.1284

log.prob

estimate for alfa- : 4.938
estimate for a- : 0.05953
estimate for BMD- : 164500
estimate for c : 0.05511

gamma

estimate for alfa- : 4.935
estimate for a- : 0.05952
estimate for BMD- : 41760
estimate for cc : 0.1268

logistic

estimate for alfa- : 4.716
estimate for a- : -2.548
estimate for BMD- : 9.027

probit

estimate for alfa- : 4.718
estimate for a- : -1.458
estimate for BMD- : 9.387

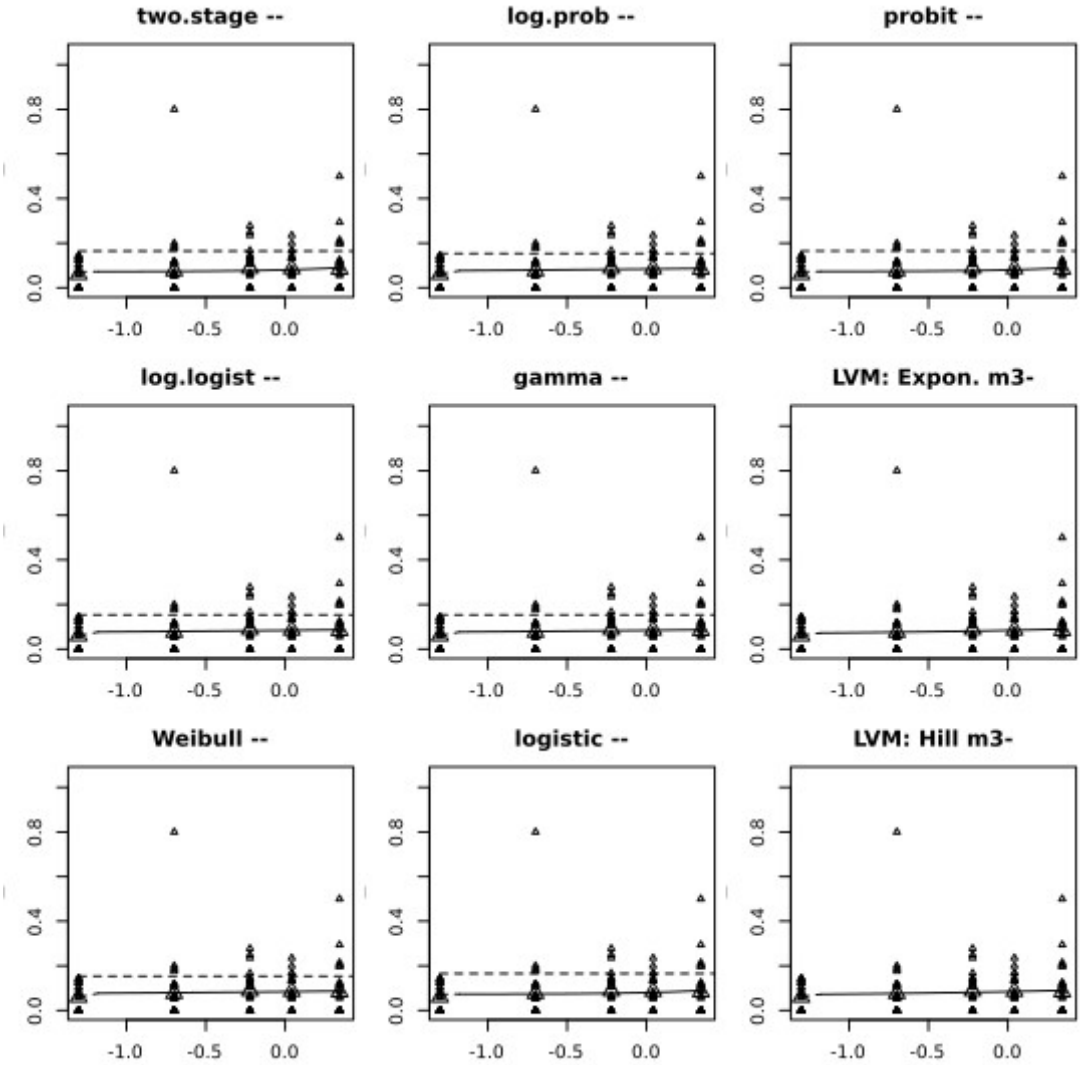
EXP

estimate for alfa- : 4.946
estimate for a- : 1.47
estimate for CED- : 110.7
estimate for d- : 0.25
estimate for th-1(fixed) : 0
estimate for sigma(fixed) : 0.25

HILL

estimate for alfa- : 4.947
estimate for a- : 1.471
estimate for CED- : 129.5
estimate for d- : 0.25
estimate for th-1(fixed) : 0
estimate for sigma(fixed) : 0.25

Visualisation



A.1.6. Data used for analysis

Animal	Dose (mg Ni/kg bw per day)	Incidence of post-implantation loss	Implantation scar count
178	0.0	0	15
179	0.0	0	16
180	0.0	1	13
181	0.0	1	10
182	0.0	2	14
183	0.0	2	15
184	0.0	2	16
185	0.0	0	13
186	0.0	0	16
187	0.0	0	16
188	0.0	2	14

189	0.0	0	16
190	0.0	0	13
191	0.0	0	15
192	0.0	1	16
193	0.0	0	9
194	0.0	2	19
195	0.0	0	13
196	0.0	2	16
197	0.0	2	14
198	0.0	1	15
199	0.0	2	16
200	0.0	0	14
201	0.0	1	17
202	0.2	0	17
203	0.2	3	15
204	0.2	1	16
205	0.2	3	17
206	0.2	2	17
207	0.2	1	16
208	0.2	3	16
209	0.2	0	18
210	0.2	0	16
211	0.2	0	12
212	0.2	1	19
213	0.2	2	17
214	0.2	1	14
215	0.2	2	17
216	0.2	0	17
217	0.2	0	17
218	0.2	1	17
219	0.2	0	12
220	0.2	1	17
221	0.2	4	5
222	0.2	1	18
223	0.2	1	16
224	0.2	0	17
225	0.2	2	19
226	0.2	1	17
227	0.2	1	17
228	0.6	0	14
229	0.6	1	16
230	0.6	0	14
231	0.6	2	19
232	0.6	4	17
233	0.6	2	14
234	0.6	1	17
235	0.6	0	0

236	0.6	3	18
237	0.6	0	18
238	0.6	2	16
239	0.6	0	14
240	0.6	5	18
241	0.6	2	15
242	0.6	2	18
243	0.6	0	11
244	0.6	2	14
245	0.6	0	15
246	0.6	2	8
247	0.6	2	18
248	0.6	0	16
249	0.6	1	18
250	0.6	1	16
251	0.6	0	15
252	0.6	1	15
253	1.1	3	15
254	1.1	2	15
255	1.1	2	15
256	1.1	4	17
257	1.1	1	15
258	1.1	1	18
259	1.1	1	16
260	1.1	0	16
261	1.1	1	15
262	1.1	1	13
263	1.1	1	18
264	1.1	0	14
265	1.1	2	15
266	1.1	3	18
267	1.1	2	14
268	1.1	2	12
269	1.1	1	12
270	1.1	1	16
271	1.1	0	14
272	1.1	0	13
273	1.1	0	16
274	1.1	1	15
275	1.1	1	17
276	2.2	3	14
277	2.2	1	12
278	2.2	0	16
279	2.2	0	15
280	2.2	0	16
281	2.2	1	5
282	2.2	0	18

283	2.2	3	15
284	2.2	0	14
285	2.2	0	13
286	2.2	0	18
287	2.2	5	17
288	2.2	2	17
289	2.2	0	7
290	2.2	2	17
291	2.2	1	18
292	2.2	2	16
293	2.2	0	15
294	2.2	0	16
295	2.2	1	16
296	2.2	1	2
297	2.2	2	22
298	2.2	3	15
299	2.2	2	18

A.2. Post-implantation loss DRF and 2GEN F0F1 studies; BMR 5%

A.2.1. Data description

The incidence of post-implantation loss as reported for the DRF study (SLI, 2000a) and the F0/F1 generation in the 2-generation study (SLI, 2000b) was used and the individual data are included in Section A.2.6 of this Annex. The incidence of post-implantation loss was calculated as follows: implantation scar count minus the number of live pups at delivery. The study was used as covariate and the litter effect was taken into account.

A.2.2. Selection of the benchmark response

A BMR of 5% (extra risk) was used as recommended by U.S. EPA (2012) for reproductive and developmental studies with nested study designs. A 90% confidence interval around the BMD was selected as recommended by the EFSA Scientific Committee (2017).

A.2.3. Software used

Results are obtained using the EFSA web tool for BMD analysis, which uses the R-package PROAST, version 67.0, for the underlying calculations.

A.2.4. Specification of deviations from default assumptions

General assumptions

No deviation from the recommended defaults (e.g. gamma distributional assumption instead of log-normal, heteroscedasticity instead of homoscedasticity) was made.

Dose–response models

No deviation from the recommended defaults (see Section A.1.4).

As a covariate is included in the analysis, these models will also be fitted assuming that some of the parameters (background response parameter (a), potency parameter (BMD) and/or variance (var)) depend on the subgroup defined by the covariate. Therefore the number of parameters in each model might be larger than indicated in the table above.

Procedure for selection of the BMDL

There was no deviation from the procedure described in the flow chart (see Section A.1.4) to obtain the final BMD confidence interval.

A.2.5. Results

Table A.2: Results for the incidence of post-implantation loss in rats studied in the F1/F2 generation of the two-generation study using a BMR of 5%

model	No.par	loglik	AIC	accepted	BMDL	BMDU	BMD	sens.subgr	conv
null	3	-830.99	1667.98		NA	NA	NA		NA
full	12	-816.37	1656.74		NA	NA	NA		NA
two.stage	4	-824.67	1657.34	no	NA	NA	2.820	–	yes
log.logist	4	-823.33	1654.66	yes	0.0730	3.05	0.666	–	yes
Weibull	4	-823.27	1654.54	yes	0.0725	3.08	0.663	–	yes
log.prob	4	-823.55	1655.10	yes	0.0711	3.03	0.641	–	yes
gamma	4	-823.21	1654.42	yes	0.0713	3.01	0.652	–	yes
logistic-b	4	-824.20	1656.40	no	NA	NA	1.770	2GEN	yes
LVM: Expon. m3-	4	-823.04	1654.08	yes	0.1730	3.15	0.653	2GEN	yes
LVM: Hill m3-	4	-823.09	1654.18	yes	0.1460	3.12	0.657	2GEN	yes

Confidence intervals for the BMD are based on generated data sets.

Estimated model parameters

two.stage

estimate for alfa- : 1.002
estimate for a-2GEN : 0.08402
estimate for a-DRF : 2.822
estimate for BMD-2GEN : 1e-06
estimate for BMD-DRF : 1.002
estimate for c : 0.08402

log.logist

estimate for alfa- : 1.024
estimate for a-2GEN : 0.05898
estimate for a-DRF : 0.6656
estimate for BMD-2GEN : 0.4933
estimate for BMD-DRF : 1.024
estimate for c : 0.05898

Weibull

estimate for alfa- : 1.025
estimate for a-2GEN : 0.05882
estimate for a-DRF : 0.6631
estimate for BMD-2GEN : 0.4714
estimate for BMD-DRF : 1.025
estimate for c : 0.05882

log.prob

estimate for alfa- : 1.02
estimate for a-2GEN : 0.05902
estimate for a-DRF : 0.641
estimate for BMD-2GEN : 0.2404
estimate for BMD-DRF : 1.02
estimate for c : 0.05902

gamma

estimate for alfa- : 1.026
estimate for a-2GEN : 0.05855
estimate for a-DRF : 0.652
estimate for BMD-2GEN : 0.4481

estimate for BMD-DRF : 1.026
estimate for cc : 0.05855

logistic

estimate for alfa- : 1.03
estimate for a-2GEN : -2.42
estimate for a-DRF : 1.771
estimate for BMD-2GEN : 4.806
estimate for BMD-DRF : 1.03

EXP

estimate for alfa- : 1.029
estimate for a- : 1.481

estimate for CED- : 0.6525
estimate for d- : 0.3373
estimate for th-1(fixed) : 0
estimate for sigma(fixed) : 0.25

HILL

estimate for alfa- : 1.028
estimate for a- : 1.48
estimate for CED- : 0.6571
estimate for d- : 0.3596
estimate for th-1(fixed) : 0
estimate for sigma(fixed) : 0.25

Weights for model averaging

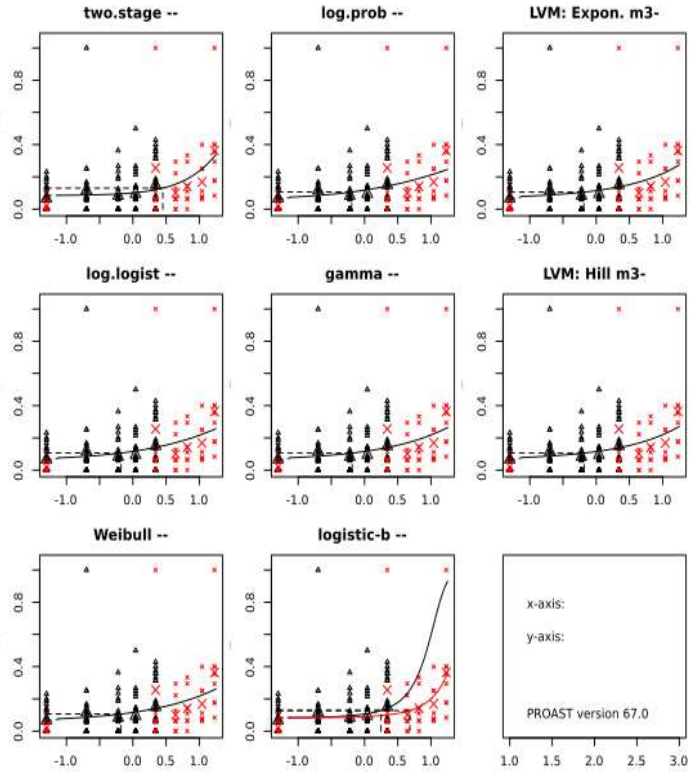
two.stage	log.logist	Weibull	log.prob	gamma	logistic	EXP	HILL
0.04	0.14	0.15	0.11	0.15	0.06	0.18	0.17

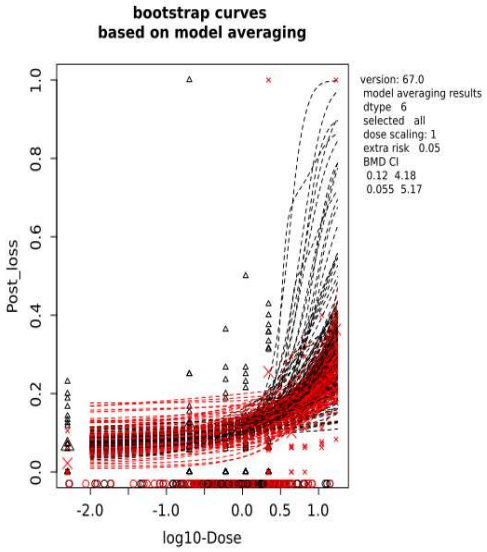
Final BMD values

subgroup	BMDL	BMDU
2GEN	0.12	4.18
DRF	0.06	5.17

Confidence intervals for the BMD are based on 200 bootstrap data sets.

Visualisation





A.2.6. Data used for analysis

Animal	Dose (mg Ni/kg bw per day)	Incidence of post-implantation loss	Implantation scar count	Study
48	0.0	0	6	2GEN
49	0.0	1	17	2GEN
50	0.0	0	14	2GEN
51	0.0	2	15	2GEN
52	0.0	2	17	2GEN

53	0.0	0	13	2GEN
54	0.0	2	14	2GEN
55	0.0	1	14	2GEN
56	0.0	3	16	2GEN
57	0.0	0	16	2GEN
58	0.0	0	5	2GEN
59	0.0	0	14	2GEN
60	0.0	0	13	2GEN
61	0.0	1	14	2GEN
62	0.0	0	16	2GEN
63	0.0	3	13	2GEN
64	0.0	0	14	2GEN
65	0.0	0	14	2GEN
66	0.0	1	6	2GEN
67	0.0	1	14	2GEN
68	0.0	0	17	2GEN
69	0.0	1	14	2GEN
70	0.0	3	15	2GEN
71	0.0	2	16	2GEN
72	0.0	0	12	2GEN
73	0.2	2	12	2GEN
74	0.2	2	13	2GEN
75	0.2	0	8	2GEN
76	0.2	1	13	2GEN
77	0.2	0	13	2GEN
78	0.2	0	13	2GEN
79	0.2	1	15	2GEN
80	0.2	11	11	2GEN
81	0.2	4	16	2GEN
82	0.2	4	16	2GEN
83	0.2	1	16	2GEN
84	0.2	1	15	2GEN
85	0.2	2	17	2GEN
86	0.2	1	13	2GEN
87	0.2	0	13	2GEN
88	0.2	1	16	2GEN
89	0.2	0	14	2GEN
90	0.2	0	14	2GEN
91	0.2	1	15	2GEN
92	0.2	2	16	2GEN
93	0.2	1	14	2GEN
94	0.2	1	18	2GEN
95	0.2	0	16	2GEN
96	0.2	0	16	2GEN
97	0.2	2	18	2GEN
98	0.2	1	18	2GEN
99	0.6	2	16	2GEN

100	0.6	0	14	2GEN
101	0.6	0	5	2GEN
102	0.6	1	15	2GEN
103	0.6	1	12	2GEN
104	0.6	4	11	2GEN
105	0.6	3	16	2GEN
106	0.6	3	15	2GEN
107	0.6	0	15	2GEN
108	0.6	1	14	2GEN
109	0.6	1	17	2GEN
110	0.6	4	15	2GEN
111	0.6	0	14	2GEN
112	0.6	4	17	2GEN
113	0.6	1	15	2GEN
114	0.6	1	12	2GEN
115	0.6	0	7	2GEN
116	0.6	1	12	2GEN
117	0.6	1	15	2GEN
118	0.6	1	14	2GEN
119	0.6	0	16	2GEN
120	0.6	0	15	2GEN
121	0.6	0	16	2GEN
122	0.6	0	13	2GEN
123	0.6	0	12	2GEN
124	1.1	3	14	2GEN
125	1.1	1	13	2GEN
126	1.1	1	15	2GEN
127	1.1	1	11	2GEN
128	1.1	3	6	2GEN
129	1.1	2	14	2GEN
130	1.1	1	16	2GEN
131	1.1	2	15	2GEN
132	1.1	1	13	2GEN
133	1.1	1	14	2GEN
134	1.1	1	15	2GEN
135	1.1	0	11	2GEN
136	1.1	0	13	2GEN
137	1.1	1	16	2GEN
138	1.1	0	14	2GEN
139	1.1	4	15	2GEN
140	1.1	1	15	2GEN
141	1.1	3	12	2GEN
142	1.1	0	14	2GEN
143	1.1	0	14	2GEN
144	1.1	1	13	2GEN
145	1.1	0	14	2GEN
146	1.1	0	16	2GEN

147	1.1	2	14	2GEN
148	1.1	3	13	2GEN
149	1.1	1	17	2GEN
150	2.2	1	16	2GEN
151	2.2	1	12	2GEN
152	2.2	5	14	2GEN
153	2.2	1	6	2GEN
154	2.2	0	15	2GEN
155	2.2	0	10	2GEN
156	2.2	2	15	2GEN
157	2.2	4	12	2GEN
158	2.2	2	14	2GEN
159	2.2	3	16	2GEN
160	2.2	0	5	2GEN
161	2.2	0	13	2GEN
162	2.2	6	14	2GEN
163	2.2	0	14	2GEN
164	2.2	1	15	2GEN
165	2.2	0	16	2GEN
166	2.2	0	14	2GEN
167	2.2	5	14	2GEN
168	2.2	0	16	2GEN
169	2.2	6	19	2GEN
170	2.2	1	16	2GEN
171	2.2	6	16	2GEN
172	2.2	1	16	2GEN
173	2.2	5	16	2GEN
174	2.2	0	4	2GEN
175	2.2	6	15	2GEN
176	2.2	1	13	2GEN
177	2.2	2	13	2GEN
1	0.0	0	17	DRF
2	0.0	1	17	DRF
3	0.0	0	16	DRF
4	0.0	0	13	DRF
5	0.0	0	17	DRF
6	0.0	2	19	DRF
7	0.0	0	16	DRF
8	0.0	0	16	DRF
9	2.2	0	6	DRF
10	2.2	1	17	DRF
11	2.2	0	18	DRF
12	2.2	16	16	DRF
13	2.2	0	14	DRF
14	2.2	2	17	DRF
15	2.2	1	15	DRF
16	2.2	1	18	DRF

17	4.4	1	15	DRF
18	4.4	1	16	DRF
19	4.4	1	16	DRF
20	4.4	0	13	DRF
21	4.4	5	17	DRF
22	4.4	0	16	DRF
23	4.4	2	9	DRF
24	4.4	2	16	DRF
25	6.6	5	17	DRF
26	6.6	0	0	DRF
27	6.6	2	14	DRF
28	6.6	2	18	DRF
29	6.6	1	16	DRF
30	6.6	5	15	DRF
31	6.6	0	13	DRF
32	6.6	1	15	DRF
33	11.0	6	15	DRF
34	11.0	1	13	DRF
35	11.0	2	18	DRF
36	11.0	4	16	DRF
37	11.0	1	14	DRF
38	11.0	4	16	DRF
39	11.0	1	16	DRF
40	17.0	6	15	DRF
41	17.0	3	17	DRF
42	17.0	6	15	DRF
43	17.0	3	17	DRF
44	17.0	5	17	DRF
45	17.0	1	12	DRF
46	17.0	6	17	DRF
47	17.0	8	8	DRF

A.3. Incidence of clinically cutaneous reactions to nickel following oral exposure in nickel-sensitive persons as reported by Jensen et al. (2003)

A.3.1. Data description

The incidence of clinically cutaneous reactions to nickel following oral exposure in nickel-sensitive persons as reported by Jensen et al. (2003) as summarised in Table A.3 was used for the BMD analysis.

Table A.3: Incidence of clinically cutaneous reactions to nickel following oral exposure in nickel-sensitive persons as reported by Jensen et al. (2003)

Dose (mg Ni/person)	N with clinically cutaneous reactions[(a)]	N
0.0	1	10
0.3	4	10

1.0	4	10
4.0	7	10

N: number of nickel-sensitive persons.
(a): Flare-up reactions and widespread clinical reactions, including any large or small clinical eruption on previously unaffected skin.

A.3.2. Selection of the benchmark response

A default BMR of 10% (extra risk) and a 90% confidence interval around the BMD were selected as recommended by the EFSA Scientific Committee (2017).

A.3.3. Software used

Results are obtained using the EFSA web tool for BMD analysis, which uses the R-package PROAST, version 67.0, for the underlying calculations.

A.3.4. Specification of deviations from default assumptions

General assumptions

No deviation from the recommended defaults (e.g. gamma distributional assumption instead of log-normal, heteroscedasticity instead of homoscedasticity) was made.

Dose–response models

No deviation from the recommended defaults (see Section A.1.4.).

Procedure for selection of the BMDL

There was no deviation from the procedure described in the flow chart (see Section A.1.4) to obtain the final BMD confidence interval.

A.3.5. Results

Table A.4: Results of the model fitting for the incidence of clinically cutaneous reactions to nickel following oral exposure in nickel-sensitive persons as reported by Jensen et al. (2003) using a BMR of 10%

model	No.par	loglik	AIC	accepted	BMDL	BMDU	BMD	conv
null	1	-26.92	55.84		NA	NA	NA	NA
full	4	-22.82	53.64		NA	NA	NA	NA
two.stage	3	-23.66	53.32	yes	0.19600	1.28	0.3840	yes
log.logist	3	-23.06	52.12	yes	0.00000	2.04	0.0358	yes
Weibull	3	-23.02	52.04	yes	0.00000	1.89	0.0249	yes
log.prob	3	-23.07	52.14	yes	0.00000	2.04	0.0431	yes
gamma	3	-23.00	52.00	yes	0.00000	1.70	0.0154	yes
logistic	2	-23.93	51.86	yes	0.44200	1.74	0.7210	yes
probit	2	-23.92	51.84	yes	0.45000	1.71	0.7030	yes
LVM: Expon. m3-	3	-23.00	52.00	yes	0.00285	1.90	0.0151	yes
LVM: Hill m3-	3	-23.01	52.02	yes	0.00166	1.79	0.0187	yes

AIC: Akaike information criterion; BMDL: benchmark dose lower confidence limit; BMDU: benchmark dose upper confidence limit; BMR: benchmark response.

Estimated model parameters

two.stage
estimate for a- : 0.1996
estimate for BMD- : 0.3844
estimate for c : 1e-06

log.logist
estimate for a- : 0.1029
estimate for BMD- : 0.03577
estimate for c : 0.5728

Weibull
estimate for a- : 0.1028
estimate for BMD- : 0.02486
estimate for c : 0.4442

log.prob
estimate for a- : 0.1023
estimate for BMD- : 0.04308
estimate for c : 0.3521

gamma
estimate for a- : 0.1021
estimate for BMD- : 0.01538
estimate for cc : 0.3438

logistic
estimate for a- : -1.113
estimate for BMD- : 0.7205

probit
estimate for a- : -0.6901
estimate for BMD- : 0.7034

EXP
estimate for a- : 1.371
estimate for CED- : 0.01513
estimate for d- : 0.2637
estimate for th(fixed) : 0
estimate for sigma(fixed) : 0.25

HILL
estimate for a- : 1.371
estimate for CED- : 0.01872
estimate for d- : 0.3055
estimate for th(fixed) : 0
estimate for sigma(fixed) : 0.25

Weights for model averaging

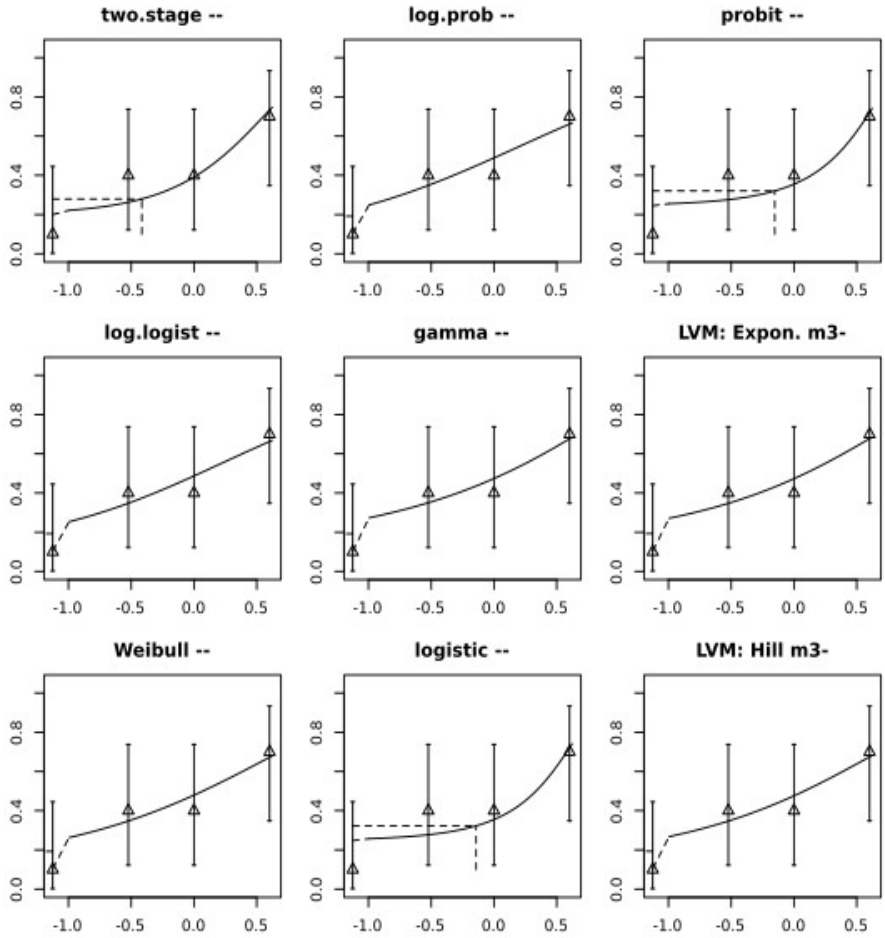
two.stage	log.logist	Weibull	log.prob	gamma	logistic	probit	EXP	HILL
0.06	0.11	0.12	0.11	0.12	0.13	0.13	0.12	0.12

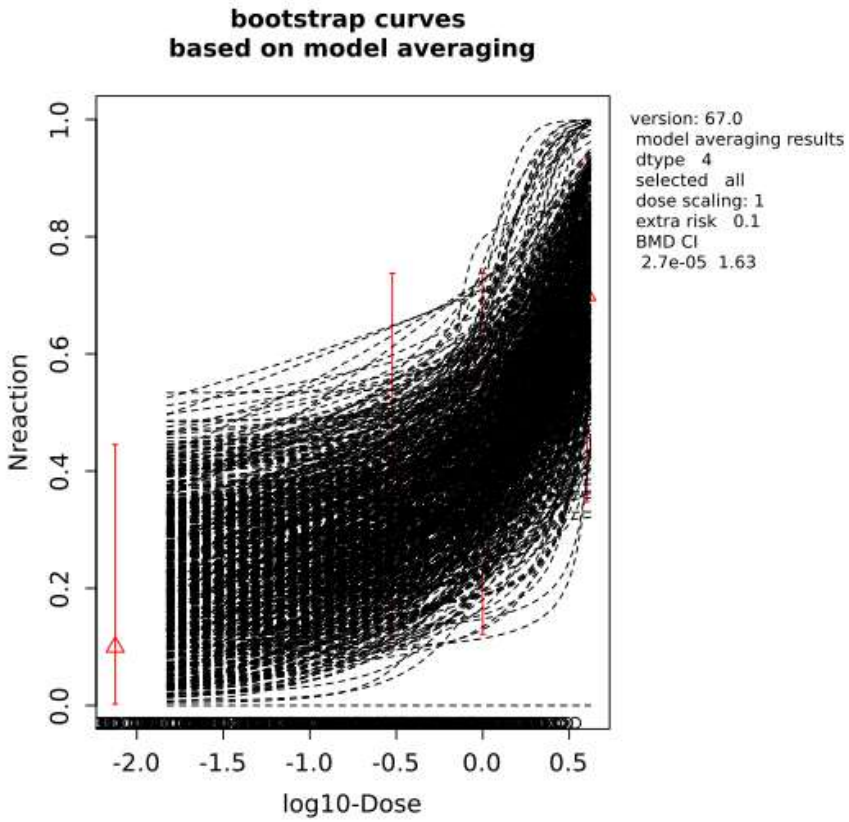
Final BMD values

subgroup	BMDL	BMDU
Jensen	2.66e-05	1.63

Confidence intervals for the BMD are based on 1000 bootstrap data sets.

Visualisation





A.4. Incidence of flare-up reactions to nickel following oral exposure in nickel-sensitive persons as reported by Jensen et al. (2003)

A.4.1. Data description

The incidence of flare-up reactions to nickel following oral exposure in nickel-sensitive persons as reported by Jensen et al. (2003) as summarised in Table A.5 was used for the BMD analysis.

Table A.5: Incidence of flare-up reactions to nickel following oral exposure in nickel-sensitive persons as reported by Jensen et al. (2003)

Dose (mg Ni/person)	N with flare-up of previous sites of dermatitis	N
0.0	1	10
0.3	4	10
1.0	4	10
4.0	6	10

N: number of nickel-sensitive persons.

A.4.2. Selection of the benchmark response

A default BMR of 10% (extra risk) and a 90% confidence interval around the BMD were selected as recommended by the EFSA Scientific Committee (2017).

A.4.3. Software used

Results are obtained using the EFSA web tool for BMD analysis, which uses the R-package PROAST, version 67.0, for the underlying calculations.

A.4.4. Specification of deviations from default assumptions

General assumptions

No deviation from the recommended defaults (e.g. gamma distributional assumption instead of log-normal, heteroscedasticity instead of homoscedasticity) was made.

Model averaging

Model averaging was not used since the aim of this analysis was to evaluate the fitting of the models.

Dose–response models

No deviation from the recommended defaults (see Section A.1.4).

Procedure for selection of the BMDL

There was no deviation from the procedure described in the flow chart (see Section A.1.4) to obtain the final BMD confidence interval.

A.4.5. Results

Table A.6: Results of the model fitting for the incidence of flare-up reactions to nickel following oral exposure in nickel-sensitive persons as reported by Jensen et al. (2003) using a BMR of 10%

model	No.par	loglik	AIC	accepted	BMDL	BMDU	BMD	conv
null	1	-26.46	54.92		NA	NA	NA	NA
full	4	-23.44	54.88		NA	NA	NA	NA
two.stage	3	-24.45	54.90	no	NA	NA	NA	yes
log.logist	3	-23.55	53.10	no	NA	NA	NA	yes
Weibull	3	-23.54	53.08	no	NA	NA	NA	yes
log.prob	3	-23.55	53.10	no	NA	NA	NA	yes
gamma	3	-23.53	53.06	no	NA	NA	NA	yes
logistic	2	-24.65	53.30	no	NA	NA	NA	yes
probit	2	-24.64	53.28	no	NA	NA	NA	yes
LVM: Expon. m3-	3	-23.58	53.16	no	NA	NA	NA	yes
LVM: Hill m3-	3	-23.55	53.10	no	NA	NA	NA	yes

None of the fitted models is better than the null model: All fitted models' AIC values are larger than null model's AIC – 2.

Estimated model parameters

two.stage
estimate for a- : 0.2221
estimate for BMD- : 0.5424
estimate for c : 1e-06

log.logist
estimate for a- : 0.1009
estimate for BMD- : 0.008858
estimate for c : 0.3769

Weibull
estimate for a- : 0.1009
estimate for BMD- : 0.005425
estimate for c : 0.2988

log.prob
estimate for a- : 0.1007
estimate for BMD- : 0.01209
estimate for c : 0.2321

gamma
estimate for a- : 0.1008
estimate for BMD- : 0.002801
estimate for cc : 0.2321

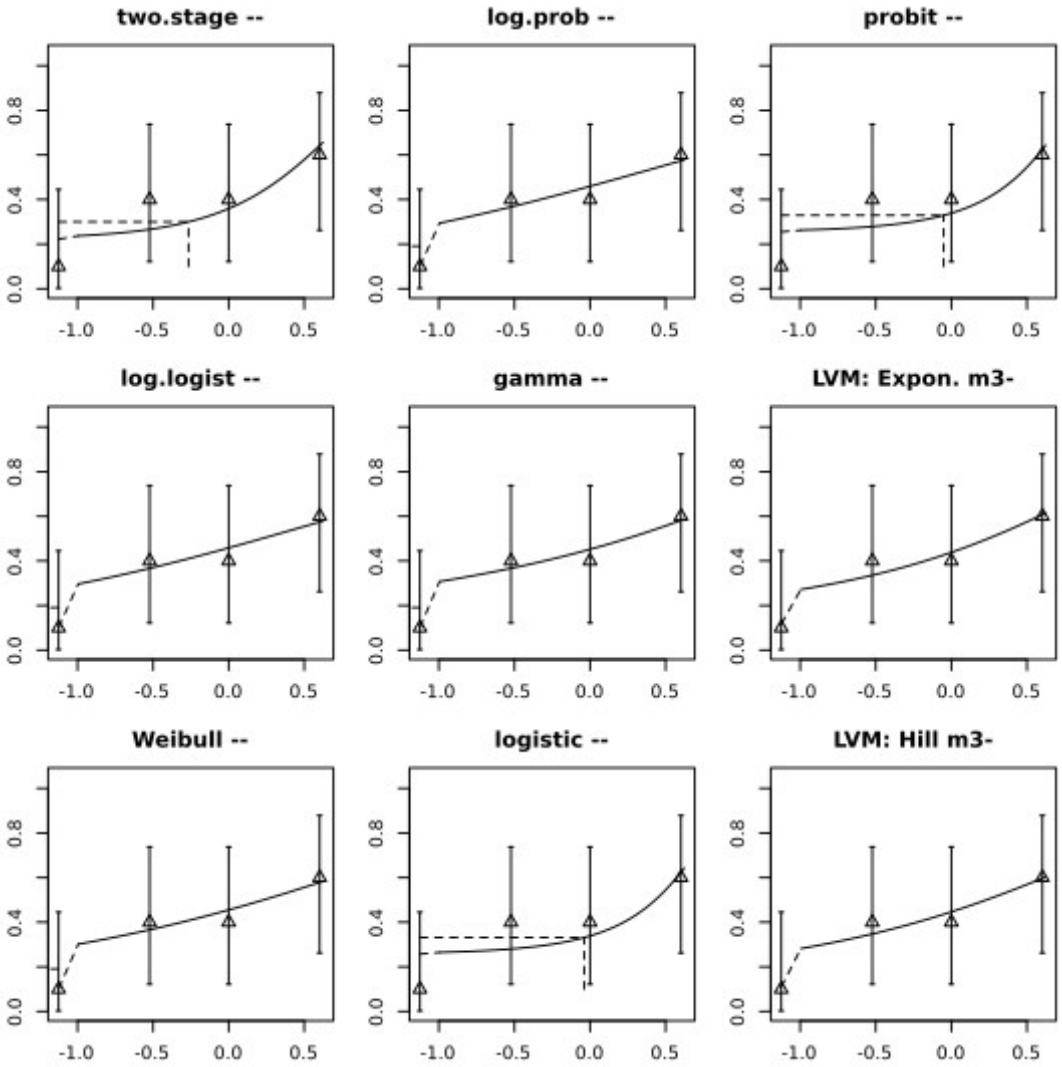
logistic
estimate for a- : -1.062
estimate for BMD- : 0.9157

probit
estimate for a- : -0.6593
estimate for BMD- : 0.8908

EXP
estimate for a- : 1.347
estimate for CED- : 0.0159
estimate for d- : 0.25
estimate for th(fixed) : 0
estimate for sigma(fixed) : 0.25

HILL
estimate for a- : 1.361
estimate for CED- : 0.01032
estimate for d- : 0.25
estimate for th(fixed) : 0
estimate for sigma(fixed) : 0.25

Visualisation



A.5. Incidence of clinically cutaneous reactions to nickel following oral exposure in nickel-sensitive persons as reported by Jensen et al. (2003) and Gawkrodger et al. (1986)

A.5.1. Data description

The incidence of clinically cutaneous reactions to nickel following oral exposure in nickel-sensitive persons as reported by Gawkrodger et al. (1986) and Jensen et al. (2003) as summarised in Table A.7 was used for the BMD analysis.

Table A.7: Incidence of clinically cutaneous reactions to nickel following oral exposure in nickel-sensitive persons as reported by Gawkrodger et al. (1986) and Jensen et al. (2003)

Dose (mg Ni/person)	N with clinically cutaneous reactions[(a)]	N
0.0	1	10
0.3	4	10
0.4	5	10
1.0	4	10
2.5	5	10
4.0	7	10
5.6	6	6

N: number of nickel-sensitive persons.

(a): Flare-up reactions and widespread clinical reactions, including any large or small clinical eruption on previously unaffected skin.

A.5.2. Selection of the benchmark response

A default BMR of 10% (extra risk) and a 90% confidence interval around the BMD were selected as recommended by the EFSA Scientific Committee (2017).

A.5.3. Software used

Results are obtained using the EFSA web tool for BMD analysis, which uses the R-package PROAST, version 67.0, for the underlying calculations.

A.5.4. Specification of deviations from default assumptions

General assumptions

No deviation from the recommended defaults (e.g. gamma distributional assumption instead of log-normal, heteroscedasticity instead of homoscedasticity) was made.

Dose–response models

No deviation of the recommended defaults (see Section A.1.4).

Procedure for selection of the BMDL

There was no deviation from the procedure described in the flow chart (see Section A.1.4) to obtain the final BMD confidence interval.

A.5.5. Results

Table A.8: Results of the model fitting for the incidence of clinically cutaneous reactions to nickel following oral exposure in nickel-sensitive persons as reported by Gawkrodger et al. (1986) and Jensen et al. (2003) using a BMR of 10%

model	No.par	loglik	AIC	accepted	BMDL	BMDU	BMD	conv
null	1	-45.72	93.44		NA	NA	NA	NA
full	7	-36.68	87.36		NA	NA	NA	NA
two.stage	3	-39.48	84.96	no	NA	NA	0.7810	yes
log.logist	3	-39.41	84.82	yes	0.00e+00	4.100	0.0390	yes
Weibull	3	-39.20	84.40	yes	0.00e+00	4.430	0.0326	yes
log.prob	3	-39.40	84.80	yes	2.30e-06	4.070	0.0472	yes
gamma	3	-39.05	84.10	yes	0.00e+00	3.670	0.0201	yes
logistic	2	-39.52	83.04	yes	4.41e-01	1.010	0.6310	yes
probit	2	-39.43	82.86	yes	4.46e-01	0.985	0.6180	yes
LVM: Expon. m3-	3	-39.06	84.12	yes	2.97e-03	3.170	2.2600	yes
LVM: Hill m3-	3	-39.12	84.24	yes	1.78e-03	3.100	2.4000	yes

AIC: Akaike information criterion; BMDL: benchmark dose lower confidence limit; BMDU: benchmark dose upper confidence limit.

Estimated model parameters

two.stage
estimate for a- : 0.2939
estimate for BMD- : 0.7809
estimate for c : 4.328

log.logist
estimate for a- : 0.1084
estimate for BMD- : 0.03898
estimate for c : 0.6312

Weibull
estimate for a- : 0.1117
estimate for BMD- : 0.03265
estimate for c : 0.5026

log.prob
estimate for a- : 0.1066
estimate for BMD- : 0.04723
estimate for c : 0.3921

gamma
estimate for a- : 0.1086
estimate for BMD- : 0.02006
estimate for cc : 0.386

logistic
estimate for a- : -0.9493
estimate for BMD- : 0.6308

probit
estimate for a- : -0.5917
estimate for BMD- : 0.6182

EXP
estimate for a- : 1.097
estimate for CED- : 2.261
estimate for d- : 3.108
estimate for th(fixed) : 0
estimate for sigma(fixed) : 0.25

HILL
estimate for a- : 1.094
estimate for CED- : 2.402
estimate for d- : 3.689
estimate for th(fixed) : 0
estimate for sigma(fixed) : 0.25

Weights for model averaging

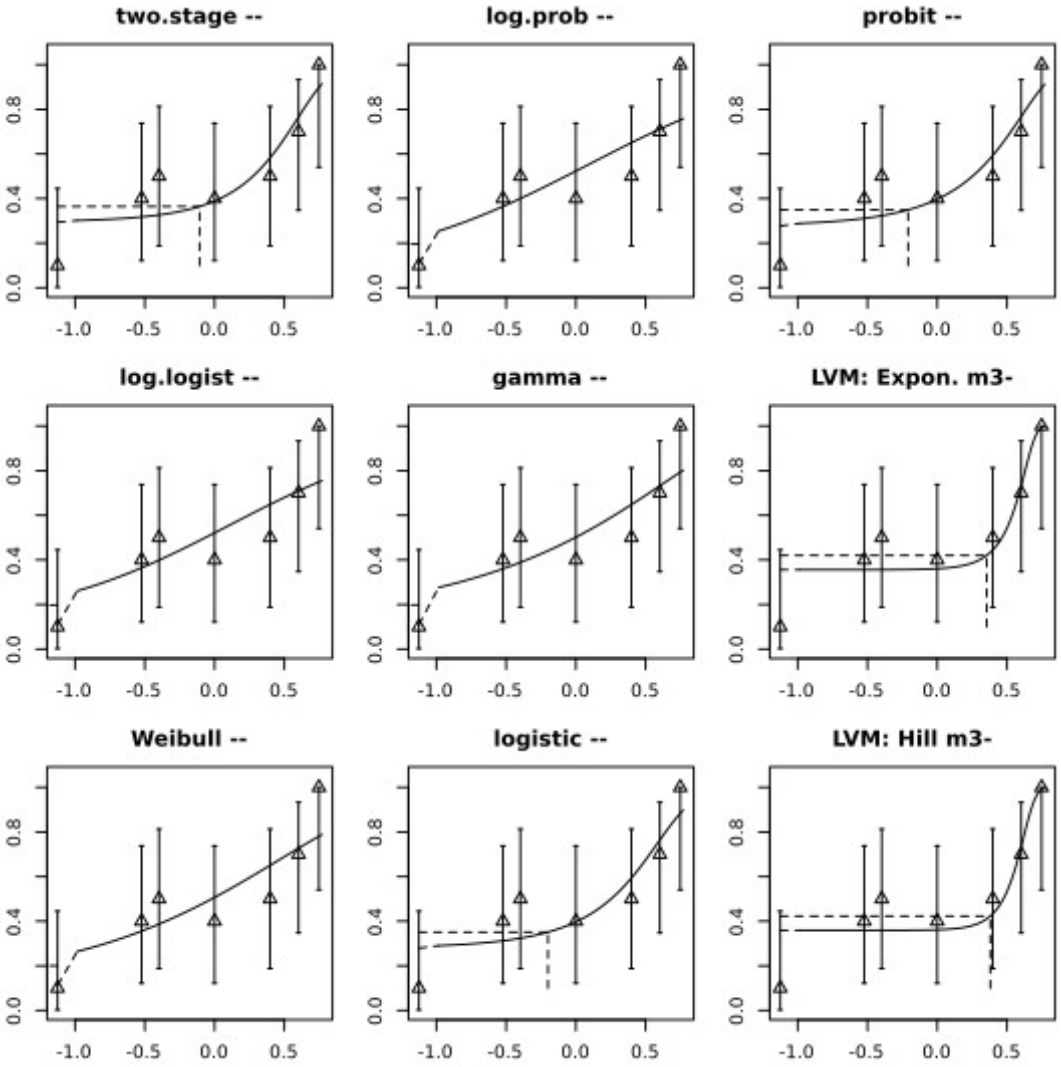
two.stage	log.logist	Weibull	log.prob	gamma	logistic	probit	EXP	HILL
0.07	0.07	0.09	0.08	0.11	0.18	0.2	0.11	0.1

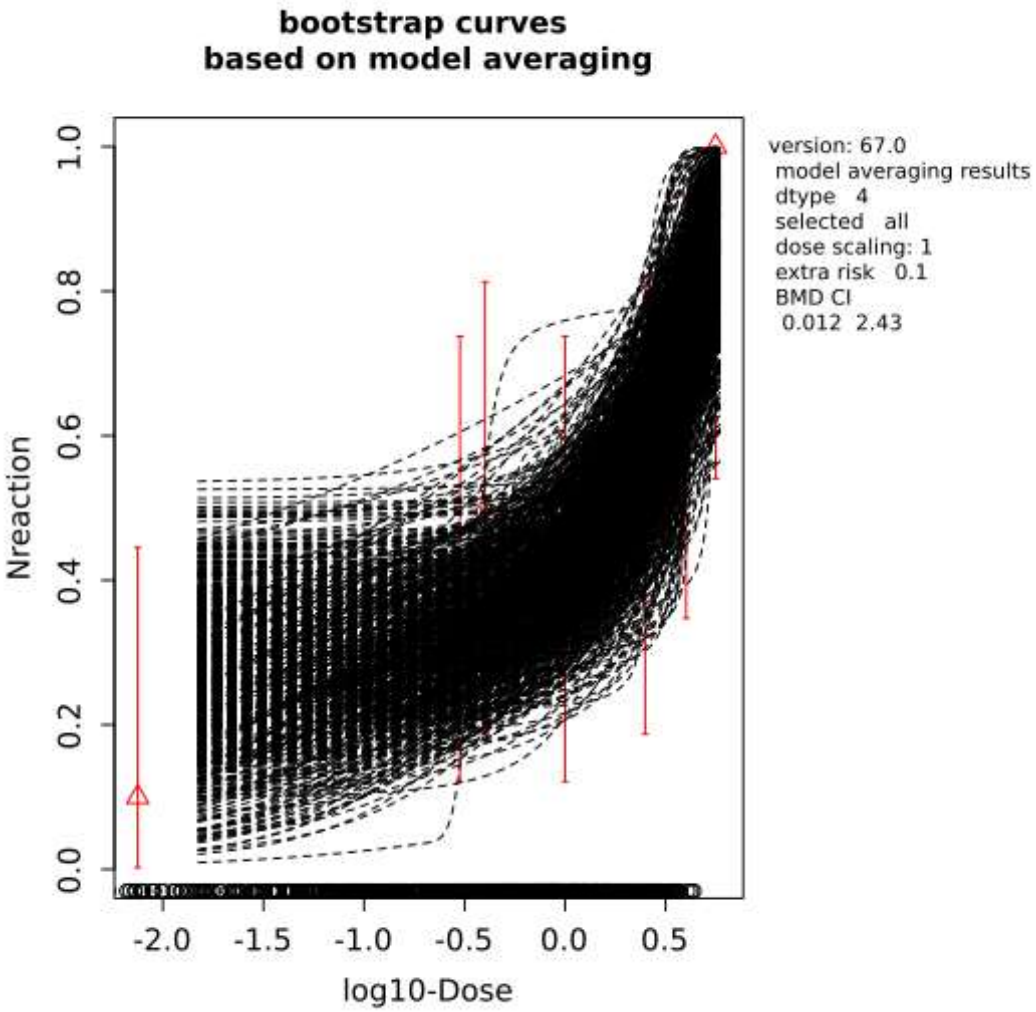
Final BMD values

subgroup	BMDL	BMDU
	0.0124	2.43

Confidence intervals for the BMD are based on 1000 bootstrap data sets.

Visualisation

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based on model averaging
version: 67.0
model averaging results
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selected all
dose scaling: 1
extra risk 0.1
BMD CI
0.012 2.43
Nreaction
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0.2
0.4
0.6
0.8
1.0
-2.0
-1.5
-1.0
-0.5
0.0
0.5
log10-Dose