Reviewer’s report

Title: Developmental Fluoride Neurotoxicity: An updated review

Version: 0 Date: 05 Oct 2019

Reviewer: Pamela DenBesten

Reviewer's report:

This manuscript reports a comprehensive assessment of fluoride related neurotoxicity. However, in its current format it is difficult to read, and needs to be reframed either as a comprehensive review of literature relating to neurotoxic effects of fluoride, or if remaining its current format, revised to clearly frame the recent epidemiological studies.

In the current format, while the abstract lays out a clear flow, the body of the manuscript does not seem to follow the abstract outline. The second paragraph (lines 53-58) lays out a somewhat confusing "roadmap", that should be clarified so that the reader knows the overall goals and structure of the paper. The paper currently lacks a Discussion section, and this should be added, with much of what is currently included in the Background and Results, moved into this section.

Specific Comments:

Abstract,

It should be clearly stated (if this is the case) that all of the studies reviewed since 2012 found a correlation between fluoride and neurotoxicity; or if otherwise, this should also be stated.

Background

Information should be included that will allow the reader to understand the relevance of the continuing review of recent studies, as described in the Methods. This should be done without drawing conclusions; these can be made in the Discussions/Conclusion section. For example, information included in the Background describing how fluoride affects the brain, including learning and memory in animal studies, seems more relevant in a Discussion section where the reasons for changes in IQ might be discussed.

line 77, include a second more updated reference, such as the article published by Featherstone et al. in the Journals of the American Dental Association, 2000.

Consider deleting the last sentence of the paragraph beginning in line 79, as the focus of this review is not to argue the benefits of water fluoridation for caries prevention. It could also possibly be moved to the discussion, where the data is put into context.
While information on fluoride crossing the blood brain barrier, and animal studies showing effects on learning and memory can be included in the background as a rationale to further assess neurotoxicity, this, and also most of the section on Experimental Neurotoxicity could be moved to the Discussion, where it adds support for the findings in the review of studies. For example the sentence in line 122, when moved to the discussion, can be used to point out that effects of fluoride, such as those found related to learning and memory in animal studies, could underline some of the findings of fluoride related effects on IQ.

The sentence beginning on line 174, stating that most animals studies of subchronic exposure did not include neonatal exposures etc, should be referenced or deleted, as it may not be accurate.

Methods

BMD and BMDL are defined and calculated, but then only 2 studies are mentioned? Does this mean that similar measurements are not available for the other studies? Please clarify.

Results:

It is confusing to begin this section with additional background. The results section should begin at line 332 (?) with the total number of cross sectional and prospective studies that were identified for review, as outlined in the Methods?

It seems that the section "Occupational and Endemic area studies" should be moved in part to the Background section, and in part to the Discussion.

Likewise, some the section on cross-sectional studies in exposed communities could be moved to the Methods and Discussion

Line 300, the previous 2012 meta- analysis published by this author, included in this Results results is confusing. These were previous results not current results? Likewise, in line 326, the discussion of the more recent 2018 published meta-analyses from China, should also be included in the discussion, rather than in the Results section.

Same question as to why discussion of prospective studies from New Zealand in prior to 2012, is included in the Results section?

Discussion:

There does not currently appear to be a Discussion section; only a short Conclusion section.

In summary, this is a comprehensive review of the literature that is included in both a Background and Results section of a paper reviewing recent epidemiological studies assessing an
association between fluoride and neurotoxicity. While comprehensive, as currently organized, the flow of the manuscript is difficult to follow and read. A reassessment of the focus and goals of this manuscript, and editing to reformat to meet these, should be done.

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