FLUORIDE-LINKED DOWN SYNDROME BIRTHS AND THEIR ESTIMATED OCCURRENCE DUE TO WATER FLUORIDATION

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SUMMARY: Down syndrome (DS) birth rates (BR) as a function of maternal age exhibit a relatively flat linear regression line for younger mothers and a fairly steep one for older mothers with the second line intersecting the first line a little above maternal age 30. Consequently, overall DS-BR for all maternal ages are not a very reliable parameter for detecting environmental influences, since they may be strongly affected by the ratio of the number of younger to older mothers. For this reason, data for mothers under age 30 were selected to detect an association between water fluoridation and DS for which the lower maternal age regression would be a much smaller contributing factor.

The early research of I Rapaport indicating a link between fluoride in drinking water and Down syndrome was followed by studies claiming there was no such association. Application of sound methodology to the data in those later investigations shows that none of the criticisms against Rapaport's work are valid. For example, in the data of J D Erickson on maternal age-specific DS births in Metropolitan Atlanta, Georgia, when the three youngest maternal age subgroups are reasonably combined into single groups for areas with and without water fluoridation, a highly significant association ($P < 0.005$) is revealed between fluoridated water and DS births.

It also appears that the dose-response line (DRL) of DS-BR for daily fluoride intake may have no allowable level that does not induce fluoride-linked DS births. Therefore fluoride may be one of the major causes of DS other than aging of mothers. The number of excess DS births due to water fluoridation is estimated to be several thousand cases annually throughout the world.

Key Words: Down syndrome; Down syndrome births; Fluoridation; Fluoride intake.

INTRODUCTION

In 1956-63 Ionel Rapaport,[1-3] a French-trained endocrinologist, working at the Psychiatric Institute of the University of Wisconsin, USA, presented evidence for a fluoride link to Down syndrome (DS, or "mongolism" – the trisomy-21 genetic disorder characterized by mental retardation, weak muscle tone, and epicanthic folds at the eyelids). Until recently, his data were compared with the mean values of Down syndrome birth rates (DS-BR) in fluoridated and non-fluoridated areas without consideration of the effects of demographic characteristics of the population.

In 1976 Erickson *et al* [4-5] (Centers for Disease Control, USA) discussed this problem in connection with their maternal age-specific DS incidence data in areas with and without fluoridated water (F and NF). Although they could recognize by inspection a higher incidence pattern of DS among younger mothers, they could not confirm the statistical significance of the difference between the two areas and concluded that there was no association between the incidence of DS and water fluoridation.

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My first purpose is to reveal the truth possibly being concealed in their paper by correcting an inadequate insight into appropriate methodology.

SUBJECTS AND METHODS

For clarifying the distribution pattern of the mean values of DS-BR ascertained by the hospital records and/or multiple sources, data collected by Lilienfeld and Benesch[6] were examined.

The main data used here for detection of the effect of fluoride on DS-BR in the five-counties of the Metropolitan Atlanta, Georgia, area were ascertained from similar multiple sources.[4]

During his research on this problem, Professor A W Burgstahler, University of Kansas, obtained from Dr Erickson the observed sample sizes of the maternal age-specific subgroups which were not given in his paper. Professor Burgstahler kindly sent me these numerical data, and the analysis presented here was performed with them.

The NIS (National Intelligence Service) data in Table 2 in Erickson's first paper[4] and the 44 large US cities data in Table 2 in Erickson's second paper[5] were used for clarifying the distribution pattern of DS-BR ascertained from birth certificates.

The statistical method applied is the usual chi-square test for 2×2-fold tables. The data-processing rule, "Not to leave the subgroups unnecessarily overstratified,"[7] was applied which led me to combine the subgroups of young mothers in Erickson's Table 2[4] into one group so as to enhance the statistical power of the analysis.

The two exponential regression models behind the DS-BR-maternal age curve were obtained from publications by Jenkins[8] and by Lilienfeld and Benesch[6].

In my analysis of a DRL (dose-response line) between the daily intake of fluoride and the DS-BR, Heyroth's formula[9] was used to transform the concentration of fluoride in drinking water into the corresponding total daily intake, and then a linear regression analysis was performed.

RESULTS

Part I.

Quality of DS-BR data ascertained by birth certificates vs multiple sources

1. Amount of information provided by the two kinds of DS ascertainment

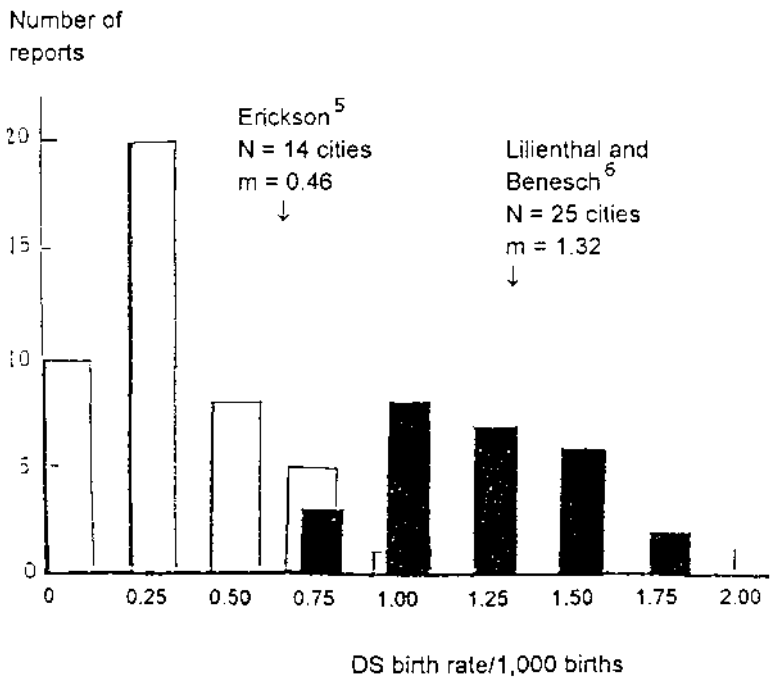
In 1969 Lilienfeld and Benesch[6] tabulated 34 studies on DS-BR (per 1,000 births) for the years 1923-1966. After eliminating six of the studies for lack of information on the method of ascertainment, the remaining 28 studies included two with ascertainment by birth certificates which gave very low rates of 0.32 and 0.52. Of the 26 studies ascertained by hospital records, one extraordinarily large rate of $X_N = 3.4$ was rejected as an unusual sample because the difference between the mean $\Delta = X_N - X$ corresponds to the rare probability of $P < 0.05$ as a random sample from this population. Finally the DS-BR from the-remaining 25 studies are shown as a histogram in the right side of Figure 1, which ranged from 0.83 to 1.90/1,000 births and gave 1.32/1,000 births as an algebraic average of 25 mean

values (Figure l). The data in about a half of these 25 studies were ascertained by hospital records and the others were further verified from multiple sources.

By contrast, Erickson *et al*[5] reported DS-BR ascertained by birth certificates in 44 large U.S. cities, among which 27 cities had a fluoridated water supply and 17 did not. The distribution of DS-BR in these cities, shown on the left side of Figure l, ranges from zero to 1.29/1,000 births and is located nearer the origin than those given by Lilienfeld[6]. The two distributions overlap only in several percent with one another. The algebraic average of 44 mean values was 0.456/1,000 births, only about one third that of Lilienfeld and Benesch. This low value of the total average is not influenced by the reported 50% sampling from birth certificates of sample size N in some of the cities, provided that the sampling was performed fairly randomly and the particular mean was obtained by dividing the total sum of the observed values N of their sample size by 2.

Therefore, DS-BR data ascertained by hospital records and/or multiple sources may be more useful than data ascertained by birth certificates alone. Whether the latter would be accompanied by reduction in quality will be discussed later.

Figure 1. Distribution of DS birth rate ascertained by birth certificates (left) and by hospital records (right) (K Takahashi 1997)



2. Two-component exponential regression model behind the DS-BR-maternal age curve

Jenkins in 1933 seems to be the first researcher who illustrated with four sets of data, DS-BR-maternal age curves on semi-logarithmic paper. He stated that the DS-BR behaved as a logarithmic function of the age of the mothers.

Over 30 years later, Lilienfeld and Benesch[6] reviewed 34 studies on DS-BR, among which only eight were stratified by quinquennial maternal ages. These eight are shown on a semi-logarithmic plot in Figure 2. These authors noted that the risk of DS remained practically constant up to 30 years, after which it continued to increase during the remainder of the reproductive period with the plots of the logarithms of the rates being almost linear. Practically, Lilienfeld and Benesch may be the first researchers who were aware of a double regression model behind the relation between DS-BR and maternal age.

Hence statistical analysis of DS-BR should be performed separately on younger mothers less than 30 (or 32 according to Jenkins) years of age and on older mothers more than 30 or 32 years of age.

Part 2.

Detection of fluoride-linked DS in Erickson's 1976 data for younger mothers

1. Data from Erickson's paper titled "Water fluoridation and congenital malformations: no association" [4]

These data were obtained primarily from the Metropolitan Atlanta Congenital Malformations Surveillance Program, which began in 1967, and were supplemented by the private survey data by Drs A J Ebbin and S Shimpler for the years 1960-1967.[4] All cases of DS were ascertained by regular staff visits to all hospitals that had obstetric or pediatric services, originally within one year after birth, and, supplemented later by a retrospective ascertainment, using multiple sources to track children born during 1960 to 1973. The DS-BR by maternal residence in areas with and without fluoridated water were recorded for five-year intervals of maternal age.

Table 1. DS birth rates, DS births, and total births for subgroups of specified maternal ages in F and NF areas of Metropolitan Atlanta, Georgia, 1960-1973

	F Area			NF Area		
Maternal age	DS birth rate*	No. of cases	Sample size	DS birth birth rate*	No. of cases	Sample size
≤19	7.7	19	24,811	3.8	7	18,319
20-24	6.9	41	59,266	4.0	15	37,612
25-29	6.8	34	49,865	4.1	11	26,884
	7.02	94	133,942	3.98	33	82,815

* per 10,000 white births

Figure 2. Incidence rates of Down Syndrome by maternal age from selected studies (Lilienthal and Benesch[6])

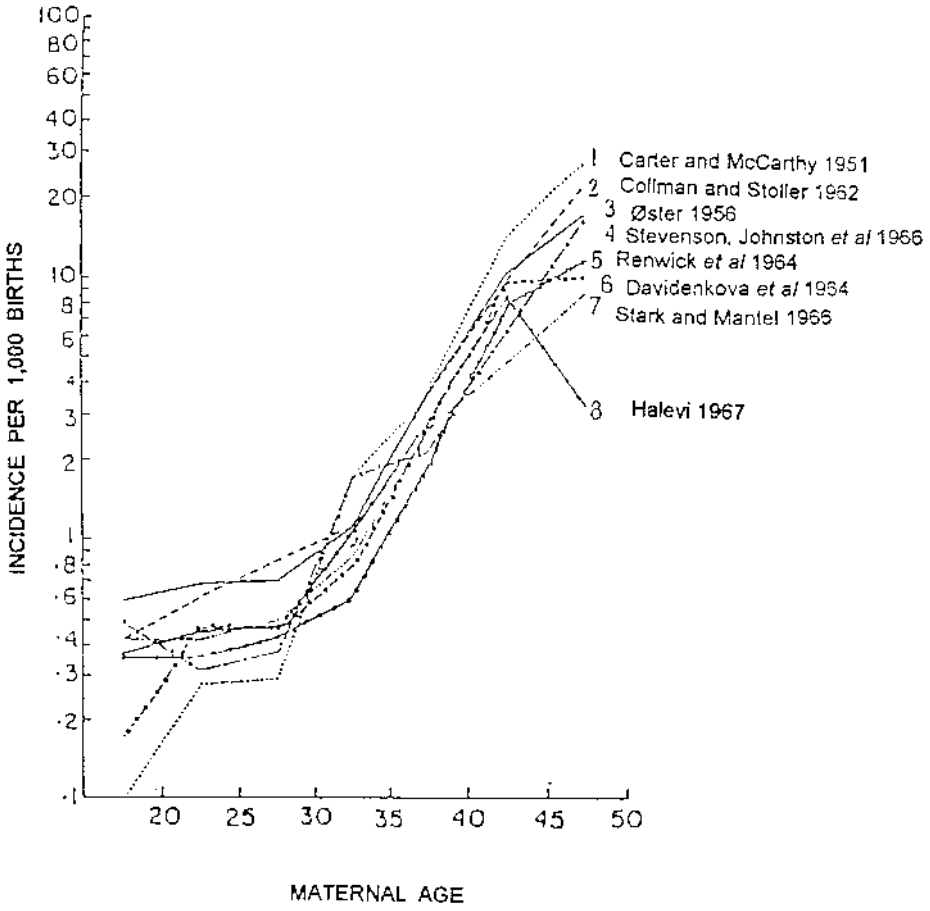


Table 2 . Significance test on DS-BR for subgroups of specified maternal ages in the F and NF areas of Table 1

Maternal	F Area			NF Area		
Age	DS +	DS -	Sum	DS +	DS -	Sum
# 19	19	24,792	24,811	7	18,312	18,319
20-24	41	59,225	59,266	15	37,597	37,612
25-29	34	49,831	49,865	11	26,673	26,884
Sum	94	133,848	133,942	33	82,782	82,815
	chi-square = 0.182 P > 0.50			chi-square = 0.021 P > 0.50		

The actual numbers of births for each maternal age interval, which were not given in Erickson's Table 2, were supplied by his reply to a request by Professor Burgstahler, and the total numbers were corrected to 166,186 for the fluoridated areas and to 101,639 for the nonfluoridated areas.

In his paper Erickson stated that the DS-BR of both data sets (Atlanta and NIS) suggested that in fluoridated areas, "there may be an increased incidence at young maternal ages". This statement shows that the possibility of an age-related fluoride link to DS was under consideration. Erickson tested the significance of the difference in DS-BR in the F and NF areas and obtained low chi-square values of 1.98, 2.93 and 1.78 for each of three younger maternal age subgroups, which seemed adequate for him to reject this hypothesis.

If Erickson had noted that the DS-BR in each of the young mother subgroups in the F and NF areas are nearly the same, he could then have considered whether to keep the three subgroups separate or to combine them into a single group according to the principle of data processing, *i.e.* "Not to leave the unnecessary over-stratification which prevents higher sensitivity of the statistical testing." [7]

Thus the preliminary procedure tried here was a chi-square test on the three DS-BR in each of the F and NF areas (Table 2). One thereby obtains very low chi-square values of 0.182 and 0.021, both of which are far from being significant. This result makes it reasonable to combine the three subgroups in each of the F and NF areas to obtain the four-fold array shown in Table 3.

The highly significant chi-square value of 8.04 calculated from Table 3 very clearly confirms the existence of fluoride-linked DS ($P < 0.005$), as Rapaport originally suggested in 1956.

Here it should be noted that Burgstahler, after he obtained the sample-size data for each subgroup from Erickson, confirmed the significant fluoride effect (chi-square = 6.8) in mothers less than 35 years of age but not in those less than age 40 in the Atlanta data, whereas not at all in the NIS data.[10,11]

The present analysis clarifies the theoretical basis for the empirical procedure by Rapaport and Burgstahler. Earlier, the present author,[12] who could not obtain a reply from Erickson, estimated the sample size for each maternal age subgroup by dividing the case number by the rate and confirmed the fluoride-linked DS by the same procedure given here.

Table 3. Number of DS births in combined young mother age groups from Table 1 specified by the F and NF areas

DS	F area	NF area	Sum
+	94	33	127
-	133,848	82,782	216,630
Sum	133,942	82,815	216,757
Rate /10, 000	7.02	3.98	

2. Loss of qualitative information in the data ascertained by the birth certificates

Although the problem of data quality is primary to the very essence of science, an appropriate set of data according to experimental design, if given, enables the statistician to deal with such a problem. Fortunately, Erickson[5,6] supplied such data but without appropriately addressing this problem.

Table 4 shows the influence of the data from the birth certificates (NIS and 44 cities, or "44C" data)[5] in comparison with those from the hospital records and/or multiple sources (Atlanta)[4] on DS-BR in F and NF areas.

The last column of Table 4 shows that the information on fluoride-linked DS seems to remain in the Atlanta data based on the hospital records and/or multiple sources, especially in those of young mothers. However, nothing remains in the NIS and 44C data based on only birth certificates, even in those of young mothers.

Table 4. Comparison of the DS-BR in the F and NF areas in three studies by Erickson

Item Survey	Maternal age	F DS/total birth	NF DS/total birth	F DS-BR*	NF DS-BR*	Δ = diff in DS-BR F and NF
Atlanta	All	166/166,182	86/101,639	10.0	8.5	1.5
	<30	94/133,942	33/82,815	7.0	4.0	3.0 †
NIS	All	115/234,300	524/1,032,100	4.9	5.1	-0.2
	<30	49/173,500	181/773,800	2.8	2.3	0.5
44C	All	178/432,580	90/204,185	4.1	4.4	-0.3
	<30	90/353,148	48/169,416	2.6	2.8	-0.2

* per 10,000 births † $P < 0.005$

This analysis thus presents evidence that, owing to loss of both quantitative and qualitative information, the data ascertained only by birth certificates has no power to negate a fluoride-link to DS birth.

Part 3. Daily fluoride intakes as one of the major causes of DS births

After we obtained a DRL (dose-response line) of DS-BR as a function of the concentration of F in drinking water, we wanted to estimate the contribution of food-borne fluoride in DS births.

For this purpose, the concentration of fluoride in the drinking water (x) must be first transformed into the total daily fluoride intake (z). In 1954 Heyroth[9] proposed a formula to do this. According to his formula, when x = 0 ppm, it will be transformed into z = 0.627 mg F/day and when x = 1.0 ppm, into z = 1.514 mg F/ day (Appendix 2).

Since fluoride other than in water fluoridation appears to be increasing year by year, Heyroth's 1954 formula may be better to apply in the USA to Erickson's survey data for 1960-1973 than any other newer formulae.

Now my task is the test of hypothesis "No allowable limit of fluoride in DS births" by the help of regression analysis, clarifying whether the dose-response line (DRL) goes through three points, namely two fluoride points $P_1(y_1\ z_1{:}\square)$, $P_0(y_0,z_0{:}\bigcirc)$ and the origin P(0,0:origin), shown in Figure 3.

As Erickson did not give the level of fluoride in the NF areas, we have to use a reasonable range for it: 0.1-0.3 ppm F. Figure 3 shows that the deviation of this DRL around the origin is less than 0.1 mg F/day on the z-axis and less than 1.3 DS/10,000 births on the y-axis.

If the estimates by Professor Burgstahler[11] starting from Rapaport's paper[2] are used (personal communication), we see that the DRL fits one theoretical and two observed points exactly without any recognizable deviation, as calculated in Appendix Table 1, in spite of the use of age-specific DS-BR for mothers under age 40 in Rapaport's study, not age 30 as in Erickson's work.

Though many environmental factors have been hypothesized for DS, *e.g.*, maternal illness, radiation exposure, viruses, endocrine factors, and others, the above analysis confirmed that there might be no other factor which promotes DS so steadily and widely as the total daily intake of fluoride except aging of mothers.

Part 4. Excess DS births linked to artificial water fluoridation worldwide

The DRL in Figure 3 enables us to estimate how many DS babies may be born to mothers ingesting 1 ppm fluoridated water. This estimate can be made as shown in Appendix 2. The number is around an additional 5-6 DS babies/10,000 births among young mothers living in fluoridated areas.

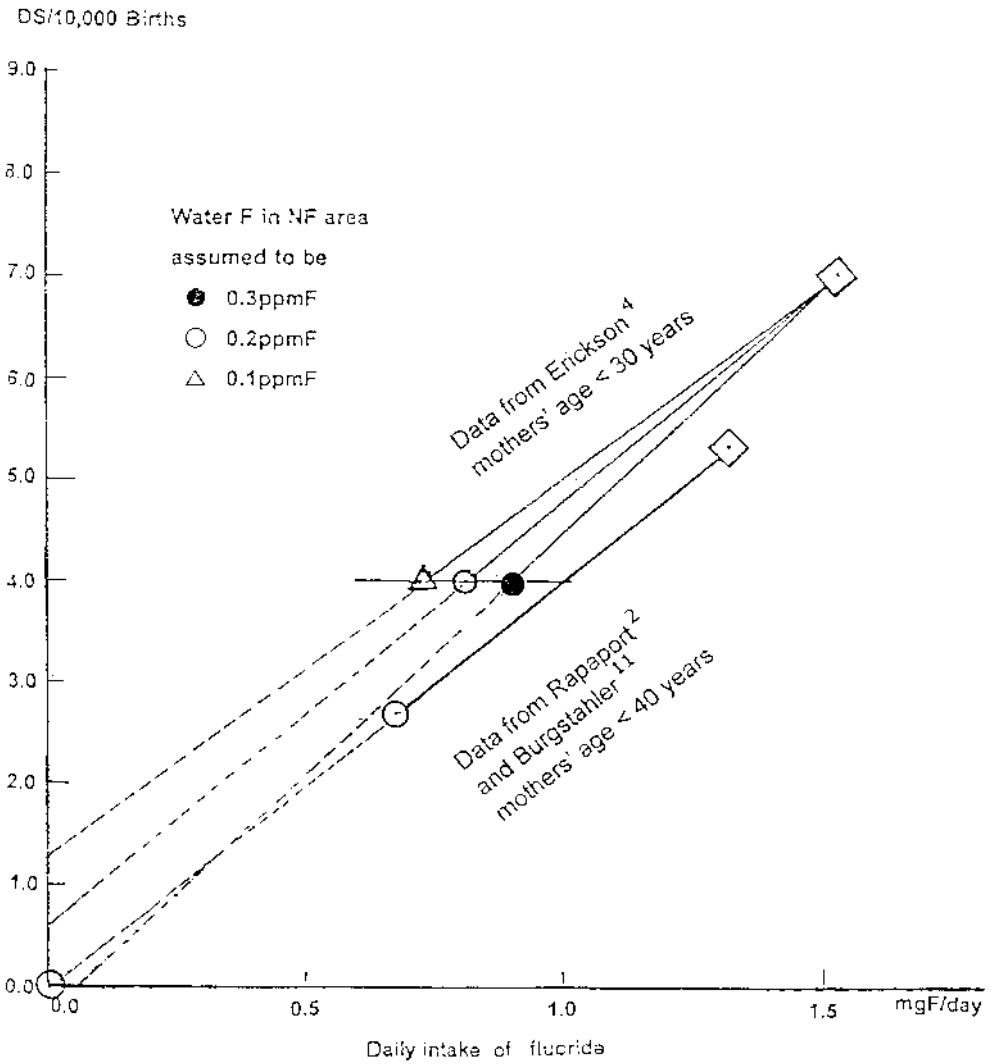
As Erickson's Atlanta data reported 7.02 cases of DS/10,000 births from mothers less than 30 years of age in the F areas and 3.98 cases in the NF areas, the excess DS births may be Δ = (7.02-3.98)/10,000 births ≈ 3.04 cases/10,000 births. Since 1990 FDI Basic Facts[13] reports that 325,000,000 people in the world are receiving artificially fluoridated water, an estimate of excess DS births linked to fluoridation worldwide may be derived from Erickson's data.

The first step is to estimate the number of births born to mothers under age 30 by multiplying the total birth rates in the countries by the percentage of births among young mothers. The second step is to adjust Erickson's lower DS-BR in comparison with those of Lilienfeld and Benesch[6] or Smith.[14] The third step is to include the increased daily intake of fluoride after Heyroth.[9]

As shown in Appendix 3, the number of DS babies linked to water fluoridation worldwide may thus be estimated to be about 3,000 cases per year (range 1,120-6,000). In any event, the excess DS births linked to artificial water fluoridation throughout the world may not be several tens but possibly several thousands annually, if fluoridation were to continue. From a humanitarian viewpoint such an enormous number of excess DS births linked to artificial water fluoridation is

not likely to be offset by a decrease in dental caries, since several communities in Japan, for example, now have less caries without use of any kind of fluoride.[15]

Figure 3. Two regression lines for DS birth rates among young mothers and the daily intake of fluoride (K Takahashi 1997)



DISCUSSION AND CONCLUSION

In 1975 Burgstahler[16] published an editorial review on DS in which he explained and supported Rapaport's papers written in French and countered the criticisms against Rapaport by Berry[17] and by Needleman *et al.*[18] In 1977 he presented his views to a committee hearing of the US House of Representatives.[19] This and his further research on this problem were also presented in Chapter 13 of the book *Fluoridation: The Great Dilemma*.[20]

In spite of Rapaport's extensive work and its subsequent validation, a recent Ad Hoc Subcommittee Report[21] published by the US Public Health Service dismissed Rapaport's research with the curt comment: "The results of three later studies conducted by other investigators with fuller ascertainment of cases did not confirm the finding." In my view the criticism of Rapaport in the Ad Hoc Subcommittee Report is completely meaningless from the viewpoint of methodology.

Lilienfeld and Benesch,[6] on the other hand, criticized Rapaport from the viewpoint of his low incidence of 0.44 DS cases per 1,000 births as proof of a low degree of ascertainment. But Rapaport accepted only cases ascertained and registered with a higher degree of accuracy by university and other research hospitals. The reduction in the number of cases due to such an advanced level of ascertainment is acceptable methodologically, provided the ascertainment was performed independently of whether the particular birth occurred in the F or NF areas.

Further, it should be noted that the DRL of the DS-BR in relation to the daily intake of fluoride according to Rapaport-Burgstahler's data[11] goes through the origin of the graph. This fact supports the accuracy of these data, despite the lower absolute values.

Taves criticized Burgstahler for his "selective use of data" (*i.e.*, use of young age maternal data). But the two-component exponential regression model behind the DS-BR-maternal age curve supports this use by Burgstahler and also by Takahashi (Figure 2).

The Ad Hoc Subcommittee Report[21] did not accept Rapaport's fluoride link to DS. However, it recommended studies to examine the reproductive toxicity of fluoride using various dose levels and the minimally toxic maternal dose. Further, it recommended studies to investigate whether fluoride is genotoxic or not. The report also stated that the US Public Health Service should sponsor scientific conferences to recommend the optimal safe level of total fluoride exposure from all sources combined (including drinking water).

Although the etiology of DS in areas with nearly a nil level of fluoride in the water supply has not been discussed until recently, my analysis reveals that fluoride from daily food may contribute to DS births. Supposedly, fluoride has been a steady environmental factor as well as an intrinsic aging factor in older mothers. Of course this interpretation will require another confirmation from various scientific disciplines. If the evidence becomes generally accepted, then fluoride might be an unavoidable public nuisance, especially for young mothers.

"The lesser is better" may be an important principle of life science in connection with fluoride.

Artificial water fluoridation for prevention of dental caries was introduced in 1945 in the USA and has been recommended and promoted by the World Health Organization. But now we must ask the people of the world whether such an amount of fluoride linked to Down syndrome can justify a possible decrease in dental caries or not. It must be stressed that the prevention of dental caries can be achieved by environmentally safer and less costly alternative procedures.[15]

ACKNOWLEDGEMENT

I thank Professor A W Burgstahler who kindly sent me large amounts of numerical data. I am also grateful for all his correspondence with me that greatly helped my methodological approach to this problem. I am also grateful to Dr Toru Murakami, former President of the Japanese Society for Fluoride Research, and Dr Kenji Akiniwa for their kind comments.

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APPENDICES

Appendix 1

Test of the hypothesis "No allowable limit of fluoride in DS births"

As Erickson did not give the level of fluoride in the NF areas, I have used a reasonable range of 0.1-0.3 ppm F. Figure 3 shows that the deviation of these dose response lines (DRL) around the origin is less than 0.1 mg F/day on the x-axis and less than 1.3 DS/10,000 births on the y-axis.

If the estimates by Burgstahler starting from Rapaport's paper for maternal age < 40 are used as data from a personal communication, we see that the DRL fits one theoretical and two observed points exactly without any recognizable deviation, as calculated in Appendix Table 1.

Appendix Table 1. Regression analysis on Rapaport-Burgstahler data

Nature of water F ppm	Geomet. mean of F ppm	(x) mg F per day	(y) DS/10,000 births
0.3-2.6	0.780	1.319	5.36
0.01-0.2	0.045	0.667	2.66
		0.000	0.00

$\Sigma x = 1.986$ $\Sigma y = 8.02$
Sx = 0.869918 (Sum of squares of x)
Sy = 14.365067 (Sum of squares of y)
Gxy=3.83482 (Product Sum of x and y)
(Water F ppm = 0 is substituted by 0.01 Which corresponds to the identification limit of F)

Factor	Analysis of Sy		Df †	F
Regr.	Cxy^2/Sz	14.363368	1	Fs=8454.41**
Remaind.	$Sy-Cxy^2/Sx$	0.001699	2-1=1	
Total	Sy	14	3-1=2	

** P < 0.01 $F^1_{,(0.05} = 161.4$, $F^1_{,(0.01)} = 4052$
† The degree of freedom of the origin is assumed to be 1

Appendix 2
Estimation of daily F intake from the concentration of F in drinking water (on the basis of Heyroth's work, 1954)

F F Heyroth in the USA[9] measured the daily amount of F ingested from food (y mg/day) in areas where drinking water contained F in 0.1 to 8 ppm (x). The contribution y showed a linear regression to x in the range of x = 0.1~6 ppm. From 2 liters of total daily use of water, two-thirds are obtained from foods or are used separately for cooking and the other one-third is drunk. The present author estimated the daily intake of F as the sum of y and 667 mL of x for each area specified by the concentration of F in drinking Water (Appendix Table 2).

Appendix Table 2. Estimated daily intake of F from food and F in drinking water (Heyroth and Takahashi)[9,12]

F in water (ppm)	F from food (mg/day)	F in 2L (mg)	F in 667mL (mg)	Daily Intake (mg/day)
0.0	0.627	0.0	0.000	0.627
0.1	0.649	0.2	0.067	0.716
0.2	0.671	0.4	0.133	0.804
0.3	0.693	0.6	0.200	0.893
0· 7	0.781	1.4	0.467	1.248
1.0	0.847	2.0	0.667	1.514
2.6	1.217	5.2	1.733	2.950

This table shows that 1-ppm water fluoridation increases the daily intake of F up to Δ = 1.514 - 0.617= 0.887 mg F/day which may correspond to the excess of 3.03 DS/10,000 births in young mothers (Erickson)[4]. Therefore a 1 mg increase of daily intake of F may correspond to a DS- BR of 3.03 x 1/0.887 = 3.42. If adjusted to the DS-BR of Lilienfeld [5] or Smith [14], the excess DS-BR may be 5.34 or 6.05.

Appendix 3.
Estimation of excess DS births among young mothers linked to fluoridation worldwide

I. Population factors

People receiving artificially fluoridated water: N = 325,000,00 (FDI, 1990).[13]

Population defining factors:

a) birth rate/1,000 population: 10/1000 - 15/100 - 20/1000

b) births from young mothers/total births: 0.75 - 0.80 - 0.85

c) Births from young mothers: n = (N × a × b)/year

II. Fluoride-linked DS factors

Excess DS birth/10,000 young mothers:

7.02(F) - 3.98(NF) = 3.04/10, 000 young mothers

DS births defining factors:

a) Ascertainment adjusting factor (DS births/10,000 population)
adjusting to Lilienfeld: 13.2 (Lilienfeld)/8.46 (Erickson) = 1.56
adjusting to Smith: 15 (Smith)/8.46 (Erickson) = 1.77

b) Adjusting to the excess daily fluoride intake (Heyroth): $d_1/d_0 = d_1/0.627$ mg/day

Estimates of the number of DS births linked to artificial water fluoridation:

min = $325 \times 10^6 \times 10/1000 \times 0.75 \times 3.04/10,000 \times 1.56 \times 1.0$ = 1,160/year

med = $325 \times 10^6 \times 15/1000 \times 0.80 \times 3.04/10,000 \times 1.67^* \times 1.5$ = 2 970/year

max = $325 \times 10^6 \times 20/1000 \times 0.85 \times 3.04/10,000 \times 1.77 \times 2.0$ = 5, 950/year

* (1.56 + 1.77)/2 = 1.67