

█ comments or questions on defining a threshold:

8.Q: Abstract section: “The meta-analysis of the association between individual-level measures of fluoride and children’s IQ found a decrease of 1.58 IQ points (95% CI: –2.63, –0.53; p-value = 0.003) per 1-mg/L increase in urinary fluoride.”

█ **comment:** Was there a threshold for this effect?

Response: No change requested

- Because we used a linear model, there is no threshold for this effect.

- Note: After adding new studies the sentence has been updated:

“The meta-analysis of studies that reported individual-level measures of fluoride and children’s IQ scores found a decrease of 1.81 points (95% CI: –2.80, –0.81; p-value < 0.001) per 1-mg/L increase in urinary fluoride.”

BSC WG Assessment:

The BSC WG considers the NTP authors’ response to the reviewer’s comment inadequate.

Because the authors fit a linear term, a threshold was not assessed. Although the authors examined non-linear exposure forms and determined the linear term to be optimal, there are very few data points from studies in the low-dose range, reducing confidence in this range of exposure. The BSC WG recommends that the authors describe any change in the shape of the dose-response curve across the range of fluoride exposure. The BSC WG is concerned that failure to do so could mask better understanding of the potential inverse association between fluoride and IQ.

See Appendix II, page II-3.

8.R: Discussion section: “There is also evidence of a dose- response relationship between lower children’s IQ and higher fluoride exposures.”

█ **comment:** Was a threshold for such relationship considered?

Response: No change requested

- As previously mentioned, results for the dose-response relationship restricted to lower fluoride exposure levels (i.e., <4mg/L and <2mg/L, <1.5mg/L) in both drinking water and urine are reported in the supplemental materials.
- The restricted cubic splines model for water fit slightly better than the linear model, however there was no obvious threshold as illustrated by the figure at either of the modelled knots.