The following critical letters were published in the *Australian and New Zealand Journal of Public Health* (Vol 21 Nos. 3 and 5 1997) following publication in that journal of *NEW EVIDENCE ON FLUORIDATION*, by M Diesendorf, J Colquhoun, B J Spittle, N E Everingham and F W Clutterbuck (reprinted in *Fluoride* Vol. 21 No. 3 pages 179-185 August 1997). The authors' response to the critiques is on pages 166-169 of this issue (published in *Australian and New Zealand Journal of Public Health* Vol. 22 No. 1 1998).

**NEED FOR EVIDENCE ABOUT FLUORIDATION**

I was disappointed to see that the recent article on fluoridation, which purports to look at new information published since 1989, references only articles that agree with the authors' viewpoint. As this is a supposedly contentious area, there must be some studies that do not support their viewpoint, and not all of these can have been published before 1989. To test this idea I did a simple search on Medline, using the search strategy fluoride (or fluoridation) and hip fractures, and fluoride (or fluoridation) and osteosarcoma, these being two of the areas mentioned. I restricted my search to articles published from 1989 onwards.

These simple searches turned up five articles on osteosarcoma and fluoride exposure and three on hip fractures and fluoride exposure that were not referenced by the authors. All eight of these found no association with fluoride. What is more, some of them were case-control studies and one was a cohort study, so should provide more reliable evidence than the ecological studies cited of whether or not there was an association. This is because both fluoride intake and the outcome were measured on individuals rather than populations. I am sure that more thorough searches would have found more articles, not all of which would agree with each other. Inclusion of these articles in the review could well have changed the conclusions.

It is well known that traditional reviews are subject to all sorts of biases. A recent series of articles in the BMJ points out the problems with traditional reviews, and looks at the advantages of systematic reviews that, despite some problems, present a more realistic view of a problem. The object of a systematic review is to specify a series of steps so that if other people do the same review they will get the same answer. This article seems to be loaded with more than the normal amount of bias, because the authors selected only articles that agree with their hypothesis, although they do not openly say this. It is a pity that the authors, in spite of saying that they 'hope that at least some kind of scholarly debate will ensue' could not provide a more solid foundation as a starting point.

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References
We read with some concern the article by Diesendorf et al., entitled ‘New evidence on fluoridation’. The article purports to be a review of recent scientific literature and claims this ‘reveals a consistent pattern of evidence’ pointing to the existence of ‘causal mechanisms by which fluoride damages bones’. The authors appear, however, to have considered only the literature that supports their point of view, and we are concerned that, as a result, the article does not present an accurate picture of this emotive issue to an uninitiated reader.

When an attempt is made to evaluate causality, a number of key issues have to be considered. The first, and possibly most crucial stage, is to ensure that such an evaluation takes into account all of the available scientific evidence. Any review must be comprehensive, with all of the literature on a given topic considered and evaluated with respect to the quality of the study and the validity of the results. There are then two main questions to consider. First, if there does appear to be an association between an exposure and ill-health in a particular
study, is this association real? Or could it be an artefact, due to chance, bias or confounding? Certain types of study allow us to rule out the possibilities of confounding with a greater or lesser degree of certainty. In ecological studies, where comparisons are made between, for example, populations rather than between individuals, it is almost impossible to rule out confounding as a possible explanation for an observed association. If two areas differ in one particular aspect, with respect to the use of water fluoridation, for example, they are also likely to differ in other ways that could equally well explain any apparent health differences between the areas. It is also impossible to relate exposure and the occurrence of ill-health in the same individuals. Case-control studies overcome this latter problem but can still be affected by issues of bias and confounding. While, in the absence of intervention studies, prospective cohort studies offer the strongest evidence for or against an association.

Only if we are fairly confident that a real association does exist can we then go on to consider whether or not this association is likely to be causal. Factors that can influence an evaluation of causality include: the strength of the association (a strong association is much less likely to be due to bias or confounding than a weak one); its consistency across a range of different studies in different populations; evidence that exposure really did precede the development of disease; and an increasing risk of disease with increasing level of exposure. A biologically plausible mechanism whereby the exposure could cause disease, and supporting data from experimental systems, including animal studies, can also influence the conclusion.

Our major concern about the article by Diesendorf et al. is that it appears to discuss only those studies that have reported a positive association between water fluoridation and ill-health. Studies that found no association are summarily dismissed because of either limited sample size or because the women studied were not exposed to fluoride before the menopause.

The authors cite five ecological studies that report higher rates of hip fracture in areas with higher levels of fluoride in the drinking water \(^2\)\(^{-6}\) and a single prospective study.\(^7\) This latter study followed only 827 women, who experienced a total of 86 fractures, and compared an area with high fluoride (4 parts per million (ppm): that is, more than four times the levels recommended for fluoridation) and low calcium levels with a control area with fluoride levels compatible with fluoridation (1 ppm) and normal calcium levels.

In addition to several earlier ecological studies that reported either no association or a negative association between fluoride levels in water and fracture, three recent ecological studies have also reported no association\(^6\)\(^{-10}\) as have another two prospective studies.\(^11\)\(^{-12}\) The majority of these studies are more recent and each had a larger sample size than one of the studies cited above.\(^3\) In addition, two of the three ecological studies included younger subjects (aged 45 or 50 upwards, compared with a minimum age of 65 in most of the studies above), who would have been more likely to have been exposed to fluoride premenopausally. Thus, the evidence for an association is clearly not consistent
and the newest data do not appear to support the view that water fluoridation increases the risk of fracture.

A similarly one-sided view is presented of the potential association between fluoridation and osteosarcoma. Diesendorf et al. cite two reports, not peer-reviewed articles, of ecological studies that show an increased risk of osteosarcoma in young men. At least another four ecological studies and three case-control studies have, however, been published since 1990, and all of these show either no association or a potential protective effect of fluoridation on osteosarcoma.

Diesendorf et al. strengthen their argument by reference to the data from the United States National Toxicology Program, which showed an increase in osteosarcoma in male rats exposed to high levels of fluoride in their drinking water but not in female rats or mice. The second paper that they cite does not, however, support their argument, concluding that 'results from this study indicate that NaF is not carcinogenic in Sprague-Dawley rats'. The results of the National Toxicology Program study have not been confirmed by other studies and, although they cannot be completely discounted, they cannot be used to prove carcinogenicity.

In summary, therefore, the authors have not met the prime criterion for a valid review because they have not considered all of the available scientific evidence. When this is done it becomes clear that there is little reliable evidence on which to base an evaluation of causality because many of the available data come from ecological studies. These can provide only very limited evidence for or against causality, because it is impossible to rule out confounding in this type of study. Furthermore, what evidence there is does not meet any of the Bradford Hill criteria for strength of association, consistency or dose-response.

We agree that, at high levels, fluoride does cause damage to bones, but maintain that there is no good scientific evidence to suggest that it does so at the levels to which people are exposed when drinking fluoridated water. Many other chemicals are beneficial at low concentrations but harmful when taken in excess. We wholeheartedly support the authors' desire for scholarly debate on the issue but request that such debate should indeed be scholarly and, as such, should consider the whole picture.

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References


The Australian Dental Association Queensland Branch is deeply concerned about your decision to publish the paper written by Drs Diesendorf, Colquhoun, Spittle, Clutterbuck and Everingham.1

Diesendorf et al. are noted anti-fluoridationists whose research work was severely criticised by Australia's National Health and Medical Research Council, in their report, The effectiveness of water fluoridation.2

The publication of such a mischievous article, which we are confident will draw criticism from the academic community, was irresponsible because an opportunity was not provided to balance the controversy and give the full facts on fluoridation of public water supplies. News stories in the popular press show how much damage is being caused by publication of the article in your journal.

Our branch is currently campaigning to introduce the well-proven health measure of fluoridation to the Queensland community. Besides the proven health benefits of water fluoridation as a safe, equitable and cost-effective public health intervention, the branch estimates that Queenslanders could save more than $20 million in unnecessary, dental treatment if this measure is introduced.

It would be our hope and expectation that you will counter the effect of the article with responsible refutation of the article and publication of articles supportive of water fluoridation.

Pat Jackman
President, Australian Dental Association
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References

REVIEW OF EVIDENCE ON FLUORIDATION
I refer to the recent article on water fluoridation, 'New evidence on fluoridation'.1 I am surprised that a reputable scientific journal has not checked the veracity of statements made in articles it publishes.

The article appears to be a mix of review of the scientific literature and commentary on water fluoridation. The review is selective and presents more of the scientific literature that suggests adverse effects of fluoride on health than that indicating inconclusive or positive findings.
In examining whether this article adds any new information to the accumulated research on water fluoridation, I have considered the report by the Public Health Commission, *Water fluoridation in New Zealand* (PHC report) which is referenced by the authors. This is a technical report, published in 1994, which analysed the published literature on fluoride, water fluoridation and fluoride's effect on oral health status.

The Jacqmin-Gadda *et al.* reference is a letter to the *Journal of the American Dental Association.* The letter reported a comparison of hip fracture rates in areas with water fluoride levels above and below 0.11 mg/L. It is the only study referred to by the authors, and published since the PHC report, that shows higher rates of hip fracture with higher water fluoride levels. A critical appraisal of the content of this letter shows dubious internal validity, as confounding variables known to affect osteoporosis and hip fractures were not considered. The results may be due to these other factors, such as dietary calcium intake, ethnicity, bone age, rather than fluoride intake. Daily individual water intake was not assessed, and data on water fluoridation levels were available only from 1991. Fracture history was self-reported. I wrote to the authors requesting a copy of the report to enable complete critical appraisal and peer review to ascertain the significance of the findings. They replied that no report was available because the study was still in progress.

I am uncertain of the validity of the assertion, used to reject the study of postmenopausal women, that 'fluoride would be expected to affect bone most before menopause'. In general, fluoride accumulates in the skeleton with age. I would also dispute the assertion that 'low levels of fluoride ingested for several decades can cause . . . skeletal fluorosis. It is very unlikely that in developed countries skeletal fluorosis would be associated with exposure to 1 part per million of fluoride in the absence of high long-term intake and/or metabolic susceptibility.'

Diesendorf *et al.* assert that:

> In three to four decades when people in areas where water is artificially fluoridated have accumulated fluoride in their bones from birth to old age, the increase in skeletal fluorosis will be larger.

If this is true, then the rates of hip fracture should be higher already in older people in naturally fluoridated communities than in unfluoridated communities. The authors present no information on this.

The PHC report comments on studies indicating that there is an association between water fluoridation and osteosarcoma. The toxicological evidence is referred to in the PHC report as 'weak and inconclusive'. Diesendorf *et al.* have no evidence that alters this summary.

There is also no mention of studies published since 1994 that have inconclusive findings or do not support the evidence cited of an association between fluoride and adverse effects on bone.

New Zealand and Australian references in the PHC report that show a difference in prevalence of dental caries associated with fluoridation are not
mentioned by the authors. The greater benefits of fluoridation for lower socio-economic groups are also not acknowledged.

Health agencies and professionals within New Zealand believe, on the basis of present evidence, that water fluoridation is a safe and effective strategy for protecting and improving health status and, in particular, in reaching those groups most at risk of dental decay.

It is not practical to respond to all the claims of the authors within the scope of a letter; these have been amply detailed elsewhere. Reports of independent experts in relevant fields of medicine, epidemiology, oral health and water engineering have been unanimous that benefits of water fluoridation outweigh any (very small) potential risks. Research studies on the safety of water fluoridation have been reviewed repeatedly by international and Australasian experts, including World Health Organization expert group. The conclusion of all these reports is uniform. There are no significant health risks associated with water fluoridation at optimal levels. Mortality rates and health statistics (other than for oral health) in fluoridated and unfluoridated communities are similar.

The New Zealand Ministry of Health has data on dental decay rates that show a real difference between fluoridated and unfluoridated areas, with children who have access to fluoridated water having lower rates of dental decay. There is no evidence of significant adverse effects on health from water fluoridation at the level recommended for New Zealand water supplies (0.7 to 1.9 mg/L).

Water fluoridation has been shown to provide significant benefits to oral health, particularly for disadvantaged people. Latest research shows it is effective in reducing root caries. Water fluoridation is of benefit to everyone with natural teeth.

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References
In our article 'New Evidence on Fluoridation' we referred to recently published comprehensive data which indicate an association between fluoridation and damage to bone (hip fracture, skeletal fluorosis and possibly osteosarcoma). We pointed out the limitations of some other studies which reported no such association. We then drew attention to other relevant studies which support a causal explanation for the association.

We reject the charge levelled at us in the June issue by Herbison, and by Webb and Donald, that we cited only studies which support our view. That charge is more fairly directed at the extensive pro-fluoridation literature. For example, Webb and Donald in their submission supporting fluoridation of Brisbane's water supply, excluded any mention, in either their text or their reference list, of the fact that fluoride accumulates in bones and reaches levels consistent with widely recognised adverse effects - an important aspect of causality which we note they also omit in their attempt to criticize our article. They likewise excluded all studies reporting harm from fluoride published in Fluoride, journal of the International Society for Fluoride Research. They also did not cite a single original paper reporting skeletal fluorosis in areas naturally fluoridated at concentrations between 0.7 and 2.5 parts per million. A 1990 review by one of us (MD) examined nine such papers from five countries. That information is very relevant to the issue of causality.

Our lengthy reference list could not possibly include all published studies, but cited representative ones, which is the usual convention. We also did not cite a recent paper reporting a positive correlation between fluoridation and hip fractures, which supported our assessment.

Our critics seem to hold a naive belief that conclusions can be based on the quantity, rather than the quality, of published papers on controversial issues. They list studies that, in their view, counterbalance the comprehensive data on which we based our conclusion that fluoridation should be discontinued. Such publications do not nullify the compelling evidence of harm represented by the comprehensive data we reviewed. In any case, even if the evidence is conflicting, so that conclusions remain in dispute, the precautionary principle is itself grounds for discontinuing the mass uncontrolled fluoride dosing of entire populations.

We wonder why our critics do not apply the same stringent requirements for proof of causality that they seem to apply to evidence of harm from fluoride to the many flawed studies claiming a fluoride dental benefit. At the Brisbane Lord Mayor's Taskforce on Fluoridation, Professor Donald was asked that question and replied that he had not examined the fluoridation studies because he had never been asked to. We wonder how many other professors at medical schools continue to advocate fluoridation without examining the evidence for it.

An examination of the quality of some of the studies our critics cite to support their case is revealing. They include two studies, which their authors claim suggest that fluoride may be protective against the rare bone cancer, osteosarcoma (which we pointed out has increased among young males aged 9 to 19 years in fluoridated areas of America, but not in unfluoridated areas).
One of these studies, from the dental literature, was based on only two cases, of unstated age and sex, who spent more than a third of their life or childhood in a fluoridated area, and seven cases, also of unstated age and sex, who spent less than a third of their life or childhood in a fluoridated area.\textsuperscript{16} In the other study, which appeared to suggest a protective effect from fluoride, the study design was based on an assumption that osteosarcoma victims would require (if ingested fluoride was the cause) higher fluoride exposure than those without the disease.\textsuperscript{17} The possibility that such victims might be more susceptible to equal or smaller fluoride exposures was not considered. A critical review of that report was not cited by our critics.\textsuperscript{18}

Other studies they cited do not, on close examination, support their claim of no fluoride/osteosarcoma link.\textsuperscript{19-21} For example, Hrudey et al. admitted that their data from small populations 'do not allow any definitive conclusions about the role of fluoridation as a risk factor for osteosarcoma in humans'.\textsuperscript{19} The claim of Mahoney et al., of no difference in bone cancer incidence between fluoridated and unfluoridated areas of New York State, can be disputed on the grounds that the authors failed to consider male rates separately.\textsuperscript{20} The Moss et al. study did not calculate the water fluoride-osteosarcoma association for 10- to 19-year-old males, the age-sex group for which the association has been reported.\textsuperscript{21} It combined both sexes for its two age groupings (under and over 45 years) and combined all ages for its female and male calculations.

Two studies that they described as 'ecological' were claimed by Webb and Donald to show no osteosarcoma-fluoride association.\textsuperscript{22,23} The first, a letter to editor by Cook-Mozaffari et al., simply expressed the same opinion of our critics, and presented no new evidence.\textsuperscript{22} The other does not deal with osteosarcoma at all, but reported instead that water fluoride reduces human male fertility.\textsuperscript{23}

Another study, claimed by Herbison to counteract our observations on a possible fluoride/osteosarcoma link, is a very good study by an eminent researcher and his associates, but is irrelevant to this discussion because it deals with male and female adult workers exposed to fluoride, not with young males growing up in fluoridated areas.\textsuperscript{24}

Other studies discounting an association between fluoride and hip fracture (for example, that of Jacobsen et al. 1993\textsuperscript{25}) are of doubtful value because, as we pointed out in our article (citing a review\textsuperscript{26}), many are of small samples or the women were not exposed to fluoride before menopause. The same applies to the more recent Cauley et al. study: of the 41 hip fracture cases aged 65 or over, only four had lived more than 10 years in a fluoridated area.\textsuperscript{27} The study by Suarez-Almazor et al. compared one fluoridated and one unfluoridated Canadian city.\textsuperscript{28} It is true that this study did not find more hip fractures in women in the fluoridated area, as other studies have done. However, it did find significantly more hip fractures in men in the fluoridated city. The authors of another recent study cited by our critics (Karagas et al.), stated: 'Our findings with respect to water fluoridation have important limitations, however'.\textsuperscript{29} These limitations included: 'Fluoride exposure was assessed at the time of fracture and thus does not necessarily reflect exposure during what may have been a more relevant time period (for example, during peak bone formation)'.

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The recent Finnish study which our critics cited reported no differences in the prevalence of female fractures in its fluoridated and nonfluoridated groups, and slightly higher (1 to 2.6 per cent) bone mineral density in women exposed to fluoride for more than 25 years.\textsuperscript{30} However, the fluoride-exposed women were younger, more physically active, and more likely to use hormone replacement therapy.

Our other critics, Pat Jackman of the Dental Association and Gillian Durham of the New Zealand Ministry of Health, objected to our views even being published, but added nothing of substance to the debate.\textsuperscript{31,32} However, we thank our critics for contributing and hope the debate continues in a scholarly manner.

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