

March 14, 2022

to: Univ. of North Carolina Chapel Hill, Office of Human Research Ethics (OHRE), Office of Director; Institutional Review Board (IRB); and IRB Compliance Office

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RE: Concerns about IRB ethical evaluation of “waterBEST” study

Dear OHRE Director, and Chair and members of the IRB:

We wish to bring to your attention serious concerns about a proposed human research study that we understand you are currently evaluating.

The study name is “Phase II, proof-of-concept randomized controlled trial to evaluate dental caries preventive effects of fluoridated bottle water” and the Principal Investigator is Dr. Gary Slade. The University of North Carolina, Chapel Hill, is the awardee for the funding of this project. Another name for the project is “Water From Bottles to Establish Strong Teeth (waterBEST)”.

Information on the project proposal is available from these websites:

<https://clinicaltrials.gov/ct2/show/NCT04893681>

NIH project number: 4UH3DE029169-02

https://reporter.nih.gov/search/lrwKQDUHGUKLBQDy_kJS-A/project-details/10458235

The project's website:

<https://waterbeststudy.com/>

The concerns with this study arise under five of the Guiding Principles for Ethical Research set forth by the National Institutes of Health (NIH), available at these websites:

<https://www.nih.gov/health-information/nih-clinical-research-trials-you/guiding-principles-ethical-research> and <https://www.cc.nih.gov/recruit/ethics.html>

The five principles we believe this study may violate are:

- **Favorable risk-benefit ratio**
- **Informed consent**
- **Independent review**
- **Fair subject selection**
- **Scientific validity**

Favorable risk-benefit ratio

The NIH Guideline requiring a **Favorable risk-benefit ratio** states:

Everything should be done to minimize the risks and inconvenience to research participants to maximize the potential benefits, and to determine that the potential benefits are proportionate to, or outweigh, the risks.

In the information available at the clinicaltrials.gov website, at the NIH's reporter.NIH.org website, and at the project's own waterBESTstudy.org website, there is no mention of any risks. There are also no quantitative estimates of the benefits which are only described as "uncertain".

The study protocol and documentation seem to have excluded mention of the strong evidence that early life fluoride exposure poses a serious neurodevelopmental risk. The National Research Council (NRC) first drew attention to this concern in 2006 in an extensive review of fluoride toxicity [[NRC 2006](#)]. The NRC recommended new rigorous research be conducted on this question. Responding to that recommendation, NIH has funded several such studies that confirmed the earlier studies finding adverse neurodevelopmental effects, including reduced IQ and greater risk of ADHD in children. In light of the accumulating evidence, in 2015 the National Toxicology Program (NTP) of NIEHS/NIH commenced a comprehensive systematic review of studies of fluoride developmental neurotoxicity. The NTP's literature search identified 159 relevant human epidemiological studies and over 300 animal studies. A large majority of the epidemiological studies found statistically significant adverse effects, such as reduced IQ. The NTP rated 27 of the studies as being of high quality (low risk of bias). Of these 27 studies, 25 found statistically significant adverse neurobehavioral effects, and 15 were at exposure levels the NTP considered directly applicable to exposures from artificially fluoridated water [[NTP 2020](#), [Neurath 2020a](#), [Neurath 2020b](#)].

The studies identified by NTP are remarkably consistent in finding large magnitude adverse effects. The size of the IQ losses has been described by experts, including the editor of *JAMA Pediatrics* as "on par with that from lead" [[Christakis & Rivara 2019](#)]. A meta-analysis conducted by the NTP of 49 studies found a pooled estimate of -7 IQ points for the children with higher fluoride exposure compared to the children with lower exposure.

One of the higher quality studies is especially relevant to the proposed waterBEST study because it focused on fluoridated water exposures in the same infancy age range as waterBEST proposes to recruit from [[Till 2020](#)]. This NIH-funded study was of a Canadian cohort and found that amongst infants who were primarily formula-fed with formula made up from tap water, the loss of IQ was -4.4 IQ points for each 0.5 mg/L increase in water fluoride concentration. The waterBEST study description at clinicaltrials.gov says the treatment group of children, who will be recruited between 2 and 6 months of age, will receive water with a fluoride concentration of 0.8 mg/L. These children therefore risk losing an average of -7 IQ points. Furthermore, several recent studies have found that children with certain genetic variants may experience 5x greater loss of IQ from fluoride than the average loss in children who do not have those variants. These more susceptible children would be at risk to potentially lose -35 IQ points, an extremely severe permanent adverse effect [[Zhang 2015](#), [Cui 2020](#), [Wang 2021](#), [Zhao 2021](#)]. But even a loss of 7 IQ points is very serious and has been estimated by economists as being associated with a lifetime loss of earnings of about \$140,000 per person [[Grosse 2007](#)].

The magnitude of these neurodevelopmental risks is out of all proportion to any possible dental benefits the waterBEST study intends to investigate. This study therefore violates any prudent interpretation of having a “Favorable risk-benefit ratio”.

The only mention of possible neurodevelopmental risk from early life fluoride exposure found in the publicly available materials about the waterBEST study comes from a “fact sheet” linked from the waterBest.org website, titled “Community Water Fluoridation”. But instead of providing any scientific information, it dismisses the risk with a blanket statement claiming a lack of scientific evidence, referencing reports that are more than 16 years out of date:

Safe

No convincing scientific evidence has been found linking community water fluoridation (CWF) with any potential adverse health effect or systemic disorder such as ... low intelligence ... ^{4,6}.

References 4 and 6 are from 2000 and 2006. They did not consider the NRC 2006 review, the current NTP systematic review, or the dozens of high quality studies published since 2006 [most recently: [Zhou 2021](#), [Zhao 2021](#), [Yu 2021](#), [Farmus 2021](#), [Till 2020](#), [Cui 2020](#), [Wang 2020](#), [Green 2019](#), [Riddell 2019](#), [Bashash 2018](#), [Bashash 2017](#), [Valdez Jiménez 2017](#)].

The Declaration of Helsinki states that “Medical research involving human subjects must ... be based on a thorough knowledge of the scientific literature” [[World Medical Association 2013](#)]. Given the lack of any mention of the risk of neurotoxicity in the waterBEST study materials, it appears this project is not based on a thorough knowledge of the scientific literature of fluoride risks.

In a legal deposition, under oath, Principal Investigator Dr. Gary Slade acknowledged that he was not an expert in any non-dental effects of fluoride and had never conducted any original research on any adverse effects, including neurotoxicity. He also acknowledged he had never done original research on dental effects of fluoride exposure during the first year of life. He also stated he was not an expert on risk-benefit assessment and would not undertake to assess the risk-benefit ratio between dental benefits and neurodevelopmental harms [Slade deposition 2019, see Appendix A below].

In his deposition, Dr. Slade also acknowledges several reasons for the uncertainty of dental benefits from fluoridated water. He acknowledges that very few studies have ever been blinded, that none of his own studies of fluoride and dental caries have used blinding, that lack of blinding can introduce bias in the direction favored by the researchers, and that no RCT has ever been done with fluoridated water [Slade deposition 2019, see Appendix B below].

Based on the information available to us, it appears Dr. Slade has neither attempted to assess the risk-benefit ratio of neurodevelopmental harm against reduced dental caries, nor attempted to acquire “a thorough knowledge of the scientific literature” on the risks, as required under the Declaration of Helsinki principles. His lack of expertise in non-dental effects of fluoride and his acknowledgement that he is not qualified to do risk-benefit assessments are not acceptable excuses for the apparent absence of one in his study proposal.

Informed Consent

The lack of any mention of neurotoxic risks raises serious concerns about whether the waterBEST study meets the NIH Guidelines for **Informed Consent**:

Potential participants should make their own decision about whether they want to participate or continue participating in research. This is done through a process of informed consent in which individuals (1) are **accurately informed** of the purpose, methods, **risks**, benefits, and alternatives to the research, (2) **understand this information** and how it relates to their own clinical situation or interests, and (3) make a **voluntary** decision about whether to participate. [emphasis added]

We have requested the Informed Consent form from Dr. Slade but have not yet received a copy. Based on the publicly available information about the waterBEST study, we are concerned the proposal has little or no accurate information about the potential neurodevelopmental risks to participating children.

We are also concerned that in a published article about public messaging to improve chances of winning local political referendums on water fluoridation, Dr. Slade, the senior author, says:

Given that the average person does not understand fluoridation scientifically ... mixed messages that introduce even some uncertainty should be enough to lead to a rejection at the polls." [Curriel 2018].

Based on this statement by Dr. Slade, we are concerned that if he was asked to accurately inform participants of the neurodevelopmental risks of his study, he might choose to avoid "mixed messages" and downplay the evidence for risks, so as to limit rejections of participation.

The NIH **Informed Consent** guideline also requires that the consent be given voluntarily. The waterBEST study proposes to recruit participants from an area with a high proportion of people living in poverty and with a high proportion of Blacks and Hispanics. The proposed study would give participants free annual dental exams, free home-delivered bottled water for 3½ years, a water cooler, shelves for water bottles, infant bottles, sippy cups, and \$480 in cash compensation. These inducements bring into question whether participation will be entirely voluntary, or whether some in this vulnerable population may agree to participate because of the substantial, for them, financial and health care inducements.

Fair subject selection

The primary basis for recruiting participants should be the scientific goals of the study — not **vulnerability**, privilege, or other unrelated factors. [NIH ethics guidelines]

The issue of the **vulnerability** of participants, although not elaborated on in this summary, is the underlying impetus to all research ethics rules and guidelines. The NIH website says:

The ethical guidelines in place today were primarily a response to past abuses, the most notorious of which in America was an experiment in Tuskegee, Alabama, in which treatment was withheld from 400 African American men with syphilis so that scientists could study the course of the disease. Various ethical guidelines were developed in the 20th century in response to such studies. [NIH ethics website]

The Lenoir County NC population is more than 50% non-white, with 40% Black, 8% Hispanic, and 3% other non-white [[censusreporter.org](https://www.censusreporter.org)]. This puts Lenoir County in the [top rankings](#) for percentage Black population amongst North Carolina counties. The percent of persons below the poverty line is 22%, which is also in the [top rankings](#) in North Carolina.

The inducements of free annual dental exams, free home-delivered bottled water for 3½ years, a water cooler, shelves for water bottles, infant bottles, sippy cups, and \$480 in cash compensation would likely exceed a value of \$1000 per participant. The offer of free annual dental exams is also a substantial inducement in a population that may otherwise have great difficulty in obtaining this basic health service.

The community chosen for this study can be considered to be vulnerable because of race, poverty, and because they are infants and young children. The financial inducements may further compromise the ethical guideline requirement that participation be completely voluntary.

The Declaration of Helsinki says “All vulnerable groups and individuals should receive specifically considered protection” [[World Medical Association 2013](#)].

Instead of special protection, there is the appearance this group was selected by the researchers because its vulnerabilities might make for easier recruitment of participants, a direct violation of the ethical principle of **Fair subject selection**.

Independent Review

We have serious concerns for Dr. Slade’s objectivity, which is a requirement under the NIH Guideline principle of **Independent Review**. NIH describes the key factors to consider during **Independent Review**:

To minimize potential **conflicts of interest** and make sure a study is ethically acceptable before it starts, an independent review panel should review the proposal and ask important questions, including: ***Are those conducting the trial sufficiently free of bias? Is the study doing all it can to protect research participants? Has the trial been ethically designed and is the risk–benefit ratio favorable?*** The panel also monitors a study while it is ongoing. [emphasis added]

We believe Dr. Slade has serious conflicts of interest, including direct financial conflicts. In 2018 Dr. Slade was recruited as a paid expert witness in a civil lawsuit, the subject of which was the neurotoxic risks of water fluoridation. He was asked to testify on the dental benefits of water fluoridation. Dr. Slade reported being compensated at the rate of \$100 per hour and had signed a contract with a total estimated fee of \$22,400 for his work for the defendant in the case, the US EPA [Slade 2019 deposition transcript, see Appendix C below].

In addition to this paid work to help defend water fluoridation in a civil lawsuit, there is evidence of Dr. Slade’s bias in promotion of water fluoridation by his membership in the Scientific Advisory Board of the advocacy organization, The American Fluoridation Society. Under oath, in his deposition, Dr. Slade said he shared the goals of the American Fluoridation Society, which are to promote and extend fluoridation in the USA, including by means of lobbying in local political campaigns [Slade 2019 deposition transcript, see Appendix D below]. Dr. Slade himself

participated in such lobbying to promote fluoridation in at least one instance, in Green Bay WI, where he defended fluoridation to local officials [archived video of public hearing, Green Bay WI, <https://www.youtube.com/watch?v=zodhMbzoJf0> at 33:33 min:sec].

Additional evidence of bias is found in several papers co-authored by Dr. Slade, in the NIH grant application, and in the waterBEST website [[Curiel 2018](#), [Curiel 2019](#), [NIH Reporter.org](#), [waterBEST.org](#)]. The NIH grant application summary justifies the study as a way to try to extend fluoridated water use in the USA:

[Fluoridation benefits] have never been tested in a randomized controlled trial (RCT). Instead ... community intervention studies were sufficient to justify addition of fluoride to many public water systems ... and to defend against fluoridation's critics. However, growth in fluoridated public water systems has stalled, leaving 100 million Americans living in places that do not have fluoridated water....

An underlying assumption in this grant application is that fluoridation needs to be defended against its critics so that fluoridated water can be extended to more Americans. Dr. Slade does not appear to be an objective researcher balancing risks and benefits in the design of the waterBEST study. His goal appears to be a study which will help campaigns to extend the use of fluoridated water.

Scientific validity

Finally, the proposed study has a fundamental weakness in terms of scientific validity. The placebo group's water will come from a different water source than the treatment group's water [[clinicaltrials.gov](#)]. Numerous minerals and contaminants in drinking water have been found or suspected to alter caries risk [[Doğan 2018](#), [Qamar 2017](#), [Pathak 2016](#), [Lippert 2013](#), [Curzon 1978](#)]. By not using identical water in the two groups, except for added fluoride, this study will not be able to rule out the possibility that any treatment-related effects are actually caused by some factor(s) other than fluoride. This violates basic RCT design principles.

SUMMARY

We have very serious concerns that the waterBEST study and its Principal Investigator, Dr. Gary Slade, violate ethical guidelines for human research, as codified by NIH and other groups. The study proposes to recruit from a vulnerable population, and expose them to a substance at levels that have been found to pose a substantial risk of developmental neurotoxicity that may result in lowering the children's IQ and other serious harms. The only conjectured benefit is a reduction in dental caries, of unknown magnitude. The NIH grant proposal acknowledges uncertainty of the "effect size of the intervention":

... RCT evidence of dental health benefits of fluoridated bottled water will be essential if public health is to embrace it as **a strategy to extend fluoridation**. In the absence of a precedent, and in the face of **uncertainty** as to compliance and **likely effect size** of the intervention [[NIH RePORTER](#)] [emphasis added]

This quote also suggests an underlying agenda of the study is to try to provide support for “a strategy to extend fluoridation”.

We do not believe this study, in this age group, could ever meet ethical guidelines because of its highly *unfavorable* risk-benefit ratio. The risks are much worse than any conceivable dental benefits. Losing 7 IQ points to save any number of cavities is not an acceptable trade-off. Furthermore, the researchers themselves acknowledge the benefits are uncertain.

We request that you consider these serious problems with this project as soon as possible. We urge the IRB to immediately put the study on hold to prevent the risk of permanent harm to the children.

We would be happy to provide more information and would also welcome further discussion and the opportunity to meet with OHRE or the IRB on this matter.

We hope OHRE and the IRB will appreciate the seriousness of these concerns. We request a prompt response and acknowledgement of receipt of this notification.

Sincerely,

Paul Connett

Paul Connett, PhD
Executive Director, American Environmental Health Studies Project (AEHSP) and Fluoride Action Network (FAN)

Dr. Connett is a graduate of Cambridge University, with a doctorate in chemistry from Dartmouth College. He taught chemistry and environmental toxicology at St. Lawrence University for 23 years. His areas of expertise include: interaction of metals with biological systems (chromium, lead); build-up of dioxins in food chains; health risk assessment; the problems, dangers and alternatives to incineration; resource management for a sustainable society (Zero Waste); the toxicity of fluoride and the dangers of fluoridation. He is co-author of the book *The Case Against Fluoride* (2011). He has been invited to testify on fluoride toxicity before numerous government and scientific bodies, including the National Academies of Science.

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APPENDICES

from Slade Deposition, August 13, 2019

From the deposition of Dr. Gary Slade, taken August 13, 2019 for the lawsuit:

IN THE UNITED STATES DISTRICT COURT FOR THE NORTHERN DISTRICT OF CALIFORNIA AT SAN FRANCISCO

FOOD & WATER WATCH, et al. Plaintiffs

versus

U.S. ENVIRONMENTAL PROTECTION AGENCY, et al. Defendants

Civ. No. 17-CV-02162-EMC

Appendix A

- Dr. Slade acknowledges not expert in non-dental effects of fluoride, in neurotoxicity, in risk-benefit analysis, and has never done a study looking at fluoride's effects from exposure in first year of life

Q Do you consider yourself an expert on any nondental health effects of fluoride?

A [Dr. Slade:] Well, I am struggling to think of any. If someone read off a long, long list, hypothetically there may be something that I have some expertise in that I'm just not coming to mind.

Q Well, let me then give you some examples. Do you consider yourself an expert on the neurological effects of fluoride?

A I do not have above, you know, undergraduate training in neurologic disease. I have had some passing involvement in my professional career with studies that were investigating dental amalgam and its potential effects on cognitive development and IQ.

So I had some passing familiarity with the field. Again, I am not calling myself an expert because I am not exactly sure what that word means.

Q Well, my question was about fluoride's neurological effects. Do you consider yourself an expert on fluoride's neurological effects?

A So I was answering about neurological disease and cognitive development. My experience with it was in that instance with amalgam. I do not call myself an expert on neurologic effects of

fluoride.

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Q Well, but what you've -- correct me if I'm wrong, but what you've just told me is you've published studies on the effectiveness of water fluoridation during childhood and childhood includes infancy. That's a broader umbrella than I'm referring to here.

I am asking if you have any studies that you've ever done which specifically present data on the effectiveness or lack thereof of fluoride exposure during the first year of life.

A So if this will help, I'm trying to think of instances where I've looked at, say -- presented tables of figures for showing fluoride exposure for this part of life versus that part of life, you know, maybe through adolescence and then adulthood, that kind of thing or that generational example.

I cannot think right now of a table that would have zero to one being, say, an exposure window. Now, if you can find one I will stand corrected, but as we're speaking now, I'm struggling to remember anything at that level that you have just described.

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Q So you know this case is dealing with neurological effects of fluoride, right?

A I believe it's -- that is one of the factors being considered.

Q Now, I know that you -- it's your opinion that water fluoridation is safe. So the questions I'm about to ask you I'm not asking you to change your opinion on that or to -- I know that you think it's safe. I'm going to ask you some hypothetical questions here; do you understand that?

A Sure.

Q But again, just to be clear, under this hypothetical you are convinced that the quality of evidence shows that water fluoridation causes mental retardation. At that point you would still need to do a risk/benefit analysis before you made your decision; is that correct?

A Well, I would want to see evidence of competing risks and benefits. So I

wouldn't necessarily -- I would not do those studies. I mean I'm not a harm/benefit type of analyst.

Appendix B

- Slade acknowledges lack of blinding can bias studies
- Slade has never done studies of fluoride and caries that used blinding
- No RCT of fluoridated water has ever been done by anyone

Q Are you aware that there have been meta-reviews published that have looked at and examined various types of health interventions to assess the effect of lack of blinding?

A I have general knowledge of that area. I mean, I teach some of this stuff to students and I make mention of that. A meta-analysis I don't recall having seen recently. No, I don't recall having seen a meta-analysis. Can you give me an example?

Q Well, I'm just asking for your awareness. So are you aware that some meta-reviews have been conducted to assess the effect of lack of blinding, and these meta-reviews have concluded that the lack of blinding is associated with an increased effect size in the ballpark of 25 to 30 percent?

A So you said meta-reviews. They sound like systematic reviews with meta-analysis that -- and if they were done in clinical trials, I could imagine that has been done. But I have -- I am not familiar with the specific studies. I suspect -- so I am not familiar with the specific study.

Q Does it surprise you to hear that meta-reviews have found that the lack of blinding is associated with an increased effect size in the ballpark of 25 to 30 percent?

A I'd want to read the studies. If we're talking about studies of treatments, you know, typical randomized control trials of therapy, you know, I -- the typical expectation is that the source of bias inflates effect estimates.

Q Okay.

A Now, if someone's done a -- you said meta-review. If someone's done a meta-analysis to quantify it, I'd be very interested to read it from my general teaching and knowledge.

Q How many of the epidemiological studies of fluoridation and caries have used a blinding procedure?

A So now we're talking about blinding of examiners, let's say, to the exposure status of the kids. Oh, not many.

Q Have any of your studies involved blinded examiners?

A Boy.

Q Any of your epidemiological studies of fluoridation and caries, have any of them used blinded examiners?

A So my studies, I haven't taken specific steps to blind examiners in my studies.

Q Okay. Now, how many -- can you -- how many studies are you aware of, epidemiological studies of fluoridation and caries, that have used blinded examiners?

A There's one, was it in Scotland, a little island or somewhere up North Country, and I believe also -- and certainly done it for radiographic-type assessments, and that's why I'm hesitating to say that none of my studies.

Marnie, I don't -- he probably doesn't use radiographs, but Hopcraft did, I reckon, and I think that was blinded. But I'm not a coauthor on that study.

So there has been a few. I'd hesitate to put a number on it.

Q Fair to say that you could count on one hand the number of studies on fluoridation and caries that have used blinded examiners?

A The studies that I know of that I can think of right now, that sort of number is what comes to mind.

Q Now, those early intervention studies by Arnold and Dean, none of those were blinded, right?

A Look, the vast majority were not. If there was an exception, I don't remember it. So I would say they're not blinded.

Q And none of those early studies by Dean, Arnold and others were -- used a randomized procedure, correct?

A Well, to randomly allocate, you mean, which is --

Q Right.

A No, they didn't. There would be no randomized control trial of, say, fluoride in drinking water.

Q Okay. So let me -- I don't think I asked you that. There has been -- there has never been an RCT of water fluoridation, correct?

A No randomized control trial of water

fluoridation's effect on dental caries, no.

Appendix C

- Dr. Slade paid to defend fluoridation in federal lawsuit

Q So when were you first asked to serve as an expert in this litigation?

A A little over a year ago. The exact date, maybe in the first half of last year.

Q So some point maybe in the summer of 2018?

A Maybe even a bit earlier.

Q And so your estimated costs at that time in, what, November of 2018 was a total of \$22,400 for your work in this case?

A Yes, that's what it's estimated at on this back side, yes.

Q Now, besides counsel -- and your hourly rate in this case is \$100, correct?

A Correct, \$100 an hour.

Appendix D

- Dr. Slade an advocate for expanding water fluoridation

Q Okay. Now Dr. Slade, you are an advocate of water fluoridation, correct?

A So I have published papers describing my interpretation of results to show that fluoridation is effective in preventing dental caries as a public health dentist. Advocacy is part of public health practice so I advocate for dental health in general and children's dental health and prevention. So I advocate for fluoridation as a -- and fluorides -- as a part of that.

So that is the extent of my advocacy.

Q You're also on the Scientific Advisory Board of the American Fluoridation Society, correct?

A Yes.

Q And the American Fluoridation Society is an organization that is dedicated to promoting water fluoridation, correct?

A That's correct.

Q Do you feel in any way uncomfortable saying that you want to do what you can to promote the expansion of fluoridated water throughout this country?

A Uncomfortable. I do advocate for expansion of fluoridation. My comfort -- I am just struggling to understand the comfort part of that question.