Female reproductive toxicity - Animal Studies - (BPA) in foodstuffs – Reproductive and Developmental Toxicity

In this guide

Female reproductive toxicity

61. In the cluster female reproductive toxicity, 17 studies were available in mice, of these seven studies had exposure during development until weaning, one had exposure during development until adulthood, one had exposure during the growth phase, in seven studies the mice were exposed as adults and four had indirect germline exposure: some of the studies tested multiple exposure periods. Of the 16 studies on rats, 11 had exposure during development until weaning, three had exposure during development until adulthood, and in four the rats were exposed as adults. There was one study in hamsters which were exposed during development until weaning. In addition, three studies were on sheep, two had exposure during the period development until weaning and one as adults.

62. The specific endpoints that were included for effects of BPA on female reproductive toxicity cluster were plasma/serum thyroid hormones, testosterone, oestrus cyclicity, age at first oestrus, fertilisation rate and implantation incidences, ovary weight and histology, uterus weight and histology.

Developmental exposure (pre-natal and/or post-natal until weaning)

Plasma/serum thyroid hormones

63. For this exposure period the following studies were identified.

- Triiodothyronine (T3): one Tier 1 rat study (NTP Clarity Report, 2018/Camacho et al., 2019
- Thyroxine (T4): two Tier 1 rat studies (Bansal and Zoeller, 2019; NTP Clarity Report, 2018/Camacho et al., 2019, one Tier 1 sheep study (Guignard et al., 2017 and one Tier 3 mouse study (Bodin et al., 2014.
- T3/ totalT4: one Tier 1 sheep study (Guignard et al., 2017).

64. No effect was seen on T3 levels in the Tier 1 rat study (NTP Clarity Report, 2018/Camacho et al., 2019. In this study, the NCTR Sprague Dawley rats were dosed with 2.5, 25, 250, 2500 or 25000 µg/kg bw per day BPA by gavage; F0 dams from GD6 to PND0 and F1 pups from PND1 to PND21 at interim sacrifice (1 year).

65. No effect was seen on T4 levels in the Tier 1 rat study (NTP Clarity Report, 2018/Camacho et al., 2019. Similarly, on PND15, no effect was observed in the Tier 1 rat study by Bansal and Zoeller, 2019 in which female NCTR Sprague Dawley rats were dosed from GD6–PND15 with 2.5, 25, 250, 2500 or 25000 µg/kg

bw BPA per day by gavage (this study is a sub project of the Clarity study). No change in T4 was observed in fetuses (GD28–132/134) in the Tier 1 study in Lacaune sheep (Guignard et al., 2017) after sub cutaneous dosing with 5, 50 or 5000 µg/kg bw BPA per day (using dose conversion factors of 125 and 37 respectively, the doses were equivalent to oral doses of 625, 6250 or 625000 µg/kg bw per day and 185, 1850 or 185000 µg/kg bw per day).

66. No change was observed on the serum ratio T3/ total T4 (TT4) in the study in sheep by Guignard et al., 2017.

67. During this exposure period the likelihood of changes in thyroid hormones (T3, T4, rT3/TT4) were judged as Not Likely by the CEP Panel as no effects were observed in Tier 1 or Tier 2 studies in rats or in a Tier 1 study in sheep.

Plasma/serum testosterone:

68. Only three Tier 3 studies in rats (Castro et al., 2018; Leung et al., 2017; Johnson et al., 2016) along with two Tier 3 studies in mice (Mahalingam et al., 2017; Tucker et al., 2018) were identified for this endpoint. The CEP Panel noted that as only Tier 3 studies were available, the likelihood for this endpoint could not be determined because of Inadequate evidence.

Oestrus cyclicity

69. For this exposure period, four Tier 1 studies (Hass et al., 2016; Ferguson SA et al., 2014; NTP Clarity Report, 2018/Camacho et al., 2019; Franssen et al., 2016) and one Tier 2 study (Santamaria et al., 2016) in rats, one Tier 1 study (Tucker et al., 2018) and one Tier 2 study (Acevedo et al., 2018) in mice and one Tier 2 study (Veiga-Lopez et al., 2014) in sheep were identified. A Tier 3 rat study (Leung et al., 2017 and a Tier 3 mouse study (Wang W et al., 2014) were also identified.

70. No change in oestrus cyclicity was observed in the Tier 1 rat studies which used a range of doses and administration methods. Similarly, no change was observed in the Tier 1 mouse study. However, in a Tier 2 mouse study (Acevedo et al., 2018) only, a decrease in oestrus cyclicity by 6 months at the lowest dose was observed in F1 females.

71. In the Tier 2 study in sheep (Veiga-Lopez et al., 2014) a change in oestrus cyclicity (decrease in follicular count trajectories) in all dose groups was

observed. Pregnant sheep were exposed to BPA from GD30–GD90 by subcutaneous injection of 50, 500 or 5000 µg/kg bw per day. The time of examination for oestrus cyclicity was not described but considered at least after 8 weeks (weaning) and when the F1 females weighed more than 40 kg.

72. Apart from the decreased oestrus cyclicity in only the lowest dose and one timepoint in the Tier 2 mouse study (Acevedo et al., 2018 and a decrease in oestrus cyclicity (decrease in follicular count trajectories) in the sheep study (Veiga-Lopez et al., 2014, no change in oestrus cycle was observed in the other five Tier 1 studies in rats and mice. Therefore, the CEP Panel considered that the likelihood of a change in oestrus cyclicity is Not Likely.

Ovary weight

73. One Tier 1 study (NTP Clarity Report, 2018/Camacho et al., 2019) and one Tier 2 study (Santamaria et al., 2016) in rats and one Tier 3 mouse study (Patel et al., 2013 were identified for this exposure period.

74. In the Clarity study, a decrease in ovary weight was observed in the high-dose group with a trend apparent in the other dose groups. Ovary weight was decreased in the F1 females at 7 weeks of age. The NTP report states that "mean absolute ovary weights, as well as ovary weights adjusted for brain and body weights, were decreased relative to the vehicle control mean by 18%, 16%, and 15%, respectively".

75. In the Tier 2 rat study by Santamaria et al., (2016) 10-12 F0 dams/group of a Wistar derived strain and their female offspring were given 0.5 µg or 50 µg/kg bw BPA per day (via drinking water) from GD9–PND21. An approximately equal decrease was observed in ovary weight in the F1 animals of both BPA-treated groups at PND90. The numbers are not given in the paper but from the figure, mean ovary weight appears to be around 50 mg in the controls and 40 mg in the treated groups, with no clear trend but a greater spread of data in the higher dose.

76. The CEP Panel considered the likelihood of the decrease of ovary weight as Likely as there was a trend in the Tier 1 study (supported by one Tier 2 study with effects at lower doses without dose–response (Santamaria et al., 2016).

Ovary histology (follicle count, cellular hypertrophy, follicular cysts):

77. For this exposure period one Tier 1 study (NTP Clarity Report, 2018/Camacho et al., 2019, one Tier 2 study (Santamaria et al., 2016 and one Tier 3 study (Patel et al., 2017 in rats and three Tier 3 studies in mice (Mahalingam et al., 2017; Wang W et al., 2014; Berger et al., 2016) were identified.

78. In the Tier 1 Clarity study, no change was observed in cell hypertrophy. The incidence in follicular cysts was increased in the highest dose group and in all dose groups there was an increased trend in the incidence of follicular cysts. In the Tier 2 (Santamaria et al., 2016) in rats, a decrease in the number of growing follicles was observed in the BPA-treated groups on PND90; the decrease was comparable in both groups.

79. The CEP Panel considered that for the exposure period developmental exposure (pre-natal and/or post-natal until weaning) the likelihood of histological changes in the ovary as Likely.

Uterus weight:

80. For this exposure period one Tier 1 study (NTP Clarity Report, 2018/Camacho et al., 2019) in rats, one Tier 1 study in hamsters (Radko et al., 2015) and one Tier 3 study in mice (Patel et al., 2013) were identified.

81. In the Tier 1 rat Clarity study, no change in uterus weight was observed. In the Tier 1 hamster study uterus weight (wet and dry) on PND21 was statistically significantly increased at the top dose of 160000 µg/kg bw BPA per day only.

82. The effect on uterus weight was considered as ALAN as no effect was observed in the Tier 1 study in rats and an increase in weaning hamsters (uterotropic assay) was only seen at the highest dose (160,000 µg/kg bw per day).

Uterus histology

83. This endpoint included observations of cystic endometrial hyperplasia, uterine dilation, squamous metaplasia, apoptosis in the luminal epithelial cells of the endometrium, endometrial hyperplasia, luminal epithelial anomalies and glands with cellular anomalies): Two Tier 1 studies in rats (NTP Clarity Report, 2018/Camacho et al., 2019; Vigezzi et al., 2015) were identified for this exposure period.

84. In the Tier 1 Clarity study, a statistically significant increase was observed in cystic endometrial hyperplasia at the interim sacrifice (1 year) in the highest dose group and at terminal sacrifice (2 years) in the two highest dose groups (2500 and 25,000 µg/kg bw BPA per day group). At the interim sacrifice, uterine dilation and squamous metaplasia were increased in the 250 µg/kg bw per day and in the 25,000 µg/kg bw per day dose groups, respectively. There was a non-significant increase observed in the incidence of apoptosis in the luminal epithelial cells in the endometrium in the high-dose group. No change was observed in endometrial hyperplasia in any of the dose groups in this study.

85. In the other Tier 1 study in Wistar rats (Vigezzi et al., 2015) the dams were given 0.5 or 50 µg/kg bw BPA per day in drinking water from GD9–PND21. The F1 females were necropsied on PND90 and 360. No changes in squamous metaplasia and luminal epithelial anomalies were observed. At necropsy on PND360, an increase in glands with cellular anomalies was observed in the 50 µg/kg bw per day; on PND90 but no effects were seen in the 50 µg/kg bw per day group or at both times of necropsy in the lower dose group.

86. The CEP Panel considered the endpoint uterus histology based on effects seen at histological examination of the uterus in two rat Tier 1 studies as **Likely.**

87. During developmental exposure (pre-natal and/or post-natal until weaning), the CEP Panel assigned a likelihood level of Likely to the cluster female reproductive toxicity of BPA. Since the likelihood level is Likely for the endpoint ovary weight in Tier 1 rat study (NTP Clarity Report, 2018/Camacho et al., 2019, for the endpoint ovary histology (follicle count and follicle cysts) in one rat study (NTP Clarity Report, 2018/Camacho et al., 2019 (Tier1)) and the endpoint uterus histology in two Tier 1 rat studies (NTP Clarity Report, 2018/Camacho et al., 2019; Vigezzi et al., 2015), these were taken forward for BMD analysis and uncertainty analysis.

Developmental and adult exposure (pre-natal and post-natal in pups until adulthood)

Plasma/serum thyroid hormones

88. For this exposure period only one Tier 1 rat study (NTP Clarity Report, 2018/Camacho et al., 2019) was identified. No effect was seen on T3 or T4 in this study. Based on this study, the CEP Panel considered an effect on thyroid hormones (T3, T4) as Not Likely.

Oestrus cyclicity

89. For this exposure period only one Tier 1 rat study (NTP Clarity Report, 2018/Camacho et al., 2019 was identified. No effect was seen on oestrus cyclicity. Based on this study, the CEP Panel judged an effect on oestrus cyclicity as Not Likely.

Ovary weight

90. For this exposure period, the one Tier 1 rat study (NTP Clarity Report, 2018/Camacho et al., 2019 and one Tier 3 mouse study (Patel et al., 2013) were identified. No effect was seen on ovary weight and based on this Tier 1 rat study, the CEP Panel judged an effect on ovary weight as **Not Likely.**

Ovary histology (interstitial cell hypertrophy and follicle cysts):

91. For this exposure period one Tier 1 rat study (NTP Clarity Report, 2018/Camacho et al., 2019 was identified. In this, a statistically significant increase was observed in interstitial cell hypertrophy in the 2,500 and 25,000 µg/kg bw per day dose groups at the interim (1 year) sacrifice. In the same study, no change in follicular cysts was observed. The CEP Panel judged the effect on interstitial cell hypertrophy as Likely.

Uterus weight

92. For this exposure period two Tier 1 rat studies (NTP Clarity Report, 2018/Camacho et al., 2019; Leung et al., 2020 and one Tier 3 mouse study (Patel et al., 2013) were identified. No effect was seen on uterus weight in either of the Tier 1 studies. Based on this, the CEP Panel judged an effect on uterus weight as Not Likely.

Uterus histology

93. This endpoint included observations of squamous metaplasia, apoptosis, uterine dilation, endometrial hyperplasia and squamous metaplasia).

94. For this exposure period two Tier 1 rat studies (Leung et al., 2020; NTP Clarity Report, 2018/Camacho et al., 2019 were identified. In the Tier 1 rat study (Leung et al., 2020 – note this study is one of the grantee studies related to Clarity) no effects were observed on squamous metaplasia and apoptosis; the protocol was the same as for the Clarity study. However, in the Clarity study the

following statistically significant effects were observed at interim sacrifice (1 year): increased uterine dilation (250 µg/kg bw per day), increased endometrial hyperplasia (2.5 or 250 µg/kg bw per day), apoptosis and squamous metaplasia (25,000 µg/kg bw per day) and a decreased cystic endometrial hyperplasia (2.5 µg/kg bw per day). No other statistically significant effects were observed at interim or terminal sacrifice in this study.

95. During the exposure period developmental until adult, no effect was seen on squamous metaplasia and apoptosis in one of the Tier 1 rat studies (Leung et al., 2020, but in the other in which the exposure time and dose range (2.5, 25, 250, 2500 and 25000 µg/kg bw per day) was the same, an effect was only observed at the highest dose tested. The other histological effects were only seen at low concentrations (uterine dilation at 250 µg/kg bw per day and cystic endometrial hyperplasia (2.5 µg/kg bw per day)). Therefore, the CEP Panel considered the likelihood for this endpoint to be **ALAN.**

Number of implantation sites

96. In the Tier 1 rat study (Boudalia et al., 2014) the dams were exposed from GD1 to last day of lactation (LD21) by micropipette with 5 µg/kg bw BPA. The examination of the dams at LD/PND21 revealed no change in the number of implantation sites. As this study is a single-dose study, the CEP Panel considered the available study data to be Inadequate evidence for any further conclusions.

97. During developmental and adult exposure (pre-natal and/or post-natal in pups until adulthood), the CEP Panel assigned a likelihood level of Likely to the cluster female reproductive toxicity of BPA. As the likelihood level is Likely for the endpoint ovary histology (interstitial cell hypertrophy in the Tier 1 study (NTP Clarity Report, 2018/Camacho et al., 2019; this study was taken forward for BMD analysis; the Likely and ALAN endpoints were considered for uncertainty analysis.

Growth phase/young age exposure

Oestrus cyclicity

98. For this exposure period one Tier 1 mouse study in which oestrus cyclicity was studied, was identified (Li et al., 2016). Mice were dosed from PND22 for 5 weeks (3 times per day) orally (via micropipette) with 0, 60 and 600 µg/kg bw per day BPA. In the high-dose group, the oestrous cyclicity was decreased (the females spent less time in pro-estrus and oestrus and more time in met and diestrus).

99. The CEP Panel judged this endpoint as **ALAN.**

Implantation rate

100. The implantation incidence was decreased in a dose-dependent manner in a Tier 1 mouse study (Li et al., 2016), in which mice were fed split doses of BPA from PND22 for 5 weeks (0, 60 and 600 µg/kg bw per day).

101. The CEP Panel judged this endpoint as Likely.

102. During the growth phase/young age, the CEP Panel assigned a likelihood level of Likely to the cluster of female reproductive toxicity based on one Tier 1 mouse study (Li et al., 2016) in which the implantation incidence was decreased in a dose-dependent manner. This study was taken forward for BMD analysis and the Likely and ALAN endpoints were considered for uncertainty analysis.

Adult exposure (after puberty)

Plasma/serum thyroid hormones

103. For this exposure period one Tier 1 sheep study (Guignard et al., 2017) and one Tier 2 rat study (Zhang J et al., 2017) were identified. The female sheep in the Tier 1 study were injected s.c. with 5, 50 or 5000 µg/kg bw per day (equivalent to oral doses of 185/625; 1850/6250; 185000/625000 µg/kg bw per day depending on the conversion factor of 37 or 125 used). In this study, no effect was observed on total thyroxine (T4). A decrease was observed in total T3 at 50 µg/kg bw per day and in free T4 at 50 or 5000 µg/kg bw per day. An increase in reverse T3/T4 was observed at a s.c. dose of at 50 µg/kg bw per day (equivalent to oral dose of 1850/6250 µg/kg bw per day).

104. In the Tier 2 rat study (Zhang J et al., 2017) the female rats were dosed with 250 and 1000 µg/kg bw per day from 6 weeks of age for 64 weeks. In this study, a statistically significant increase was seen on free T4 at 1000 µg/kg bw per day and no changes in free thyroid triiodothyronine (T3).

105. The effects on T3 were judged as Not Likely as, at approximately the same dose, no effects were measured in rats (Zhang J et al., 2017), but an effect without dose relationship was seen in sheep; This was considered to be a variation.

106. The effects on T4 were judged as Not Likely as no dose–response was seen in sheep (Guignard et al., 2017) for FT4 and an effect in opposite direction (increase) was observed in rats (Zhang J et al., 2017) at a similar dose was observed.

107. In the sheep study (Guignard et al., 2017), the increase on reverse T3/T4 was only seen at 50 µg/kg bw per day, the mid dose. Therefore, this effect was judged as Not Likely.

108. During this exposure period the likelihood of changes in thyroid hormones (T3, T4, FT4 rT3/TT4) was considered as Not Likely by the CEP Panel as no consistent effects were observed in a Tier 2 study in rats and in a Tier 1 study in sheep.

Plasma/serum testosterone:

109. For this exposure period one Tier 3 rat study (Rashid et al., 2018) and two Tier 3 mouse studies (Hu et al., 2018; Xu XH et al., 2015) were identified. Therefore, the data were deemed Inadequate to judge the likelihood of an effect of BPA on testosterone levels. (Note; Hu et al., 2018 is listed as being Tier 2 in Annex F to the opinion which lists the animal studies used and their tiers).

Fertilisation rate:

110. One Tier 1 mouse study (Moore-Ambriz et al., 2015) in which the fertilisation rate was determined was identified for this exposure period. In adult female mice exposed from the day of the first oestrus until the completion of three oestrous cycles orally (via pipette) at a dose of 50 µg/kg bw per day, a decreased fertilisation rate was observed. However, as only one single-dose Tier 1 mouse study was available data were Inadequate to judge the likelihood of an effect on fertilisation rate.

Implantation rate:

111. Only one single-dose Tier 1 study (Boudalia et al., 2014) in rats and two Tier 3 studies in mice (Yuan et al., 2018; Dobrzynska et al., 2018) are available for this endpoint, the panel concluded that there was Inadequate evidence to conclude on a likelihood of an effect.

Oestrus cyclicity:

112. For this exposure period one Tier 1 study (Moore-Ambriz et al., 2015 and one Tier 3 study (Cao et al., 2018) in mice and one Tier 2 rat study (Zaid et al., 2014) were identified.

113. No effect on oestrous cyclicity was observed in the Tier 1 study in adult female mice, exposed orally (via pipette) from the day of the first oestrus until the completion of three oestrous cycles at a dose of 50 µg/kg bw per day (Moore-Ambriz et al., 2015). In the Tier 2 rat study (Zaid et al., 2014) the number of females which were in persistent diestrous was increased after daily dosing of 10000 µg/kg bw per day (single-dose level) from PND28 for 6 weeks.

114. No effect was seen in the lower dose (50 µg/kg bw per day) Tier 1 mouse study, but an effect at higher dose level, 10000 µg/kg bw per day was observed in the Tier 2 rat study; both studies were single-dose studies. The effect on oestrous cyclicity was judged **ALAN.**

Ovary weight

115. One Tier 2 rat study (Zaid et al., 2014) was identified for this exposure period. No change in absolute ovary weight was observed after daily dosing of female rats from PND28 for 6 weeks with 10000 µg/kg bw per day. Therefore, data were Inadequate to judge the likelihood of an effect on ovary weight.

Ovary histology

116. For this endpoint, observations were follicle count, premature activation of primordial follicles, large antral-like and atretic cystic-like follicles): For this exposure period one Tier 1 study (Moore-Ambriz et al., 2015) and one Tier 2 study (Hu et al., 2018) in mice and one Tier 2 rat study (Zaid et al., 2014) were identified.

117. No effect on follicle count was observed in adult female mice (Tier 1 study Moore-Ambriz et al., 2015 exposed orally (via pipette) from the day of the first oestrus until the completion of three oestrous cycles at a dose of 50 µg/kg bw per day. In the Tier 2 mouse study (Hu et al., 2018) a dose-related decrease was observed in the number of primordial follicles and the premature activation of primordial follicles in all dose groups; in this study adult (6 week old) female CD-1 mice were dosed orally for 28 days with 1 µg, 10 µg, 100 µg, 1000 µg and 10000 µg/kg bw per day (oral -route not stated). In the Tier 2 rat study (Zaid et al., 2014) female rats were dosed orally from PND28 for 6 weeks with 10000 µg/kg bw per day (the only dose tested). In this study, the numbers of atretic follicles, atretic

cystic-like and large antral-like follicles were increased in the BPA-treated group when compared with the controls.

118. The effects on ovary histology were judged as Likely. As the Tier 2 rat study (Zaid et al., 2014) is a single-dose study, only the Tier 2 mouse study (Hu et al., 2018 was taken forward for BMD analysis

Uterus histology

119. This endpoint included observations of gland nests density, gland nests.

120. For this exposure period a Tier 1 study in CD1 mice (Kendziorski and Belcher, 2015) and a Tier 3 study in C57Bl/6J mice (Kendziorski and Belcher, 2015 were identified. In the Tier 1 study, CD-1 mice were exposed for 12– 15 weeks via the diet to BPA doses equivalent to 4, 40, 400, 4000 and 40000 µg/kg bw per day. Gland nests density and the number of gland nests were increased in the high-dose group. The design of the Tier 3 study in C57Bl/6J mice was identical. In this study, no effect on the number of gland nests was observed but the gland nests density was increased in the 4, 4000 and 40000 µg/kg bw per day group. The reference related to strain differences and it is unclear why the study has a different tiering for each strain.

121. The likelihood of effects on uterus histology was considered as ALAN as gland nest number and density showed inconsistent effects; in the Tier 1 study in CD-1 mice an increase in gland nest number and density was observed only at the high dose, in the Tier 3 study with a low number of C57Bl/6J mice, varying effects were seen.

122. The CEP Panel assigned a likelihood level of Likely to the female reproductive toxicity cluster in the exposure period adulthood. The likelihood for the endpoint ovary histology is Likely. In a Tier 2 mouse study (Hu et al., 2018), a dose-related decrease in the number of primordial follicles and the premature activation of primordial follicles was observed. This study was taken forward for BMD analysis. In addition, an increase in follicle abnormalities was reported in a single dose rat Tier 2 study (Zaid et al., 2014). As this study tested only one dose, it was not taken forward for BMD analysis. The Likely and ALAN endpoints were also considered for uncertainty analysis.

Indirect (germline) exposure

123. For this exposure period five studies were assessed: three Tier 3 mouse studies (Ziv-Gal et al., 2015; Berger et al., 2016; Mahalingam et al., 2017), in which the F2 and F3 generation were studied and two Tier 3 mouse studies (Dobrzynska et al., 2015; Mahalingam et al., 2017) in which the F2 generation were studied. In the study by Ziv- Gal et al. (2015) the age at first oestrus, in the study by Dobrzynska et al. (2015) the embryo implantation incidence and in the study by Berger et al. (2016) and Mahalingam et al. (2017) the follicle count (ovary histology) were reported.

124. The CEP Panel noted that since for indirect (germline) exposure only Tier 3 studies were available, the likelihood for this endpoint could not be determined due to Inadequate evidence.

Overall cluster selection for endpoints/studies for BMD for female reproductive toxicity

125. Overall, the CEP Panel assigned a likelihood level of Likely, to the female reproductive toxicity cluster in the exposure periods developmental (pre-natal and/or post-natal until weaning), developmental and adult (pre-natal and/or post-natal until adulthood) and growth phase/young age, and of Inadequate Evidence in the adult and indirect (germline) exposure periods.

126. The overall likelihood across all exposure periods, i.e. the highest likelihood given in the cluster female reproductive toxicity was Likely.

127. The CEP Panel considered that the evidence from the studies available showed a:

- Likely effect for ovary weight (NTP Clarity Report, 2018/Camacho et al., 2019, for uterus histology (NTP Clarity Report, 2018/Camacho et al., 2019 and Vigezzi et al., 2015)
- Likely effect for ovary histology (NTP Clarity Report, 2018/Camacho et al., 2019) during the developmental exposure period,
- Likely effect for ovary histology (NTP Clarity Report, 2018/Camacho et al., 2019) during developmental and adult exposure and
- Likely effect for ovary histology (Hu et al., 2018) during adult exposure
- Likely effect for decreased implantation incidence during the growth phase (Li et al., 2016).

Therefore, these endpoints were taken forward for BMD analysis.