Comments on NTP Research Proposal - Fluoride and Developmental Neurotoxicity - by Dr Ken Perrott (MSoF)

I thank you for the opportunity to submit comments on this proposal.

As the proposal involves a systematic literature survey it would be pointless to submit my own survey. Instead I will select just a few papers to illustrate problems I think the project should consider in the survey and analysis of the literature. In a sense, my highlighting of these problems goes beyond a literature survey– it is more a suggestion that analysis of the literature should take into account some factors that may not be obvious in the literature itself.

I restrict my comments to the question of fluoride and developmental neurotoxicity in humans, rather than other animals.

In summary my concerns are related to the following areas:

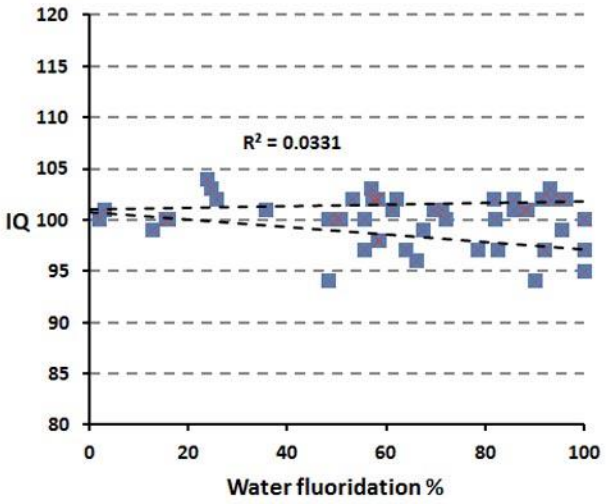
1. The need to clearly differentiate between studies relevant to low fluoride concentration used in community water fluoridation and studies in areas of endemic fluorosis where concentrations may be higher and symptoms of fluorosis are widespread.
2. The publication bias inherent in these sort of studies and the selection bias resulting from motivated searches and selected translation by an ideologically driven organisation opens up a possibility that the review could be skewed.
3. Problems inherent in cross-sectional studies such as the comparison of mean IQ values for two villages.
4. Problems inherent in statistical analyses where confounding factors are ignored or not properly incorporated in the analysis.
5. Problems arising from preoccupation with chemical toxicity hypotheses and ignoring other hypotheses related to psychological issues.

1: Relevance of studies to community water fluoridation or endemic fluorosis

The vast majority of studies to be considered relate to areas of endemic fluorosis. In fact, the study of Broadbent et al., (2014) may be the only one directly relevant to community water fluoridation (CWF). This did not find any statistically significant effects of CWF or IQ.

Considering the political controversy surrounding CWF there may be need for more studies like Broadbent et al., (2014). Especially as much of this controversy is fuelled by inappropriate use of studies from areas of endemic fluorosis or high dietary fluoride. In fact, data may already be publicly available for such studies and I hope more papers like that of Broadbent et al (2014) appear in the future.

I personally used some publicly available data for the USA to investigate this using the approach of Malin and Till (2015). Those authors did regression analyses for the state by state prevalence of ADHD against the state by state percentage of population with access to fluoridated water.



I used the IQ estimates by state in 2000 based on Scholastic Aptitude Test scores and percentage fluoridation for 1992. The correlation was not statistically significant at the 95% confidence level (data in graph). I have reported this simple investigation online at *IQ not influenced by water fluoridation.*

Anti-fluoride campaigners generally attempt to ignore (or argue against) Broadbent et al., (2014) and put a lot of effort into attempts to translate the studies from areas of endemic fluorosis to CWF. In the process they often gloss over problems like the higher dietary fluoride intake and the generally poor quality of most of these studies.

This is not to say such studies are worthless – they may in fact point to significant problems in areas of endemic fluorosis. But they are not relevant to CWF.

2: Objective factors which could skew the review's conclusions.

This area inevitably suffers from publication bias. Researchers may be less likely to publish data not supporting their hypothesis of fluoride influencing IQ. Despite this, there are a number of papers from such sources which contradict the majority favouring an effect of fluoride on IQ. For example, Eswar et al., (2011) did not find any statistically significant effect. And Hu and Yu (1989) reported no statistically significant difference in IQ for children from low and high fluoride villages. One can only speculate on the possibly of similar results being buried in the Chinese or Indian literature but not available in English for the proposed systematic review.

There is also a possibility of a selection bias. Not by the people involved in this systematic review. But by the simple fact that the available and accessible literature, is already objectively skewed because so many of the papers have been located by, and translated by, the Fluoride Action Network which have "irons in the fire" on this subject.

This has resulted in the artificial introduction into English language science journals of many papers from mostly Chinese sources - many of which are of poor quality and would have been otherwise obscure and probably not included in such a systematic review like this.

Given there is a strong reliance on these papers by those promoting a negative view of CWF I think the NTP need to keep this problem of preselection of studies by motivated translation in mind.

3: Problems with simple comparison of villages

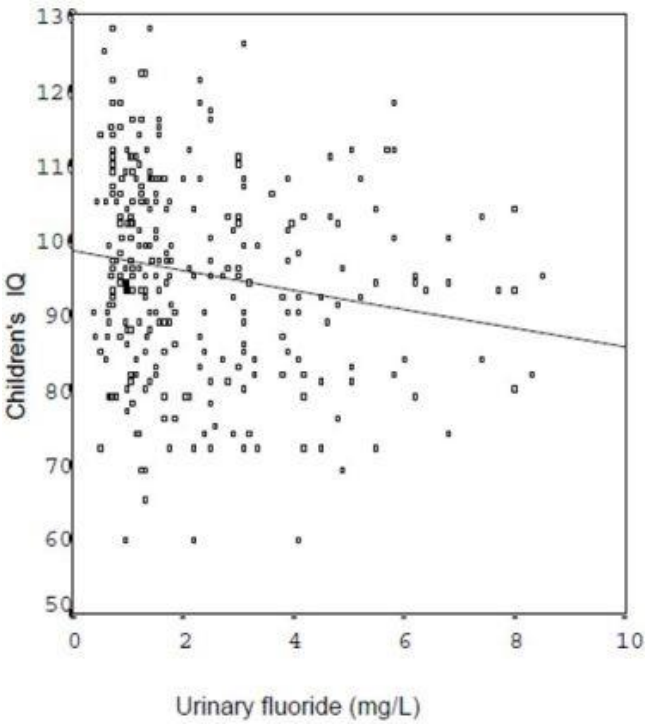
The epidemiological literature is full of studies where simple comparisons have been made between different regions. Such studies are easy to do but are prone to confirmation bias and often suffer from ignoring other confounding factors.

I hope reviewers will especially note that comparisons between villages like this suffer from scientific weaknesses that make them particularly available for motivated cherry-picking and

confirmation bias. They simply do not have the power or objectivity of studies based on data for individuals.

4: Regression analysis to determine correlations

The maxim "correlation does not mean causation" is well known. However, a regression analysis provides far more information than a simple comparison of average values often involved in cross-sectional studies.



Unfortunately, the fluoride and IQ literature rarely involves such regression analyses. But the following from Xiang et al., (2003) illustrates their advantages. This paper found a statistically significant difference in the average IQ values from children from a village with low levels of drinking water fluoride (mean IQ = 100.4; mean F = 0.36 mg/L) and one with higher levels (mean IQ = 92.0 mean F = 2.5 mg/L).

While Xiang et al., (2003) did not do a regression analysis involving drinking water fluoride they did do it for urinary fluoride (see figure). The correlation of IQ with urinary F was significant at the 95% confidence level but could explain only 3% of the variance in IQ (Pearson correlation coefficient –0.174, p = 0.003). This strongly suggests other factors are far more important. Once other factors are considered, it is likely that fluoride would have no explanatory power.

Even a simple glance at the scatter of the data in the figure will warn that confounding factors should not be neglected.

Unfortunately, Xiang et al., (2003) did not perform multiple regressions including possible confounding factors. Such checking was generally limited to comparing mean values of arsenic, iodine, education, etc., for the villages. This is really not an adequate check as a confounding factor may show up as significant in a regression analysis of the data for individuals but not be significantly different in a simple comparison of the means for each village.

We should note that this has not stopped anti-fluoride campaigners from misrepresenting such analyses. For example, activists from the Fluoride Action Network have cited Xiang et al., (2003) as showing a significant correlation of IQ with urinary fluoride without mentioning the fact that the correlation explains only 3% of the IQ variance. They have also claimed that confounding factors were "controlled for" when they were not included in the regression analyses.

Inclusion of confounding factors in a regression analysis is important even where the data appears favourable to one's preferred model. This can be seen with the paper of Malin & Till

(2015) where a significant correlation between ADHD prevalence and percent fluoridation was reported. This result was satisfying to anti-fluoride campaigners. But their study suffered from lack of consideration of important confounders. I showed in my article *ADHD linked to elevation not fluoridation* that more of the variance in ADHD was explained by a model including mean state elevation, house ownership and poverty (48%) than by their model which included only percent state fluoridation and a measure of socioeconomic status (22-31%). When elevation, home ownership and poverty were included in the multiple regression there was no significant contribution from CWF percent.

Huber et al (2015) used a similar analysis to Malin & Till (2015) and produced a better model involving elevation (38% of variance in ADHD explained). They included low birth weight, ethnicity, and household size as confounders.

5: Preoccupation with chemical toxicity means other confounders tend to be ignored.

I believe that while the literature usually used to imply a detrimental effect CWF on IQ is not relevant to CWF it may still be telling us something about the situation in areas of endemic fluorosis. However, preoccupation with a chemical toxicity mechanism may mean the real causes of cognitive deficits is being obscured.

Choi et al., (2015) performed a pilot study on Chinese children where, in contrast to the findings they reported in their previous metareview (Choi et al 2012), they did not find any significant effect of drinking water concentration on cognitive tests. However, they did report a significant effect of the prevalence of the more severe forms of dental fluorosis. They chose to interpret dental fluorosis as simply a measure of historic fluoride intake, rather than a possible factor in its own right.

This led me to suggest (Perrott 2015) they should, in future studies, include other possible causes in their considerations. In particular, I suggested they should consider the possible effect of the known role of dental fluorosis in decreasing quality of life.

I am unaware of studies specifically relating measured IQ to degree of dental fluorosis but the psychological effects of dental fluorosis, and other dental health problems like caries, are well reported. For example, Husain et al., (2014) discuss "Psychological Fluorosis:"

> *"Fluorosis may above all affect people socially and psychologically. Many fluorotic persons tend to hide their teeth and to constrain their smiles, and that may affect their personalities, their behaviour and their social potential for life time. This phenomenon is very well known in some regions and may be called "Psychological Fluorosis". This type of fluorosis is still to be studied and quantified professionally."*

Others have also used this term – for example:

> *"Psychological fluorosis: Life lasting tendency to constraint smile, unclear pronunciation and cover of mouth during conversation are phenomena that are often seen in fluorotic areas. Such behavioral attitudes that can be designated "Psychological fluorosis", may determine the socioeconomic potential of the victim.*

There are also scientific studies which consider psychological effects of dental fluorosis. For example:

The National Research Council's 2006 scientific review of EPA's standards for drinking water says in Chapter 6 – "Aesthetic and Psychological Consequences of Enamel Fluorosis:"

> *"The potential for psychological and behavioral problems to develop from the aesthetically displeasing consequences of enamel fluorosis has been a long-standing concern. In 1984, an ad hoc panel of behavioral scientists convened by the U.S. Environmental Protection Agency (EPA) and the National Institute of Mental Health to evaluate the issue concluded that "individuals who have suffered impaired dental appearance as a result of moderate and severe fluorosis are probably at increased risk for psychological and behavioral problems or difficulties" (R.E. Kleck, unpublished report, Nov. 17, 1984, as cited in 50 Fed. Reg. 20164 [1985]). The panel recommended research on the social, emotional, and behavioral effects of enamel fluorosis."*

Rodd & Davidson (1997) make the following comment on dental fluorosis:

> *"Although in its mild form the condition is not considered to be of cosmetic significance, the more severe forms can cause great psychological distress to the affected individual. "*

De Castilho et al., (2009) surveyed attitudes toward dental fluorosis and its effect on the life and prospects of sufferers: They reported:

> *"Lesions from severe dental fluorosis appear to be a stigmatizing factor and have contributed toward suffering and self-exclusion among an entire generation of adolescents and young people."*

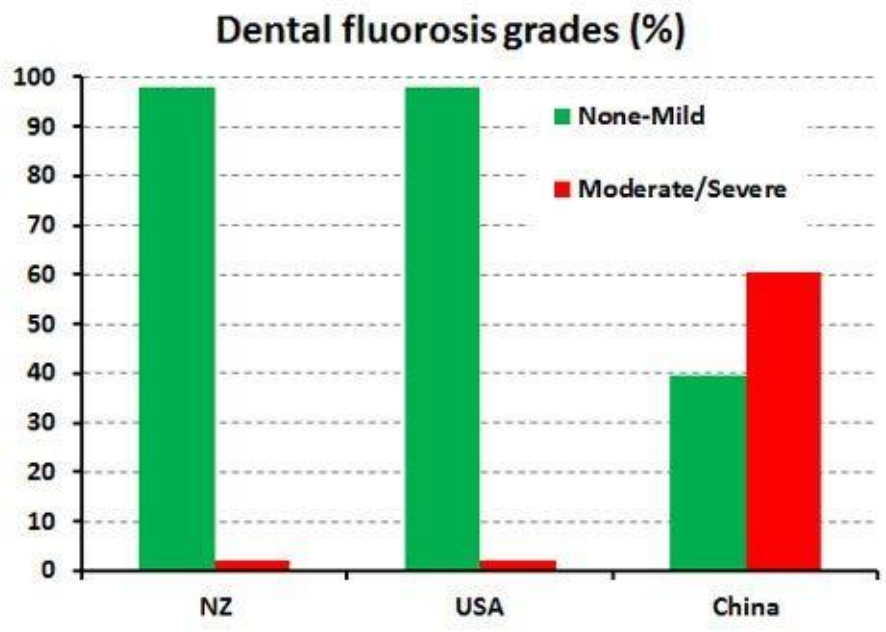
Severe dental fluorosis not a problem where CWF is used.

Just maybe, fluoride in drinking water is not directly implicated in the measured IQ deficits reported for areas of endemic fluorosis. Maybe the direct effect is from severe and moderate dental fluorosis as discussed above. But this should not be used to argue that dental fluorosis could affect IQ where CWF is used.

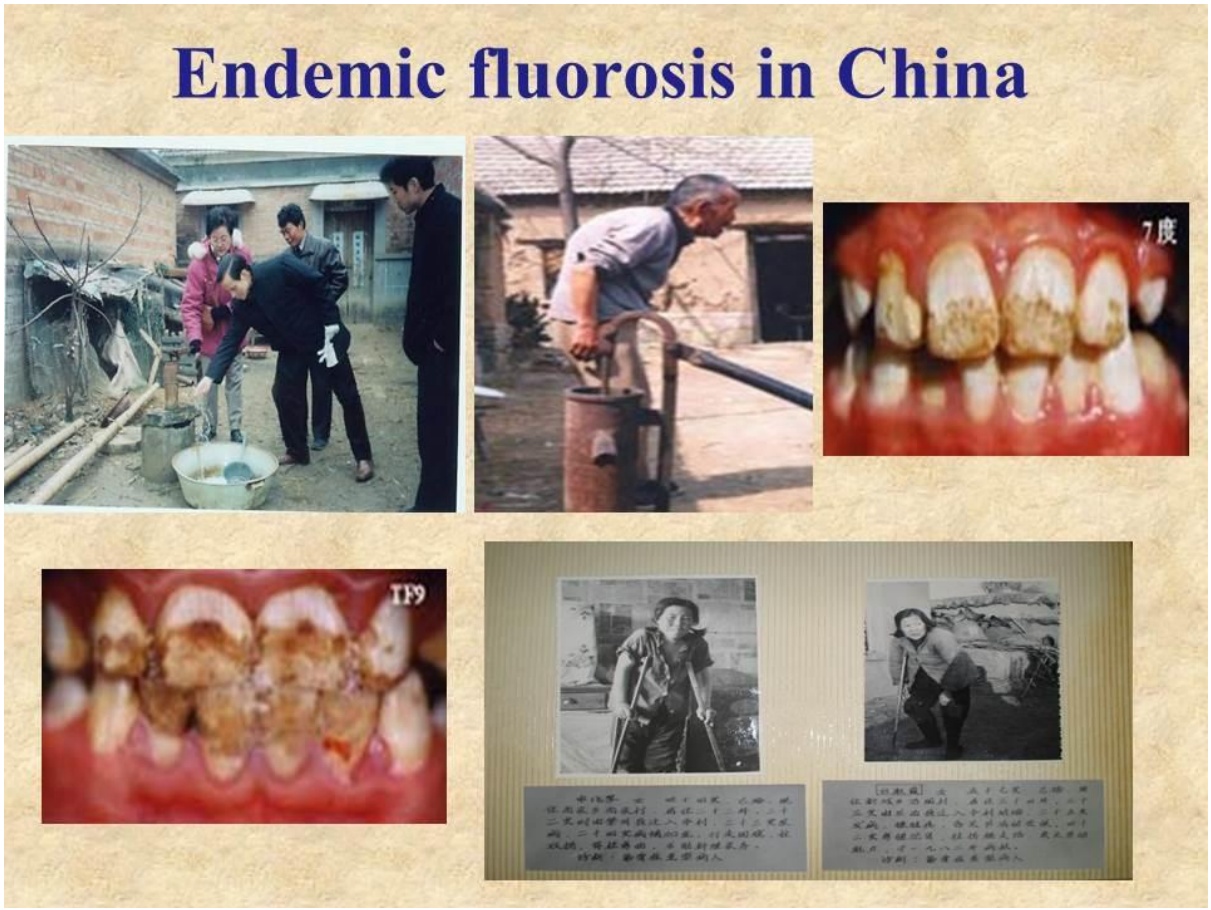
The important difference is that where CWF is used the moderate and severe forms of dental fluorosis which could be related to IQ deficits are only present in very small amounts and are not caused by CWF. For example, Riordan (1993) reported that CWF is not a risk factor for incidence of the more severe forms of dental fluorosis:

> *"Major risk factors for more severe fluorosis (TF ≥2) were early weaning and swallowing toothpaste (ORs 2.77 and 2.64, respectively).* ***Residence in a fluoridated area (OR 2.2) was not a statistically significant risk factor.*** *These findings confirm a high prevalence of mild fluorosis among children who have been exposed to fluoride in their earliest years." [My emphasis.]*

I can highlight this by comparing the prevalence of milder forms of dental fluorosis and the moderate and severe forms for countries like USA and New Zealand compared with China. Here I use the data for dental fluorosis in China from Choi et al., (2015) compared with that in New Zealand (MoH 2010) and the USA (Beltrán-aguilar & Barker 2010).



Finally, this image used by Xiang (2014) in a presentation to a Fluoride Action Network conference illustrates the special problems in areas of endemic fluorosis where most of the studies to be reviewed took place. This image should be a warning about the translation of these studies to countries which do not suffer the illustrated problems – countries like USA and New Zealand where CWF is used.



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Making Sense of Fluoride, Inc.