An attempt to estimate the global burden of disease due to fluoride in drinking water

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ABSTRACT

A study was conducted to examine the feasibility of estimating the global burden of disease due to fluoride in drinking water. Skeletal fluorosis is a serious and debilitating disease which, with the exception of one area in China, is overwhelmingly due to the presence of elevated fluoride levels in drinking water.

The global burden of disease due to fluoride in drinking water was estimated by combining exposure-response curves for dental and skeletal fluorosis (derived from published data) with model-derived predicted drinking water fluoride concentrations and an estimate of the percentage population exposed. There are few data with which to validate the output but given the current uncertainties in the data used, both to form the exposure-response curves and those resulting from the prediction of fluoride concentrations, it is felt that the estimate is unlikely to be precise. However, the exercise has identified a number of data gaps and useful research avenues, especially in relation to determining exposure, which could contribute to future estimates of this problem.

Key words | dental fluorosis, disease burden, drinking water, exposure estimates, fluoride, skeletal fluorosis

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INTRODUCTION

Elevated levels of fluoride in drinking water (i.e. levels above the World Health Organization (WHO) guideline value of 1.5 mg/l – WHO 2003) have been identified in numerous countries around the world (Bailey *et al.* 2006). High levels of fluoride ingestion are known to cause both dental and skeletal fluorosis (IPCS 2002) and therefore this is a cause for concern.

Global disease burden estimates are used by international agencies, such as WHO, for:

- assessing the performance of a country or region in terms of interventions to improve health,
- mapping out geographical or population-specific differences,
- monitoring trends,
- identifying, quantifying and ranking health priorities and, thus
- informing policy decisions (Prüss & Havelaar 2001).

An accepted metric in disease burden quantification is the disability adjusted life year (DALY), which is a summary measure of population health that combines mortality and morbidity into a single unit (Murray & Lopez 1996). Traditionally, public health policy has concentrated on mortality, with the severity of disease being expressed in death rates or number of years lost due to certain causes. However, not all diseases lead to premature mortality, but they may still represent a major burden of ill health. DALYs, allow comparisons between widely differing outcomes; for example, the burden resulting from a decrease in IQ points caused by exposure to lead (Fewtrell *et al.* 2004) and skeletal fluorosis.

This is the first attempt to examine the adequacy of existing data to determine the global burden of disease resulting from elevated fluoride in drinking water supplies.

METHODS

Exposure-response relationship

A literature review was conducted to identify studies on dental and skeletal fluorosis that could be used to establish tentative exposure-response relationships. These were identified through database searches (including Medline and Poltox), bibliographic lists from the collected references and the Internet. Twelve studies were identified for dental fluorosis, outlined in Table 1.

In order to compare the results of the various studies, which used different indices to score the degree of fluorosis, data were transformed into the simple grading system proposed by Haimanot *et al.* 1987 (shown in Table 2).

Data for skeletal fluorosis were found to be less extensive. Here, only four studies presented data on skeletal fluorosis attributed to drinking water fluoride concentrations and suggested exposure-response relationships (Choubisa *et al.* 1996, 1997; Liang *et al.* 1997; Wang *et al.* 1997). The studies were performed in India and China.

For both dental and skeletal fluorosis, the percentage of the population exhibiting fluorosis (grade 2 or greater for dental fluorosis) was plotted against drinking water fluoride concentration in an 'Excel' spreadsheet and the dose-response relationship defined by plotting the best fit trend line from the Excel options.

Exposure

Geological data might provide information suitable for estimating likely drinking water fluoride concentrations, using data on the distribution of rock types to indicate likely fluorine, calcium and sodium exposures from which the population fluoride exposure could be derived. Precise geological data of this nature are, however, not available at the global level.

In this assessment, a multivariate analysis was used to predict the drinking water fluoride concentration. The data for this analysis were derived as follows. Fluoride concentration data from the rural areas outlined in Table 3 were used for the dependent variable.

Table 1 | Studies used to derive a dose-response relationship for dental fluorosis

Study location	Age group studied	Range of fluoride concentration (mg/l)	Reference
Saudi Arabia	12–15	0.5–2.8	Akpata *et al.* 1997
Norway	5–18	0.1–8.0	Bardsen *et al.* 1999
India	<18	1.1–9.8	Choubisa *et al.* 1996
India	<16	0–10.8	Choubisa *et al.* 1997
USA	8–16	<0.3–4.07	Driscoll *et al.* 1983, 1986
Tanzania	9–13	18.6†	Grech 1966
Ethiopia	7–20	1.5–36.0*	Haimanot *et al.* 1987
India	5–15	3.7–6.2	Kodali *et al.* 1994
China	not specified	<0.3–5.0	Liang *et al.* 1997
Kenya	11–15	0.1–0.93	Manji *et al.* 1986*a*
USA	8–10 & 13–16	<0.3–1.0	Selwitz *et al.* 1998

†Range not available.
*11 of 14 data points were used in the exposure-response curve (i.e. those below 20 mg/l) – see Results section for further details.

Table 2 │ The grading of dental fluorosis (adapted from Haimanot *et al.* 1987)

Grade	Description	Effect
0	Normal	No mottling, surface of teeth like glazed white porcelain
1	Mild	White chalky opacities or patches on enamel, with or without faint yellow lines
2	Moderate	Distinct brown colouring
3	Severe	Pitting of surface and sometimes chipping of the teeth

A number of independent variables, suggested in the literature, were explored (Hudson & Espenshade 1995; UN 1999, 2000; WRI 1999; World Bank 2000), including:

- mean annual precipitation aggregated into bands (<250 mm/year, 250–500 mm/year and so on);
- population density;
- water resource use;
- gross national product;
- level of agriculture;
- level of industrial employment; and
- WHO comparative risk assessment (CRA) region.

For the purposes of the WHO comparative risk assessment 14 regions have been defined (Afr D; Afr E; Amr A; Amr B; Amr D; Emr B; Emr D; Eur A; Eur B; Eur C; Sear B; Sear D; Wpr A; Wpr B) based on geographical location and the level of infant and adult mortality.

Multiple least squares linear regression (SPSS version 9 1999) was used to determine the relationship between drinking water fluoride concentration and the predictor variables defined above. The model was then applied to countries for which no fluoride data were available.

Disease burden

Predicted elevated drinking water fluoride concentrations (i.e. concentrations above 1.5 mg/l), derived from the multivariate analysis, were used as the predictor (x-axis) variable in the exposure-response curve defined from the literature to estimate the percentage of the population affected by dental and skeletal fluorosis. These figures were

Table 3 │ Fluoride data sources

Country	Reference
Australia	Riordan & Banks 1991; Slade *et al.* 1995
Brazil	Cortes *et al.* 1996
China	Wang *et al.* 1999
Germany	Kunzel & Fischer 1997
Greece	Larsen *et al.* 1989
Greenland	Larsen *et al.* 1989
Iran	Zohouri and Rugg-Gunn 2000
Ireland	Larsen *et al.* 1989
Italy	Angelillo *et al.* 1999
Japan	Miyazaki and Morimoto 1996
Kenya	Larsen *et al.* 1989
Kuwait	Vigild *et al.* 1996
Moldova	Toma *et al.* 1999
Morocco	Haikel *et al.* 1989; Abdennebi *et al.* 1995
Nigeria	El-Nadeef & Honkala 1998
Poland	Oporowska-Moszczyk & Senczuk 1997
Singapore	Lo & Bagramian 1996; Loh 1996
South Africa	Moola 1996
Sri Lanka	Dissanayake 1996
Sudan	Smith *et al.* 1953
Uganda	Moller *et al.* 1970
United Kingdom	Hillier *et al.* 2000
USA	Hinman *et al.* 1996
Venezuela	Acevedo *et al.* 1997
Zimbabwe	Sathananthan *et al.* 1996; Tobayiwa *et al.* 1991

used to calculate the number of disability adjusted life years (DALYs) attributable to elevated drinking water fluoride concentration, using a DALY calculation template made available by the WHO. (http://www3.who.int/whosis/menu.cfm?path = whosis,burden,burden_manual,burden_-manual_other&language = english)

In this part of the analysis it was necessary to make a number of assumptions:

- The age of onset for dental fluorosis is eight years. Dental fluorosis is acquired through exposure to fluoride during tooth maturation (i.e. from birth to approximately six to eight years of age). It is not possible to account for individual variability in estimates such as this, so a single onset age of eight was chosen.
- The age of onset for skeletal fluorosis, for the purpose of this estimation, has been set at 40 years. The number of people affected with skeletal fluorosis (along with the severity of their illness) increases with the length of time exposed to fluoride. Although there are reports in the literature of people with skeletal fluorosis below the age of 40, this was considered to be a reasonable median for a global estimate of disease burden. It may, however, not be appropriate for estimates conducted at a national level.
- The severity of dental fluorosis is low (0.003) and constant with age. There are no official WHO severity weights for dental or skeletal fluorosis, however severity weights have been set according to the disability classes

and indicator diseases outlined by Murray 1996, and information on similar disease outcomes (Murray & Lopez 1996). The severity of dental fluorosis, therefore, has been considered to be similar to vitiligo on the face (i.e. disability class one) and set at 0.003.

- The severity of skeletal fluorosis is relatively high and increases with age (0.24 to 0.50). This is based upon the severity weight for untreated rheumatoid arthritis (Murray & Lopez 1996), increasing to the upper end of disability class five (Murray 1996). For simplicity, the severity weight of 0.24 is assumed to apply between the ages of 40 to 59, while the weight of 0.5 is assumed to apply to those aged 60 and above.
- Life expectancy is 80 years.
- Neither health outcome is reversible after onset.
- Fluorosis is not fatal; therefore the DALY calculation is based on YLD (years lived with disability) only.

RESULTS

Exposure-response relationship

Figures 1 and 2 show the exposure-response relationships for dental and skeletal fluorosis obtained from the literature-derived data.

The data points shown in Figure 1 relate to fluoride concentrations of 20 mg/l or less. Higher levels of fluoride (3 out of 14 data points, based on a single study – Haimanot *et al.* 1987) appear to produce less fluorosis than would be
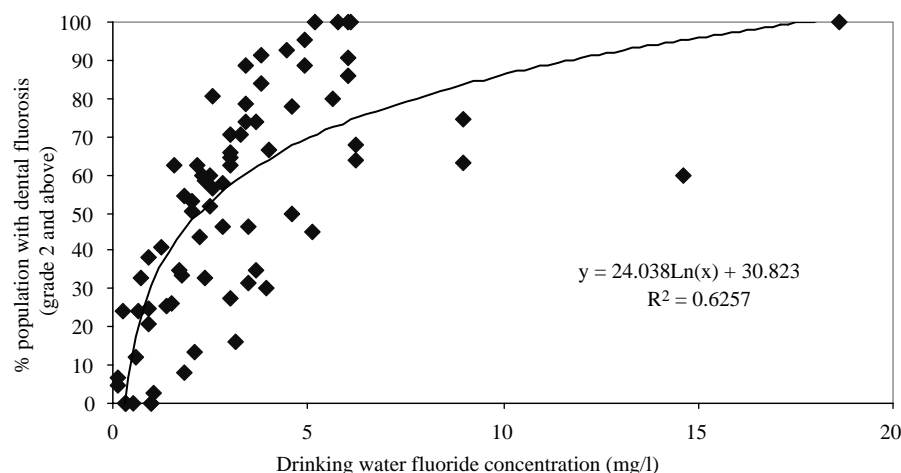
$$y = 24.038\text{Ln}(x) + 30.823$$
$$R^2 = 0.6257$$

Figure 1 │ Exposure-response relationship for dental fluorosis (grade 2 and above) and drinking water with fluoride concentrations up to 20 mg/l.
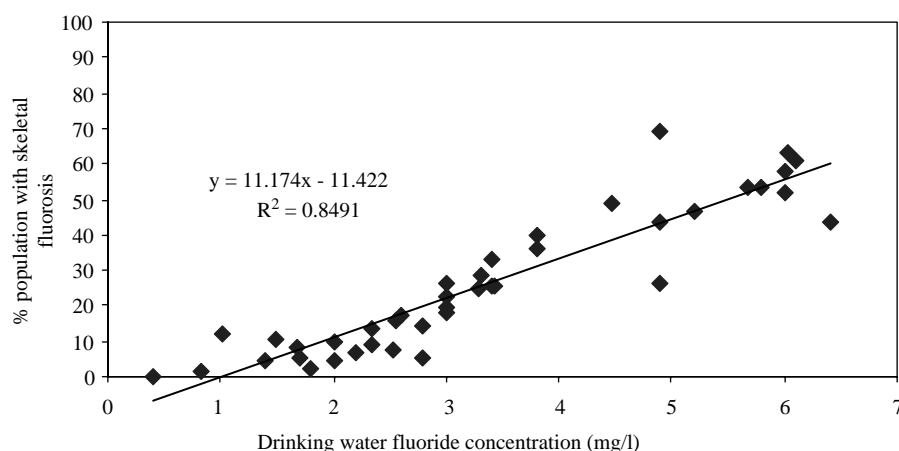
Figure 2 | Exposure-response relationship for skeletal fluorosis and reported drinking water fluoride concentration.

expected from the exposure-response relationship. There is not a strong dose-response relationship exhibited by the Haimanot study and the level of dental fluorosis at fluoride concentrations above 20 mg/l does not show a consistent trend with intra-study or inter-study (looking at the other 11 studies) data. This may reflect aversion behaviour (e.g., the use of alternative water sources) in the population apparently exposed to very high (>20 mg/l) fluoride.

Exposure

Forward selection stepwise regression analysis identified the natural log of gross national product (GNP), mean annual precipitation and whether a country is within regions 'Sear D' or 'Wpr B' as the most effective predictors of fluoride concentration as shown in Table 4. The relationships used to predict fluoride concentration are shown in Equations 1 and 2.

The model-adjusted coefficient of determination (R^2), however, suggested that the model explained only 26.4% of the observed variations in drinking water fluoride concentration. Data gaps meant that drinking water fluoride concentrations could not be estimated for all countries. The remaining countries were assigned a mean value based on the other countries within the appropriate region. The mean regional values and the number of countries ascribed a mean value is shown in Table 5.

Predicted drinking water fluoride concentrations (or the predicted regional mean) greater than 1.5 mg/l were entered

into the exposure-response relationships for dental and skeletal fluorosis, outlined in Figures 1 and 2 above, to estimate the percentage of the population affected by each illness. Waters high in fluoride are found mostly in calcium-deficient ground waters in many basement aquifers, such as granite and gneiss, in geothermal waters and in some sedimentary basins (Bailey *et al.* 2006). Thus, high drinking water fluoride concentrations tend to be experienced by discrete areas and the whole population of a country would rarely be subjected to uniform elevated exposures. There are few data available in the literature to estimate population exposed to elevated levels of fluoride. Research conducted in India, estimated that 6.9% of the population is at risk of

Table 4 | Variable weightings and significance of fluoride concentration prediction parameters

Variable	Coefficient	Standard error	Probability
Constant	3.251	0.505	0.000
GNP (ln)	− 0.189	0.057	0.000
Precipitation	− 0.000642	0.000	0.001
Regions Sear D and Wpr B	2.046	0.369	0.014

140 observations F ratio = 16.70 $P < 0.000$ Adjusted $R^2 = 0.264$

[F] = (ln GNP∗ − 0.189) + (Precipitation∗ − 0.000642) + (1∗ 2.046) + 3.25 (1) (Sear D and Wpr B).
[F] = (ln GNP∗ − 0.189) + (Precipitation∗ − 0.000642) + (0∗ 2.046) + 3.25 (2) (all other regions).

Table 5 │ Mean predicted fluoride concentrations and countries ascribed a mean value

Region	Predicted mean (mg/l)	Countries ascribed a mean value
Afr D	1.33	Mauritius
		Cape Verde
		Liberia
Afr E	1.47	None
Amr A	1.11	Cuba
Amr B	0.87	Trinidad and Tobago
		Barbados
		Bahamas
Amr D	1.09	None
Emr B	1.47	Libyan Arab Jamahiriya
		Oman
		Kuwait
		Qatar
Emr D	1.91	Somalia
		Iraq
		Djibouti
		Afghanistan
Eur A	0.84	None
Eur B	1.47	Turkmenistan
		Yugoslavia
		Bosnia and Herzegovina
		Tajikistan
Eur C	1.45	None
Sear B	0.87	None
Sear D	3.02	Democratic People's Republic of Korea
		Myanmar
Wpr A	0.41	Brunei Darussalam
Wpr B	2.92	None

exposure to elevated fluoride in drinking water (FRRDF 1999). This has been used as the upper estimate of exposure (since most countries are likely to have far lower exposure – Bailey *et al.* 2006). In this study, 1% has been assumed as the lower estimate of exposure and 3% as a mid-point estimate.

Disease burden

The population estimated to be affected by dental and skeletal fluorosis for a number of countries is shown in Table 6 and the mid-point estimate of disease burden in DALYs per 1000 population by WHO CRA region due to skeletal fluorosis is shown in Figure 3.

The estimates suggest that the greatest levels of disease burden due to skeletal fluorosis are seen in Wpr B (which includes China); Afr E (which includes Eritrea, Tanzania, Ethiopia, Kenya and South Africa) and Sear D (which includes India). This is in agreement with the literature in terms of where fluorosis problems have been reported (Bailey *et al.* 2006).

DISCUSSION

This study has produced an estimate of the population, on a region by region basis, that may be suffering from dental and skeletal fluorosis. While there are local studies of occurrence in some countries, there are almost no empirical country-wide data with which to compare this estimate. The exception is China, where it has been estimated that over 1 million people are thought to be suffering from skeletal fluorosis and 26 million from dental fluorosis as a result of elevated fluoride levels in their drinking water (Liang *et al.* 1997). The dental fluorosis estimate of 24 million produced in this study (see Table 6) is close to the local estimate. The estimate for skeletal fluorosis, of 10 million, does not. In this preliminary examination it was not possible to account for factors such as aversion behaviour (i.e., the use of water sources containing lower fluoride concentrations), engineering or other mitigation techniques. This may explain why the estimate seems to be reasonable for the relatively minor health outcome of dental fluorosis, where aversion factors are unlikely to come into play, but not for the more severe health outcome of skeletal fluorosis.

Table 6 │ Estimated population affected by dental and skeletal fluorosis in selected countries (mid point estimate)

		Population estimated to be suffering from fluorosis (000 s)	
WHO CRA region	Country	Dental fluorosis	Skeletal fluorosis
Afr D	Niger	159	41
Afr D	Senegal	119	18
Afr E	Eritrea	57	15
Afr E	Ethiopia	868	184
Amr A	USA	0	0
Amr B	Brazil	0	0
Amr D	Peru	0	0
Emr B	Saudi Arabia	263	35
Emr D	Pakistan	2,234	517
Emr D	Egypt	928	182
Eur A	UK	0	0
Eur B	Kyrgyzstan	68	16
Eur C	Kazakhstan	219	43
Sear B	Thailand	0	0
Sear D	India	18,197	7,889
Wpr A	New Zealand	0	0
Wpr B	China	23,523	10,887

Examination of the data used in this study, suggest that it is currently not possible to produce a precise global burden of disease estimate. Determining exposure remains the biggest problem. There are few data available in the literature describing actual concentrations of fluoride in drinking water with which to determine global exposure. The model outlined to predict fluoride concentration only accounted for a quarter of the variability seen in fluoride concentrations, and resulted in the prediction of elevated fluoride levels in a number of countries where these have not been reported in the identified literature (e.g. Uzbekistan, Kyrgystan and

Kazakhstan). Conversely, in a number of cases elevated levels were not predicted from countries where high levels have been reported (e.g., Mexico, Brazil and Sri Lanka – Díaz-Barriga *et al.* 1997; Cortes *et al.* 1996; Dissanayake 1996). It is also unlikely that a mean fluoride value will adequately predict illness levels. Fluoride concentrations are only one element in assessing population exposure. A second element is the number of people experiencing elevated fluoride concentrations. In this study, this is based on an estimate of those thought to be affected in India (FRRDF 1999) and some circumspection in the use of this estimate is therefore prudent. In addition, exposure also depends on the volume of fluoride-rich water consumed and also the amount of fluoride obtained from elsewhere in the diet.

It is unlikely that the exposure-response curves are globally applicable. This is especially true for the exposure-response curve derived for skeletal fluorosis which, although it seems to demonstrate a robust relationship (as shown in Figure 2), is only based on data from two countries, with three-quarters of the data being from a single region within India. There are many factors that may modify the percentage of the population affected by the same fluoride concentrations in drinking water. These include the volume of water consumed, nutritional status, altitude and other fluoride exposures (Manji *et al.* 1986*b*; Liang *et al.* 1997; Rwenyonyi *et al.* 1998; Teotia *et al.* 1998). Additionally, in many instances, the studies used to derive the exposure-response curve provide limited information on case diagnosis for skeletal fluorosis, and it is likely that the illness has not been uniformly diagnosed between each of the studies cited above. Another consideration is that dental and skeletal fluorosis are chronic diseases. It is possible that the 'snapshot' of current fluoride exposure, reported in most studies, may not be an appropriate measure of past exposure.

Converting the population figures into DALYs adds another layer of uncertainty, relating to both the severity of illness and duration. It should also be noted that the fluoride-attributed DALYs relate to the current prevalence of these chronic conditions and not simply incidence in a specific year. Other global burden of disease estimates use incidence data and may therefore not be directly comparable with the fluoride case study presented above.

Additional health outcomes have been suggested in relation to the ingestion of fluoride, including cancer,
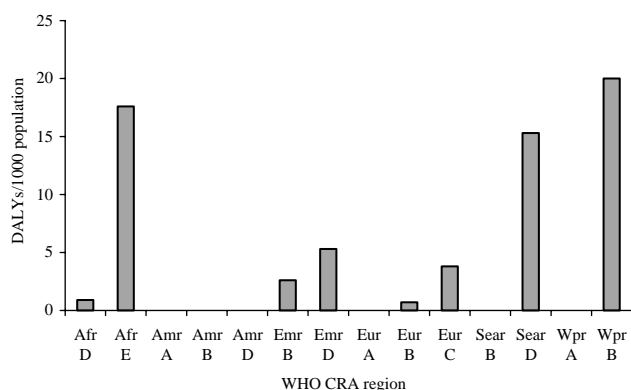
Figure 3 | Estimate of DALYs per 1000 population due to skeletal fluorosis by WHO CRA Region.

increased bone fractures, Down's syndrome and reproductive effects (IPCS 2002). Currently, however, there is no consistent evidence for most of these (IPCS 2002) and so only dental and skeletal fluorosis have been considered in this estimate.

CONCLUSIONS

Although it is likely that skeletal fluorosis causes a major disease burden in some countries, it is not currently possible precisely to quantify this burden of illness on a global scale. More data are needed on drinking water fluoride concentrations, the number of people exposed to such levels and also sensible and validated exposure-response relationships accounting for major confounding factors such as differences in nutritional status, dose and other fluoride sources. This suggests the need for a series of targeted studies at country level if the actual burden of illness from this cause is to be estimated.

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