Spatial distribution mapping of drinking water fluoride levels in Karnataka, India: fluoride-related health effects

INTRODUCTION
Inorganic fluoride is freely available in nature, and is the only known cariostatic elemental anion.\(^1,2\)
Fluoride is of much importance in view of its ability to enhance the remineralisation of hard tissues. The use of fluoride in dentistry goes back to the 1930s when it was discovered that fluoride exerts a preventative effect on dental caries.\(^2,4\) Several systematic reviews have also revealed that fluoride has the ability to elevate bone density, for example, it has a positive therapeutic effect towards skeletal ailments, including osteoporosis.\(^8\)

Currently, there is no evidence to suggest that high fluoride concentrations (\(\geq1\) ppm) in drinking water that derived from natural sources have a detrimental effect on dental and musculoskeletal health.\(^9,10\) Despite the knowledge that an individual may be supplementing their fluoride intake from other sources such as diet, toothpaste and regulated fluoride application by dental clinicians.

The risk of developing dental caries is higher if the concentration of fluoride in a population’s drinking water is diminished below the optimal concentration range of 0.8–1.5 ppm.\(^11–16\)

However, if the fluoride concentration in drinking water is above the optimal range, the risk of developing dental fluorosis is increased.\(^5,6\) Dental fluorosis can be defined as an alteration to the enamel of teeth, which can affect their appearance, and may also affect the teeth’s ability to withstand certain types of wear.\(^7\)

Materials and Methods: Aqueous standard solutions of 10, 100 and 1,000 ppm fluoride (\(\text{F}^-\)) were prepared with analytical grade Na\(^+\)/\(\text{F}^-\) and a buffer; TISAB II was incorporated in both calibration standard and analysis solutions in order to remove the potentially interfering effects of trace metal ions. This analysis was performed using an ion-selective electrode (ISE), and mean determination readings for n=5 samples collected at each Karnataka water source were recorded.

Results: The \(\text{F}^-\) concentration in drinking water in Karnataka state was found to vary substantially, with the highest mean values recorded being in the north-eastern zone (1.61 ppm), and the lowest in the south-western one (only 0.41 ppm). Analysis of variance (ANOVA) demonstrated that there were very highly significant ‘between-zone’ and ‘between-districts-within-zones’ sources of variation (\(p<10^{-6}–10^{-9}\)), results consistent with a substantial spatial variance of water source \(\text{F}^-\) levels within this state.

Conclusions: The southern part of Karnataka has low levels of \(\text{F}^-\) in its drinking water, and may require fluoridation treatment in order to mitigate for dental caries and further ailments related to fluoride deficiency. However, districts within the north-eastern region have contrastingly high levels of fluoride, an observation which has been linked to dental and skeletal fluorosis. This highlights a major requirement for interventionial actions in order to ensure maintenance of the recommended range of fluoride concentrations (0.8–1.5 ppm) in Karnataka’s drinking water sources.

Keywords: fluoride; drinking water sources; Karnataka State of India; environmental temperature; fluorosis sources; Karnataka State of India; environmental temperature; fluorosis

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water is higher than 1.5 ppm, then the possibility of dental fluorosis increases. Variable ecosystems, lifestyles and climatic changes influence the availability and intake of fluoride in humans, and hence, estimated values of fluoride bioavailability may differ in view of seasonal variations. Therefore, there is a major requirement for health researchers and healthcare professionals to gain relevant knowledge regarding the fluoride concentration of drinking water available in order to promote good oral and general health.

In view of the above considerations, this study aimed to investigate the fluoride concentrations of drinking waters from natural sources, and also to develop an effective and reliable spatial mapping profile of available drinking water fluoride concentration (and hence the prevalence of fluoride-related health effects) in differing districts of India’s Karnataka state.

**MATERIALS AND METHODS**

**Water sample collection and preparation**

A total volume of 50 ml of special polypropylene containers (Chemtron Analytical Instrument Private Limited, New-Delhi, India) were employed to collect the samples. Prior to collection, these containers were thoroughly cleansed and washed with deionised water and then autoclaved in order to sanitise them. While collecting the samples, the container was washed 3 times with water from the same source as the sample collected. The samples were labelled with the following information: source of drinking water, date of collection and temperature, together with the weather condition of the day of collection and the location of the district. A dust-free environment and uniform temperature (monitored by a thermometer) were maintained within the laboratory during F⁻ determination experiments.

**Preparation of F⁻ standard solutions**

Deionised water was employed to adjust the volume of the total ionic strength-adjusted buffer (TISAB), and standard solutions were also prepared using this (the deionised water was checked for any traces of fluoride present). The TISAB II solution was prepared using 5.80 g of NaCl, 0.30 g of NaOH, 0.40 g of trans-1,2-diaminocyclohexane N,N,N',N'-tetracetate monohydrate (CDTA), and 5.70 ml of acetic acid (glacial), and then adjusted to a final volume of 100.0 ml with deionised water.

**Water sample collection**

The source was water samples collected from 5 equidistant sites within each of 29 districts located within 4 zones (north-east, north-west, south-east and south-west) of Karnataka. Each zone was identified from Karnataka state geographical areas. The north-east, north-west, south-east and south-west zones contained 6, 5, 9 and 9 districts, respectively. Distances between districts-within-zones ranged from 600 to 900 km. The water collected was from the same source as that available for the local population to acquire for drinking purposes.

**Analysis of water samples with a fluoride ion-selective electrode**

Samples were analysed for their F⁻ concentrations using standard methods in the Fluoride Research Division of the Department of Oral Biology and Genomic Studies at AB Shetty Memorial Institute of Dental Sciences, Nitte University, Mangalore, India.

This analysis was performed using an ion-specific electrode (ISE) purchased from ELIT Ion-selective Electrodes, Nico2000 Ltd, UK. The analysis of F⁻ was performed by an adaptation of the method described in Rajkovic and Novakovic.¹⁷ A fresh standard solution of analytical grade Na⁺/F⁻ was prepared with final concentrations of 10, 100 and 1,000 ppm. Freshly prepared TISAB was added to the standard fluoride solutions in order to adjust the pH of the sample and to chelate trace levels of potentially interfering, F⁻-complexing metal ions such as iron(III) and aluminium(III). The instrument was calibrated with three of the standard solutions followed by analysis of the water sample(s), and the ratios displayed on the personal computer (PC) monitor were checked and printed. The electrode was clamped to a stand in order to retain its lower body immersed in the solution for 5.0 min., and the reading was recorded at a stable potential for the sample. The calibration curves, their gradients and resulting sample F⁻ concentrations, together with responses to the standard solutions were taken for every set of samples and checked for any abnormal variations; any errors detectable were recorded. The necessary measures were taken in order to ensure the validity of data acquired, together with maintenance of the specificity and sensitivity of the electrode. The F⁻ concentration in the deionised water was analysed before estimating that in individual samples. Finally, any very low trace deionised water F⁻ levels detectable were deducted from those of the samples tested in this manner.

**Statistical analysis of experimental drinking water sample fluoride levels**

The experimental design for this investigation was a two-factor model with districts (n = 5–11) ‘nested’ within the four zones (north-east, north-west, south-east and south-west, Model I). Variance component analysis comprised these two main effect factors (‘between-zones’, and ‘between-districts-within-zones’) and fundamental error. Analysis of variance (ANOVA) was performed on both the untransformed dataset, and that subjected to the Box–Cox transformation, the latter to further satisfy assumptions of normality, variance homogeneity (homoscedasticity) and additivity. A further ANOVA model employed involved only the four zones as a main ‘between-zones’ effect factor, and analysis was again performed on both untransformed and Box–Cox transformed datasets (Model II). Further analysis of the differences between the mean values of all factor classifications was performed by Tukey’s honestly significantly difference (HSD), Fisher’s least significant difference (LSD), and the Bonferroni and Dunn–Sidak tests.

Primarily, Pearson correlation coefficients (r values) between each of the district temperature, rainfall, district area (km²) and
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water source F\textsuperscript{-} variables were computed in order to investigate the significance of any relationships between them.

Subsequently, partial correlation coefficients (i.e. \( r_{ab(c)} \)) values and their corresponding two-tailed significance (\( p \)) values were computed between a multivariate (MV) dataset containing the district temperature, rainfall and water source F\textsuperscript{-} concentration dataset (since the district area (km\(^2\)) variable was not found to exert any significant, nor even minor influence on drinking water F\textsuperscript{-} levels, it was excluded from this analysis). All statistical analyses of our datasets were performed with XLSTAT2014.

Ethical approval
Ethical clearance for this study was obtained from the Central Ethics Committee of Nitte University, Mangalore, India.

RESULTS
The drinking water concentrations of F\textsuperscript{-} in the different districts of Karnataka ranged between 0.07 ppm (lowest) and 5.70 ppm (highest), with the overall mean value being 0.83 ppm; the distribution of fluoride in drinking water collected from different zones of Karnataka state is shown in Table 1. The mean fluoride concentration of drinking water is the highest in the north-eastern zone (1.61 ppm), and that in the south-eastern one is 0.79 ppm, followed by 0.65 ppm in the north-western, and 0.41 ppm in the south-western zones of this state. For rapid and convenient reference purposes, the spatial map shown in Figure 1 has been developed in order to visually demonstrate the overall distribution of fluoride ion concentration in drinking water in each district of Karnataka state. Clearly, the drinking water supply available in the Koppal and Kolar districts of this state have markedly elevated F\textsuperscript{-} concentrations, and for the latter one, the mean district value recorded was as high as 5.7 ppm. This spatial map also demonstrates that there is a marked and clear ‘between-district-within-zone’ variation in these fluoride concentrations, in addition to that notable ‘between-zones’.

Indeed, very highly significant differences in water fluoride concentration were found ‘between-zones’ and ‘between-districts-within-zones’ with our Model I analysis (\( p = 10^{-9} \)) for both the ‘between-zones’ and ‘between-districts-within-zones’ factors for both untransformed and Box–Cox transformed datasets. Similarly, for Model II, the ‘between-zones’ factor was highly significant for both the untransformed and Box–Cox transformed datasets (\( p = 9.03 \times 10^{-6} \), and \( < 10^{-9} \) respectively). These results are displayed in Figures 2(a) and (b); for Figures 2(c) and (d), deviations of the zone mean from the overall Karnataka state value are shown, so that positive and negative mean zonal values reflect higher and lower values, respectively, than that of the overall state.

Partial correlation coefficients (and their corresponding two-tailed significance (\( p \)) values) were computed between a multivariate (MV) dataset containing the mean district temperature, mean district rainfall and individual water source F\textsuperscript{-} concentration dataset in order to explore inter-relationships and similarities/dissimilarities between these three variables. Partial correlation was selected as an optimal method for the investigation of these relationships since it serves to provide realistic representations of relationships between pairs of the above three parameters independent of the influence of (i.e. co-correlations with) the third (potentially interfering) variable, unlike simple Pearson correlation coefficients. The corresponding partial correlation coefficient (\( r_{ab(c)} \)) matrix between these variables is shown in Table 2.

Although all partial correlation coefficients computed were low, those between the drinking water sample F\textsuperscript{-} concentration and (1) district temperature (\( r_{dI} = -.175 \)) and (2) geographic rainfall level values (\( r_{fI} = -.259 \)) were significant (\( p = .038 \) and .002 respectively), the latter highly so. Corresponding Pearson correlation coefficients (\( r \) values) between the F\textsuperscript{-} water level variable and their localised temperature and rainfall parameters were \(-0.221 (p = .008) \) and \(-0.290 (p = .004) \) respectively. That between district temperature and rainfall levels was small and positive, although weakly statistically significant (\( r = .193, p = .021 \)). No significant relationship was found between drinking water F\textsuperscript{-} content and the overall areas (size in km\(^2\)) of the districts tested.

DISCUSSION
In this investigation, we have explored the spatial distribution status of drinking water fluoride concentrations in all of the Indian state of Karnataka’s zones and districts. We collected replicated samples of drinking water from all these districts and determined the fluoride level using an F\textsuperscript{-} ion-selective electrode. Overall, an effective spatial distribution/fluoride mapping of this Indian state was provided, and much evidence for substantial and very highly significant ‘between-zone’ and ‘between-district-within-zone’ components of variation was provided.

The fluoride level of drinking water recommended by the Bureau of Indian Standards (BIS) is 1.5 ppm, although it should be noted that the Indian Council of Medical Research (ICMR) recommends a concentration of 1.0 ppm. Similarly, the Committee of Public Health Engineering, Government of India also recommends that drinking water should have a level of 1.0 ppm. However, the World Health Organization (WHO) recommends that drinking water should contain a fluoride concentration of between 0.8 and 1.5 ppm.\(^{18}\) According to the US Center for Disease Control and Prevention (CDC), when the fluoride level of drinking water exceeds 1.5–2.0 ppm, the risk of developing fluorosis is enhanced, especially in children of age <8 years.\(^{4}\) This observation has been corroborated by the International Society of Fluoride Research (ISFR) and the British Fluoridation Society.\(^{19-21}\) In view of this consideration, we elected to visit some of the fluorosis-prone districts of Karnataka, and for this preliminary examination found that 98% of schoolchildren within the 12- to 15-year age group had dental fluorosis in these areas (Figure 3) – the Tumkur district of Pavagada featured in Figure 3 is located in the south-eastern zone (although the mean drinking water F\textsuperscript{-} level is only
Table 1: Fluoride ion concentrations in the drinking water of Karnataka state districts

<table>
<thead>
<tr>
<th>Zones</th>
<th>Districts</th>
<th>Mean F− concentration (ppm)</th>
<th>Water source</th>
<th>Mean environmental temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North-western</td>
<td>Bijapur</td>
<td>0.29</td>
<td>Tap water, bore well water; water filtered through aqua-guard system</td>
<td>30.6</td>
</tr>
<tr>
<td>Mean F− concentration:</td>
<td>Belgaum</td>
<td>0.48</td>
<td>Tap water</td>
<td>20.1</td>
</tr>
<tr>
<td>0.65 ppm</td>
<td>Bagalkot</td>
<td>0.83</td>
<td>Tap water; bore well water</td>
<td>30.5</td>
</tr>
<tr>
<td></td>
<td>Dharwad</td>
<td>0.66</td>
<td>Tap water</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Gadag</td>
<td>0.84</td>
<td>River water; bore well water</td>
<td>29.4</td>
</tr>
<tr>
<td>North-eastern</td>
<td>Bidar</td>
<td>0.32</td>
<td>Open well water; bore well water</td>
<td>37.5</td>
</tr>
<tr>
<td>Mean F− concentration:</td>
<td>Gulbarga</td>
<td>0.37</td>
<td>Tap water</td>
<td>29.3</td>
</tr>
<tr>
<td>1.61 ppm</td>
<td>Yadgir</td>
<td>0.80</td>
<td>Tap water</td>
<td>32.5</td>
</tr>
<tr>
<td></td>
<td>Raichur</td>
<td>0.91</td>
<td>Tap water</td>
<td>31.1</td>
</tr>
<tr>
<td></td>
<td>Koppal</td>
<td>5.70</td>
<td>Tap water; bore well water</td>
<td>29.0</td>
</tr>
<tr>
<td>South-eastern</td>
<td>Bellary</td>
<td>1.58</td>
<td>Tap water; bore well water</td>
<td>29.3</td>
</tr>
<tr>
<td>Mean F− concentration:</td>
<td>Chitradurga</td>
<td>0.47</td>
<td>Tap water</td>
<td>28.1</td>
</tr>
<tr>
<td>0.74 ppm</td>
<td>Tumkur</td>
<td>0.24</td>
<td>Tap water</td>
<td>28.5</td>
</tr>
<tr>
<td></td>
<td>Bangalore</td>
<td>0.24</td>
<td>Tap water</td>
<td>29.6</td>
</tr>
<tr>
<td></td>
<td>Chikaballapura</td>
<td>1.00</td>
<td>Tap water; bore well water</td>
<td>27.9</td>
</tr>
<tr>
<td></td>
<td>Ramnagar</td>
<td>0.24</td>
<td>Tap water</td>
<td>30.5</td>
</tr>
<tr>
<td></td>
<td>Kolar</td>
<td>3.06</td>
<td>Tap water</td>
<td>27.0</td>
</tr>
<tr>
<td></td>
<td>Chamrajanagar</td>
<td>0.22</td>
<td>Tap water; bore well water</td>
<td>32.0</td>
</tr>
<tr>
<td></td>
<td>Mysore</td>
<td>0.75</td>
<td>Tap water</td>
<td>39.0</td>
</tr>
<tr>
<td></td>
<td>Mandya</td>
<td>0.42</td>
<td>Tap water</td>
<td>38.3</td>
</tr>
<tr>
<td>South-western</td>
<td>Karwar</td>
<td>0.68</td>
<td>Tap water</td>
<td>28.5</td>
</tr>
<tr>
<td>Mean F− concentration:</td>
<td>Haveri</td>
<td>0.28</td>
<td>Tap water</td>
<td>39.1</td>
</tr>
<tr>
<td>0.41 ppm</td>
<td>Davengere</td>
<td>0.67</td>
<td>Tap water</td>
<td>27.5</td>
</tr>
<tr>
<td></td>
<td>Shimoga</td>
<td>0.07</td>
<td>Tap water</td>
<td>29.5</td>
</tr>
<tr>
<td></td>
<td>Udipi</td>
<td>0.37</td>
<td>Tap water</td>
<td>29.0</td>
</tr>
<tr>
<td></td>
<td>Dakshina kannada</td>
<td>0.63</td>
<td>Open well water</td>
<td>28.5</td>
</tr>
<tr>
<td></td>
<td>Chikamangalore</td>
<td>0.68</td>
<td>Tap water; bore well water</td>
<td>31.0</td>
</tr>
<tr>
<td></td>
<td>Hassan</td>
<td>0.14</td>
<td>Tap water</td>
<td>39.8</td>
</tr>
<tr>
<td></td>
<td>Kodagu</td>
<td>0.15</td>
<td>Tap water</td>
<td>38.0</td>
</tr>
</tbody>
</table>

Concentrations of fluoride ion in drinking water collected from each district of Karnataka state. The bore well water source arises from a well dug mechanically at an underground level via the drilling of a pipe system through soils in order to achieve water flow through the pipes (also known as a tube-well). An electrically driven pump or manual pressure is employed to provide water from this sub-surface source. The open well source represents a well dug via a conventional approach; the well opening has a larger diameter and is retained open. The tap water supply source is that collected from a main source (river or underground) and reserved in an overhead tank or underground reservoir for public supply through pipelines (a task usually performed by municipalities). The aqua-guard system involved is an apparatus available for water filtration processes which is commercially available.
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0.24 ppm within this zone, it nevertheless contains a number of small district area compartments with elevated drinking water F− concentrations, that is, those >2 ppm). The full study performed will be reported in detail elsewhere.

The present study also found that water sampled from the districts of Kolar, Bellary and Koppal contained higher fluoride concentrations than those of the other districts investigated, an observation similar to that found in previous studies. Although districts such as Bijapur, Belgaum, Dharwad and Haveri have lower water fluoride levels than the permissible limit, previous investigations conducted found that these values were higher than those determined here. In contrast, mean fluoride concentrations in the districts of South Kannada (0.63 ppm) and Mysore (0.75 ppm) are lower than the recommended lower limit, the former strikingly so. Using a zone-wise spatial mapping profile of Karnataka state, we find that among the four zones selected (north-east, north-west, south-east and south-west, Table 1), the fluoride concentration is highest in the north-east (mean value 1.61 ppm) and lowest in the south-west zones (mean value 0.41 ppm), although it is important to note that for the former value, this effect predominantly arises from the extremely high fluoride level present in Koppal, which exerts a large weighting effect on the overall mean value determined for the north-east zone. The temperature varies from 20.1°C to 38.8°C during the rainy season, water consumption therein will, of course, elevate with increasing temperatures.

This investigation also revealed that drinking water from selected sources of the north-eastern and south-eastern zones (particularly the districts of Koppal and Kolar, respectively) is unsuitable for human consumption in view of the high fluoride concentrations of these sources, especially during the summer season when there is a higher rate of consumption by humans. Table 1 reveals that the temperature is relatively higher in the northern districts of Karnataka, and the concentration of fluoride is also much higher ($p < 10^{-9}$). Partial correlation analysis performed here confirmed that there are weak but nevertheless significant and highly significant negative correlations between drinking water F− concentrations and (1) mean district temperature and (2) mean district rainfall level, respectively. The negative partial correlation observed between rainfall and water F− content is not unexpected since an enhanced availability of water from this rainfall source will serve to effectively dilute the F− level at available drinking water sites. Notwithstanding, the weak negative correlation observed between district temperature and the aqueous concentration of F− is not simply explicable. However, we also noted a positive, albeit non-significant partial correlation between district temperature and rainfall values ($r_{ab}(c) = .139$), and this is likely to account for this confounding effect (a simple Pearson correlation coefficient between these two variables was also found to be positive but nonetheless statistically significant).

According to the United Nation’s International Children Emergency Fund
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Table 2

<table>
<thead>
<tr>
<th></th>
<th>T (°C)</th>
<th>Rainfall (mm)</th>
<th>F⁻ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T (°C)</td>
<td>1</td>
<td>0.139 (ns)</td>
<td>−0.175</td>
</tr>
<tr>
<td>Rainfall (mm)</td>
<td>0.139 (ns)</td>
<td>1</td>
<td>−0.259</td>
</tr>
<tr>
<td>F⁻ (ppm)</td>
<td>−0.175 (p = .038)</td>
<td>−0.259 (p = .002)</td>
<td>1</td>
</tr>
</tbody>
</table>

T: mean environmental temperature.
Partial correlation coefficient matrix for district temperature, rainfall and drinking water F⁻ content within the Karnataka state of India.

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Shimoga and Kolar. Although this Bangalore rural, Mysore, Mangalore, Dharwad, Gadag, Bellary, Belgaum, affected districts in Karnataka comprise Karnataka performed in 2005 and 2015 in districts within the south-western zone of focused on the incidence of dental caries strongly with our findings here. information is generic, it correlates according to UN addition to a marked zonal one. district-within-zone-dependence, in that is, there is a very high level of district-within-zone-dependence, in addition to a marked zonal one. Indeed, according to UNICEF, the fluorosis-affected districts in Karnataka comprise Dhawad, Gadag, Bellary, Belgaum, Raichur, Bijapur, Gulbarga, Chitradurga, Tumkur, Chickmangalur, Mandya, Bangalore rural, Mysore, Mangalore, Shimoga and Kolar. Although this information is generic, it correlates strongly with our findings here.

It should also be noted that studies focused on the incidence of dental caries in districts within the south-western zone of Karnataka performed in 2005 and 2015 concluded that the prevalence of dental caries among the pre-school and 5- to 13-year age groups in such districts was notably high. Indeed, the incidences of missing and decayed teeth were found to be 6.1% and 58.0%, respectively, for male, and 3.5% and 67.6%, respectively, for female pre-school children. Dental caries still represents a significant oral health problem in the majority of industrialised countries, and is known to affect 60%–90% of children, together with the great majority of adults. It is highly prevalent in selected Asian and South-American countries, and pre-school children from disadvantaged communities exhibit a higher incidence of this oral disease than that of the population in general.

Moreover, it will also be of much value to explore the incidence and severity of further fluoride-related or fluoride-dependent conditions such as dental caries in each of the districts of Karnataka, and relevant experiments to evaluate these are currently in progress.

**CONCLUSION**

In conclusion, although this study provides evidence that the concentrations of drinking water fluoride in some districts of Karnataka are within the optimum limits set (an observation contrasting with previous reports of this phenomenon but focused on its north-eastern districts only), that consumed in selected northern districts have much higher fluoride contents, and in these areas up to 98% of children suffer from dental fluorosis. Given the detrimental impact of fluorosis on oral health and quality of life in general, it is imperative that this issue is addressed. Therefore, this study recommends further investigations to determine the severity of dental fluorosis in such fluorosis-endemic areas. Conversely, there is also a major requirement for fluoridation of the drinking water supply in fluoride-deficient areas. Hence, there remains a stringent demand for the performance of an operational study to investigate means with which to maintain the normal range of fluoride concentrations in drinking water throughout the state of Karnataka. Additionally, it is of fundamental importance for healthcare professionals to ensure that the local population is adequately educated regarding the internationally accepted requirements for maintenance of the recommended daily allowance (RDA) of fluoride within their dietary intakes. Therefore, there is a major exact for frequent determinations of drinking water fluoride concentrations in each of the different regions of Karnataka state, since there are substantial ‘between-zone’ and ‘between-district-within-zone’ variations in this critical but readily measurable, health-related parameter. Moreover, judicial suplementations of fluoride should represent a major consideration for this state’s health authorities.

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**CONFLICT OF INTEREST**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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