International Peer Review of the Royal Society/PM Science Advisor's Office Fluoridation Review: *Health effects of water fluoridation: A review of the scientific evidence*

The Report was sent to five independent international experts for peer review. Two of these were members of the US National Research Council (NRC) review panel, whose report was published in 2006 following three years of reviewing the scientific literature. The reviewers were chosen for their particular expertise on the science around fluoridation, and their standing in the scientific community.

The following review was prepared by Dr Kathleen Thiessen, PhD, Environmental Risk Specialist on the NRC panel.

This review is endorsed by Dr Hardy Limeback, PhD, the second former NRC panel member, and Head of Preventive Dentistry, University of Toronto; Spedding Micklem, PhD, and James Beck PhD, co-authors of *The Case Against Fluoride*, a critically acclaimed contribution to the fluoridation debate.

The fifth reviewer is finalizing a more detailed review of the neurotoxicity question, which is an area of current focus for him. That review will be added in due course.

A third review is currently in draft, and will be added once finalized.

Dr Beck has also authorized publication of the following comment:

> "This report is a clear example of cherry picking, where only select studies that support the 'safe and effective' viewpoint were cited.
> It is far from a REALLY critical review of the literature. It is NOT a meta analysis."

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Comments on the RSNZ/OPMCSA report on "Health effects of water fluoridation: A review of the scientific evidence"

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The following comments do not constitute a thorough critique of the RSNZ report. I have primarily tried to give examples of the lack of scientific rigor in the report, including several inconsistencies and inaccuracies contained in the report. Page numbers below refer to the RSNZ report unless otherwise stated.

(1) General comment

This report from the Royal Society of New Zealand and the Office of the Prime Minister's Chief Science Advisor in general falls short of the standards one expects for a "review of the scientific evidence" and instead seems to concentrate on demonstrating a consensus favoring community water fluoridation (CWF). For example, "the scientific consensus confirmed in this review" (p. 5); "Analysis of the peer-reviewed scientific literature reveals a clear consensus on the effectiveness of CWF" (p. 16); "the weight of peer-reviewed evidence supporting the benefits of water fluoridation at the levels used in New Zealand is substantial, and is not considered to be in dispute in the scientific literature" (p. 16); and "while the scientific consensus is that these [cancer, effects on cognitive development of children] are not significant risks" (p. 16).

The review mentions that "the effectiveness of CWF continues to be questioned by a small but vocal minority" (p. 16), but fails to acknowledge that both the safety and efficacy of CWF have been questioned for decades by scientists, physicians, dentists, and other professionals, based on the available evidence. For example, a 1944 editorial in the Journal of the American Dental Association stated that the current "knowledge of the subject certainly does not warrant the introduction of fluorine in community water supplies" and that "the potentialities for harm far outweigh those for good" (JADA 1944). The Director of Laboratories for the utilities department of the City of New York concluded that the "fluoridation of public water supplies is a hazardous procedure, people are bound to get hurt, it remains to find out how many and when" (Nesin 1956). When a former Principal Dental Officer of Auckland, New Zealand, compared decay rates for all children in all communities of the South Island, he found essentially no differences in tooth decay rates with respect to fluoridation status (Colquhoun 1997).

(2) Margin of safety

The report and the cover letter accompanying the report refer in several places to safety or to a margin of safety:

> The "safety margins are such that no subset of the population is at risk because of fluoridation." (Cover letter, p. 2)

> "The fluoride concentrations recommended for CWF have been set based on data from both animal toxicology studies and human epidemiological studies to provide a daily oral exposure that confers maximum benefit without appreciable risk of adverse effects." (pp. 4-5)

> "The amount of fluoride added to water in CWF programmes is set to minimise the risk of this condition [dental fluorosis] while still providing maximum protective benefit against tooth decay." (p. 6)

> "Community water fluoridation (CWF) entails an upward adjustment of the fluoride concentration in fluoride-poor water sources to a level that is considered optimal for dental health, yet broadly safe for the population that drinks the water." (p. 14)

In spite of these mentions of safety or a margin of safety, the report nevertheless indicates that many people exceed the supposedly "safe" levels:

> "In some cases the fluoride intake by these groups [formula-fed infants, young children who are likely to swallow toothpaste] can approach or exceed the currently recommended conservative upper intake level." (p. 6)
>
> ". . . there is a narrow range between optimal dental health effectiveness and a risk of mild dental fluorosis." (p. 10)
>
> Reconstituting infant formula with fluoridated water "can provide infants with fluoride at levels approaching or exceeding the recommended upper level for daily intake." (p. 25)
>
> ". . . infants who are exclusively fed formula made with water fluoridated at 1.0 mg/L will thus regularly exceed the current UL for fluoride." (p. 28)

If identifiable parts of the population predictably exceed the standards for fluoride intake, then the fluoride concentration in drinking water is too high and should be greatly lowered, so that there indeed exists a margin of safety between intake and a level at which health risks occur, and so that all subsets of the population are adequately protected.

(3) Adequacy of the standards for fluoride intake

In principle, the fluoride concentrations are set (in part) with respect to a demonstrated "safe" concentration. For New Zealand, this concentration is referred to as a "tolerable daily intake" (TDI), defined as "a daily oral exposure to the human population (including sensitive groups) that is estimated to be without an appreciable risk of deleterious effects during a lifetime" (p. 18) and which is "determined by applying a safety margin of several orders of magnitude" to a "no observed adverse effect level (NOAEL)" (p. 18). The TDI appears to be based on the U.S.

Environmental Protection Agency's Reference Dose (RfD), defined as "An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime" (EPA 2009). Properly understood, the RfD or TDI should not normally be exceeded by any individual, and any sort of allowable intake or, in this case, concentration in drinking water, should be set so that the RfD or TDI is not exceeded under ordinary circumstances. Individuals, including members of susceptible population subgroups ("sensitive subgroups"), should not normally have exposures in excess of the RfD or TDI.

For fluoride, the U.S. EPA has an existing RfD of 0.06 mg/kg/day (EPA 1989) and has proposed a new RfD of 0.08 mg/kg/day (EPA 2010). Another U.S. government organization, the Agency for Toxic Substances and Disease Registry, has a Minimal Risk Level (MRL, similar in concept to the USEPA's RfD) for fluoride of 0.05 mg/kg/day (ATSDR 2003). New Zealand has an "adequate intake" (AI) value for fluoride of 0.05 mg/kg/day and a "safe upper level of intake" (UL) of 0.1 mg/kg/day (p. 27, Table 2). Thus, New Zealand has set an "adequate" or "optimal" level of fluoride intake at or just below values considered by the U.S. government to be an upper

level of "safe," and has set the "safe upper level of intake" above the U.S. values. The UL for older children and adults is based on an intake of 10 mg/day, considered a "NOAEL" for skeletal fluorosis (p. 26). The TDI, which is supposed to be set by "applying a safety margin of several orders of magnitude" to the NOAEL (p. 18), has in fact been set equal to the NOAEL, with no safety factor at all. There is only a factor of 2 between the AI and UL values (0.05 and 0.1 mg/kg/day; p. 27, Table 2). As pointed out above, some identifiable subsets of the population will have fluoride intakes that exceed the UL.

The report ignores entirely the central question of whether EPA's RfD values (old or new) and New Zealand's TDI are adequately protective. EPA's proposed (but not yet official) new RfD of 0.08 mg/kg/day was based on protection of the population from severe dental fluorosis (EPA 2010). However, in order to obtain this value, EPA inappropriately included an assumption of benefit in its risk assessment for fluoride, including the preservation of an intake of 0.05 mg/kg/day as desirable (based on IOM 1997) and exclusion of possible adverse health effects below an intake of 0.07 mg/kg/day (EPA 2010). In other words, EPA had to ignore other, more sensitive, adverse health effects ("known or anticipated adverse health effects"; EPA 2009) and the association of dental fluorosis (all levels) with increased risk of other adverse health effects (e.g., thyroid disease, lowered IQ, and bone fracture; Alarcón-Herrera et al. 2001; Zhao et al. 1996; Li et al. 1995; Lin et al. 1991; Desai et al. 1993; Yang et al. 1994; Jooste et al. 1999; Susheela et al. 2005). A number of adverse health effects can be expected to occur in at least some individuals when estimated average intakes of fluoride are around 0.05 mg/kg/day or higher (NRC 2006; 2009); in other words, a LOAEL for some adverse health effects is lower (less protective) than EPA's new (or old) RfD, which is supposed to protect the population, including sensitive subgroups, from deleterious effects during a lifetime (EPA 2009; 2011). For persons with iodine deficiency (one example of a sensitive subgroup), average intakes as low as 0.01-0.03 mg/kg/day could produce effects (NRC 2006). Proper derivation of an RfD or TDI would consider these more sensitive endpoints and apply appropriate safety factors to obtain values much lower than those currently considered desirable by the New Zealand government.

(4) Effects of CWF in New Zealand

The RSNZ report states that "No severe form of fluorosis has ever been reported in New Zealand" (p. 6), "The prevalence of fluorosis of aesthetic concern is minimal in New Zealand, and is not different between fluoridated and non-fluoridated communities" (p. 56), and "Water fluoridation in New Zealand has been ongoing since the 1950s, with notable benefits to the oral health of its residents" (p. 55), while offering little documentation. However, the RSNZ has not even mentioned the reports by John Colquhoun, former Principal Dental Officer of Auckland, which report contrary evidence. For example: "When I obtained the decay rates for *all* children in *all* the fluoridated and *all* the nonfluoridated areas in that part of New Zealand [South Island], as well as the decay rates for *all* children in the recently defluoridated town, they revealed that there are virtually no differences in tooth decay rates related to fluoridation" (italics in the original) and "25 percent of children had dental fluorosis in fluoridated Auckland and around 3 percent had the severer (discolored or pitted) degree of the condition" (Colquhoun 1997).

(5) Carcinogenicity and genotoxicity

The RSNZ report states that "Multiple thorough systematic reviews conducted between 2000 and 2011 all concluded that based on the best available evidence, fluoride (at any level) could *not* be classified as carcinogenic in humans" (pp. 7, 46, italics in the report). The report is inaccurate to say that the U.S. National Research Council "could not" classify fluoride as carcinogenic to humans. While the U.S. National Research Council did not assign fluoride to a specific category of carcinogenicity (i.e., known, probable, or possible), the NRC committee did not consider either "insufficient information" or "clearly not carcinogenic" to be applicable. The committee report (NRC 2006) includes a discussion of how EPA establishes drinking water standards for known, probable, or possible carcinogens; such a discussion would not have been relevant had the committee not considered fluoride to be carcinogenic. The question remains how strongly carcinogenic fluoride is, and under what circumstances. The NRC (2006) specifically discussed the limitations of epidemiologic studies, especially ecologic studies (those in which group, rather than individual, measures of exposure and outcome are used), in detecting small increases in risk—in other words, most of the studies are not sensitive enough to identify small or moderate increases in cancer risk; therefore a "negative" study does not necessarily mean that there is no risk (see also Cheng et al. 2007). In particular, a "negative" study that does not address a key condition involved in a "positive" finding (e.g., the failure to include age-specific, individual exposure or to separate young and old people in the analysis) cannot be considered evidence of no risk.

The RSNZ report dismisses the Harvard osteosarcoma study (Bassin et al. 2006) on the basis of a letter by Douglass and Joshipura (2006) that contained no actual data. Douglass approved Bassin's dissertation (Bassin 2001), on which her paper was based, and both Douglass and Joshipura were coauthors on an earlier paper by Bassin et al. (2004) describing the exposure analysis used in the study. The dissertation (Bassin 2001) and peer-reviewed paper (Bassin et al. 2006) contain essentially the same results. The key finding reported by Bassin et al. (2006) was an increased risk of osteosarcoma in young males, based on an age-specific analysis of fluoride exposure. Given this finding, studies that do not look at age-specific exposure of young males cannot be said to be negative.

Douglass and Joshipura (2006) mentioned, but did not provide, an analysis of the fluoride content of bone specimens from the osteosarcoma patients and a lack of association between bone fluoride concentration and excess risk of osteosarcoma; however, fluoride concentration in bones of diagnosed patients constitutes a measure of cumulative fluoride exposure which would not necessarily be expected to be correlated with the risk of osteosarcoma. Given that there is a "lag time" of a few years between onset of a cancer and its diagnosis, use of cumulative fluoride exposure until time of diagnosis is potentially misleading, as fluoride exposure during the last several years (during the "lag time" between initiation and diagnosis of a cancer) cannot have contributed to the initiation of a cancer but could have a significant effect on the estimate of cumulative fluoride exposure.

The RSNZ report mentions a later Harvard paper (Kim et al. 2011) which "reported that bone fluoride levels in these samples did not correlate with the occurrence of osteosarcoma" (p. 46). Kim et al. reported no significant difference in bone fluoride levels between cases and controls and no significant association between bone fluoride levels and osteosarcoma risk. The RSNZ report does not mention that Kim et al. (2011) specifically say that "if risk is related to exposures at a specific time in life, rather than total accumulated dose, this metric [bone fluoride content] would not be optimal," thus admitting that they did not address the key finding of Bassin et al.

(2006). Comparison of the distributions of bone fluoride concentrations between cases and controls indicates that the ranges are not greatly different; the median was higher for the controls than the cases, which Kim et al. attribute to the older ages of the controls. Given that the median age of the controls is more than twice the median age of the cases (41.3 vs. 17.6), the obvious conclusion is not a lack of association between fluoride exposure and osteosarcoma, but considerably higher average exposure (by about a factor of 2) in cases and controls, in order to reach similar bone fluoride concentrations. Rather than refuting the work of Bassin et al., these findings by Kim et al. support an association between fluoride exposure and osteosarcoma.

In its discussion of animal studies of carcinogenicity (p. 45), the RSNZ report fails to point out that in most, if not all, of these studies, the fluoride exposures started after the age corresponding to the apparent most susceptible age in humans (based on Bassin et al. 2006), and thus these animal studies may have completely missed the most important exposure period with respect to initiation of the majority of human osteosarcomas.

With respect to genotoxicity (p. 44), the RSNZ should be aware that *in vitro* genotoxic, cytogenetic, or transformational effects (i.e., positive results) have been observed in many studies at fluoride concentrations at or above about 5 mg/L (reviewed by NRC 2009). In addition, a recent paper by Zhang et al. (2009) describes a new testing system for potential carcinogens, based on induction of a DNA-damage response gene in a human cell line. Sodium fluoride tests positive in this system, as do a number of other known carcinogens, representing a variety of genotoxic and nongenotoxic carcinogenic mechanisms. Known noncarcinogens—chemicals not associated with carcinogenicity—did not test positive. For fluoride, a positive effect was seen at a fluoride concentration of about 0.5 mg/L, or a factor of 10 lower than in the other systems.

A fluoride concentration of 0.5 mg/L in urine will routinely be exceeded by many people consuming fluoridated water (NRC 2006); for people with substantial fluoride intake, serum fluoride concentrations may also reach or exceed 0.5 mg/L. Acute fluoride exposures (e.g., accidental poisoning, fluoride overfeeds in drinking water systems) have resulted in fluoride concentrations in urine well in excess of 5 mg/L in a number of cases (e.g., Penman et al. 1997; Björnhagen et al. 2003; Vohra et al. 2008). Urine fluoride concentrations can also exceed 5 mg/L if chronic fluoride intake is above about 5-6 mg/day (less than New Zealand's upper level of intake for older children and adults; p. 27, Table 2). At intakes between New Zealand's "adequate" and "upper level" intakes, kidney and bladder cells are probably exposed to fluoride concentrations in the ranges at which genotoxic effects have been reported *in vitro*, especially when the more sensitive system of Zhang et al. (2009) is considered. Based on the results of Zhang et al. (2009), most tissues of the body are potentially at risk if serum fluoride concentrations reach or exceed 0.5 mg/L. In addition, cells in the vicinity of resorption sites in fluoride-containing bone are potentially exposed to very high fluoride concentrations in extracellular fluid (NRC 2006) and thus are also at risk for genotoxic effects.

(6) Neurotoxicity

The RSNZ report is not accurate in its characterization of the Choi et al. (2012) article on effects of fluoride on children's IQ. They indicate that Choi et al. found a "shift of less than one IQ point" (p. 7), and that "the standardised weighted mean difference in IQ scores between "exposed" and reference populations was only -0.45" (p. 49). In fact, the difference is about one-half (-0.45) of a standard deviation, or about 7 IQ points, not one-half of an IQ point. This was clarified for nontechnical readers in a September 5, 2012, correction to the original (July 25, 2012) press release from Harvard University.

While many of the articles included in Choi's meta-analysis had reference levels similar to CWF levels, and "high" levels somewhere above that, several studies had "high" levels within the legal limits for fluoride concentrations in drinking water in the U.S. One study had "high" at 0.88 mg/L, quite relevant to CWF. Also, studies that have "reference" levels similar to or higher than CWF levels can say nothing about the safety of CWF. Rather, for something like neurotoxicity for which there is likely no threshold (the current U.S. assumption for lead exposure, for example), finding that sort of dose response ought to suggest the likelihood of a response at lower (e.g., CWF) levels compared to very low or negligible levels, and the importance of looking for possible effects at lower (CWF) levels is obvious. One extremely important finding by the NRC (2006) and then Choi et al. is the consistency of the effect. Even the one study in Choi's list that did not clearly show lower IQ still showed a tendency in that direction (just not statistically significant), and it certainly did not show clear absence of any effect.

The RSNZ report ignores the fact that Choi et al. (2012) excluded several studies from their meta-analysis because they used individual measures of exposure rather than group exposures--in other words, some excluded studies might have been of better design than the ones that their meta-analysis could consider. There are also a few studies too recent to have been considered by Choi et al. but that should have been mentioned by the RSNZ report (e.g., Saxena et al. 2012; Seraj et al. 2012; Shivaprakash et al. 2011). While some of the neurotoxicity studies did not

address confounders, some did handle them responsibly, a detail not mentioned in the RSNZ report.

The RSNZ report (p. 50) describes as "relatively high quality" a recent paper from New Zealand reporting no evidence for an effect of CWF on IQ (Broadbent et al. 2014). However, the assessment of exposure provided in that paper is inadequate and probably results in comparisons between groups with similar, or at least overlapping, exposures to fluoride. For example, children in the non-CWF group who received fluoride tablets probably had similar exposures to children in the CWF group. Broadbent et al. report that breastfeeding was associated with higher IQs but fail to point out that this effect was larger for CWF areas than non-CWF areas. (Fluoride concentrations in breast milk are quite low, regardless of the mother's fluoride intake.) Broadbent et al. defined breastfeeding as lasting at least 4 weeks, suggesting that further analysis, including duration of breastfeeding, might show a larger effect.

Both Broadbent et al. and the RSNZ report inaccurately state that no plausible mechanism exists for an effect of fluoride on IQ. The fact that no mechanism has been established reflects the absence of research effort, not the absence of a mechanism. One possible mechanism is reduction of maternal and/or infant thyroid function (NRC 2006). Others involve damage to the developing brain or disrupted neurochemistry (e.g., Blaylock and Strunecka 2009). Several studies have shown changes in brain chemistry in fetuses due to maternal fluoride exposures (Dong et al. 1997; Du et al. 2008; He et al. 2008; Yu et al. 2000; 2008).

(7) Significance of animal studies

The RSNZ report dismisses many of the animal studies as involving greatly higher fluoride intakes (or fluoride concentrations in drinking water) than those experienced by people with CWF (pp. 45, 49). However, animals require much higher exposures (5-20 times higher, or more; see NRC 2006; 2009) than humans to achieve the same effects or similar fluoride concentrations in bone or serum. In other words, humans are considerably more sensitive to fluoride than are most animal species that have been studied. The animal studies cannot so easily be dismissed. This difference in sensitivity should have been discussed in the report.

(8) Endocrine effects

The RSNZ report mentions the extensive review of "potential fluoride effects on endocrine organs and hormones" by the U.S. National Research Council (p. 51), but they fail to mention that the NRC's report concluded that "fluoride affects normal endocrine function or response" and "Fluoride is therefore an endocrine disruptor" (NRC 2006). The RSNZ mentions a paper on childhood goitre in South Africa by Jooste et al. (1999) as included in the York review (p. 52). They have not mentioned the NRC's discussion of the same paper, specifically that the town with the lowest prevalence of goitre also had the lowest prevalence of "undernutrition." When that town is excluded from the analysis, a clear dose response is observed between goitre prevalence and fluoride concentration in drinking water.

(9) Monitoring of fluoride concentrations in water

The RSNZ indicates that "fluoridated drinking water supplies must be sampled at least weekly" (p. 24). It should be mentioned that the American Water Works Association recommends at least once per day (Lauer and Rubel 2004). The AWWA also mention the advantages of continuous monitors, in particular, having one equipped with an alarm to alert operators to a malfunction. Fluoride overfeeds do occur and can cause illness and even death (e.g., Gessner et al. 1994; Penman et al. 1997).

(10) CWF recommendations in the U.S.

The RSNZ report indicates that "optimally fluoridated" drinking water in the U.S. is now 0.7 mg/L (p. 54). However, while the U.S. Department of Health and Human Services proposed a new recommendation of 0.7 mg/L instead of the existing temperature-based recommendation of 0.7-1.2 mg/L (Federal Register 2011), this is not yet anything but a "proposed" new recommendation. As of this date (September 2014), this proposed recommendation has not become an official recommendation, and to the best of my knowledge has not had wide implementation in the U.S.

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