

## ATTACHMENT D

### POTENTIAL HEALTH EFFECTS OF FLUORIDE ON THE GUT MICROBIOME

The plurality of generally accepted scientific evidence does not support the hypothesis that fluoride ingestion has an adverse effect on the gut microbiome, certainly not at recommended levels of exposure.

Most of the peer-reviewed publications on the topic are animal studies, and those studies have had mixed results that cannot be extrapolated to human beings. In fact, one systematic review identified in FDA's May 13 press release for this meeting concluded that "none of the studies retrieved examined the effects of ingested fluoridated water on the human microbiome."<sup>1</sup>

Another systematic review cited in that press release included a total of two human studies, both of which were conducted in endemic fluorosis regions of China.<sup>2</sup> One was a cross-sectional study that included 32 adults who had skeletal fluorosis for at least 10 years and whose fluoride exposure was from indoor burning of coal with exceptionally high fluoride content and 33 healthy controls.<sup>3</sup> Skeletal fluorosis does not occur in the United States.

The other study included 9 children with dental fluorosis and 13 children without fluorosis.<sup>4</sup> Both studies had major limitations in design, conduct, and reporting, both were conducted in regions with levels of fluoride exposure that have no relevance to the United States, and neither study can determine whether fluoride ingestion alters the gut microbiome.

Another study included in that systematic review was a Chinese *ex vivo* experimental study in which investigators examined the microbiome in fecal samples from four young, healthy volunteers.<sup>5</sup> The researchers mixed fecal material with water with varying concentrations of fluoride (0, 1, 2, 10 and 15 mg fluoride per L) and measured changes in gut microbiome. They found no microbiome changes at 1 mg/L or 2 mg/L, the fluoride concentrations most relevant to exposure levels in the United States from fluoridated water or fluoride supplements.

The ADA would welcome additional research on this topic. But for now, the question of whether the human microbiome is altered by fluoride ingestion is just a hypothesis in search of a plurality of generally accepted evidence.

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<sup>1</sup> Moran GP, Zgaga L, Daly B, Harding M, Montgomery T. Does fluoride exposure impact on the human microbiome? *Toxicol Lett.* 2023 Apr 15;379:11-19. doi: 10.1016/j.toxlet.2023.03.001. Epub 2023 Mar 4. PMID: 36871794.

<sup>2</sup> Yasin M, Zohoori FV, Kumah EA, Subramanian M, Dean P, Orr CH. Effect of Fluoride on Gut Microbiota: A Systematic Review. *Nutr Rev.* 2025 Jul 1;83(7):e1853-e1880. doi: 10.1093/nutrit/nuae202. PMID: 40063073; PMCID: PMC12166178.

<sup>3</sup> Wang J, Yu C, Zhang J, Liu R, Xiao J. Aberrant gut microbiota and fecal metabolites in patients with coal-burning endemic fluorosis in Guizhou, China. *Environ Sci Pollut Res Int.* 2023 Jun;30(27):69913-69926. doi: 10.1007/s11356-023-27051-9. Epub 2023 May 4. PMID: 37140865.

<sup>4</sup> Zhou G, Li Q, Hou X, Wu H, Fu X, Wang G, Ma J, Cheng X, Yang Y, Chen R, Li Z, Yu F, Zhu J, Ba Y. Integrated 16S rDNA sequencing and metabolomics to explore the intestinal changes in children and rats with dental fluorosis. *Ecotoxicol Environ Saf.* 2023 Feb;251:114518. doi: 10.1016/j.ecoenv.2023.114518. Epub 2023 Jan 12. PMID: 36640576.

<sup>5</sup> Chen G, Hu P, Xu Z, Peng C, Wang Y, Wan X, Cai H. The beneficial or detrimental fluoride to gut microbiota depends on its dosages. *Ecotoxicol Environ Saf.* 2021 Feb;209:111732. doi: 10.1016/j.ecoenv.2020.111732. Epub 2020 Dec 26. PMID: 33373928.