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# Barium exposure of an invasive breast cancer cluster investigation – quantitative drinking water chemistry for carcinogen search

Paul Kamlade

P.O. Box 473, Dubbo, NSW 2830, Australia

E-mail: paul.lifetree2@gmail.com

## Abstract

Quantitative review of oral barium exposure was conducted using drinking water metals data from the confirmed sixfold (18-fold$_{15–39\ years}$) Brisbane Australia invasive breast cancer cluster (IBC) investigation, which also included fivefold duct carcinoma *in situ* (DCIS). The new approach here was to assess sub-guideline on-site water system barium fluctuations and use cancer slope factor (CSF) firstly to profile match barium as a carcinogen, then correlate risk. Dissolved barium was converting, up to 71%, into non-dissolved forms in the cluster location; with only up to 3% in a comparison location. A CSF of approximately 330 (mg L$^{-1}$)$^{-1}$ gave a chemistry-based number of women of 12, consistent with 14 originally (mostly IBC), less 2 per general population biostatistics. The comparison location gave null women numbers. One-woman IBC correlated to 0.0018 mg/L barium, comparable to the US Environmental Protection Agency's (USEPA) 0.002 mg/L, 10$^{-4}$ cancer risk for arsenic. The two- to fivefold San Diego USA IBC cluster had barium as the only metal in common with Brisbane; and, breast cancer alcohol risk factor fingered barium qualitatively. It is put that barium causes IBC and DCIS; proof submitted hereby to wider scrutiny. The relevant barium exposure was likely calcium coprecipitated.

**Key words:** barium, breast cancer, Brisbane, sub-guideline, water

## INTRODUCTION

### Objective

Goodman *et al.* (2012) have called for creative, multidisciplinary input following a 20-year retrospective of 428 US cancer cluster investigations, with some 70 cancer types confirmed by incidence increase though without a clear cause. There is discussion on whether cancer clusters are worth further pursuit or funding. Hypothesised exposures for breast cancer included barium and unspecified drinking water contaminants (p. 484, Table 2).

The objective of this mini-review was to conduct drinking water barium detailed chemical determinations in view to resolve the Brisbane Australia breast cancer cluster.

### The Brisbane Australia breast cancer cluster

Armstrong *et al.* (2007) (AEA7) reported the statistically confirmed sixfold (18-fold$_{15–39\ year}$) Brisbane invasive breast cancer (IBC) cluster that occurred in the TV building of the Australian

Broadcasting Corporation (ABC) in the suburb of Toowong. The biostatistics (p. 13) were subjected to international peer review (p. 35). The seriousness of the case was augmented by the determination that the IBC risk increased significantly by about 12% for a 1-year increase in the duration of past work at the ABC (p. 13). Despite many on-site environmental health measurements, including for public supply drinking water metals, no cause was identified by the (medical) panel (p. 40).

AEA7 includes an extensive literature review on risk factors for breast cancer (pp. 25–34). However, no related textual discussion has arisen specifically on barium and drinking water. Appendix 2 has additional references (pp. 66, 68). Of these, McElroy *et al.* (2006) titled on cadmium, leads water metals testing, and on a 'Suspected' basis only, not a 'Known' basis (p. 68). Water metals science is on p. 64, but this does not cover barium (refer 'Barium fate,' below).

Water testing aspects of AEA7 were documented: general (pp. 19, 64); test specification (pp. 65–67); and laboratory report (pp. 69–70). Barium appears on pp. 19, 67, and 70.

AEA7 on-site water system barium readings, typically 0.03 mg/L (p. 70), were mostly some 20-fold less than the 2004 ADWG barium 'Guideline value…*' of 'Health' '0.7' listed in the cited (p. 67), Table 10.10 with footnote, '* All values mg/L unless otherwise stated.' AEA7 eliminated against this 0.7 mg/L figure (pp. 19, 64, and 66–67).

The supplemental information here has links to a three-page condensed version of AEA7 and associated documents.

IBC and duct carcinoma *in situ* (DCIS) are cancers which begin in cells that line the milk ducts with (non-invasive) DCIS considered an early stage of IBC (American Cancer Society 2016).

## Literature – barium toxicity

Literature reviews are conducted under the ADWG NHMRC (Australian Drinking Water Guidelines by the National Health and Medical Research Council) and documented within fact sheets for each contaminant. These guidelines are subject to rolling update against peer-reviewed international research, with the latest ADWG being released in 2011. Minor updates, through to August 2018, do not involve barium (NHMRC 2011, pp. iii–iv). The guideline at the time of the AEA7 study was the 2004 version.

*Established toxicity*: 'At high concentrations, barium causes strong vasoconstriction (constriction of blood vessels), peristalsis (contractions of the alimentary canal), convulsions and paralysis' (NHMRC 2004, Barium fact sheet). The 2011 ADWG referred major reviews, focussing on health end point determinations for barium, 'In rodents, kidney toxicity appears to be the most sensitive effect, whereas in humans, cardiovascular (hypertension) effects have been of prime concern' (NHMRC 2011, Barium fact sheet). The barium fact sheets have guideline levels of 0.7 mg/L in 2004 and increased to 2 mg/L in 2011. Technology and resources considerations were included for the latter.

*Carcinogenicity*: 'There is no evidence that barium causes cancer. Barium chloride is not mutagenic in tests with bacteria and does not damage DNA' (NHMRC 2004, Barium fact sheet). In 2011, this was clarified, 'There is no evidence from chronic rodent studies that barium causes cancer. The weight of evidence indicates barium is not mutagenic in tests with bacteria and does not damage DNA' (NHMRC 2011, Barium fact sheet). The NHMRC (2011) reference list includes the (USA) National Toxicology Program (1994) (NTP) barium chloride, drinking water rodent studies, and the International Programme on Chemical Safety (2001) (IPCS), below.

*IBC related*: IPCS (2001, Section 11.1.1) states, 'The design of the rat and mouse NTP (1994) oral studies was adequate to assess carcinogenicity … No carcinogenic effects … In fact, significant negative trends in the incidence of … mammary gland tumours were observed in the rats.'

**Prelude to an alternate methodology**

This review holds that the AEA7 outcome may possibly be advanced following a more in-depth scientific garnering of the ADWG. Perhaps, the 0.7 mg/L above may be too high for cancer elimination. This is backed up somewhat in that the US Environmental Protection Agency (USEPA) has set maximum contaminant limit goals (MCLGs) for carcinogenic chemicals in drinking water as zero (Khan 2010, p. 10; USEPA 2018, e.g. arsenic, bromate, lead, and radionuclides). This, in turn, implicates that emerging drinking water carcinogens may be active in their respective sub-guideline regimes.

ADWG (NHMRC 2004) scientific content directing an alternate approach is as follows:

- **Barium fate**
Table 10.10 has the comment for barium, 'Primarily from natural sources.' This gave context to the on-site barium readings that they should reflect a steady, original concentration from the utility supply pipe. Table 10.3, assuming water was sourced from a large storage, nominates quarterly testing only for barium as 'Concentrations are generally stable…' However, perusal of on-site barium levels (AEA7, p. 70) shows (sub-guideline) fluctuations, of up to 70% (0.009 mg/L versus typical of 0.03 mg/L)!

- **Sampling protocol**
The footnotes of Table 10.10 include 'Note: All values are as "total" unless otherwise stated.' Information Sheet 2.1 'Sampling for Heavy Metals' has 'total' described, 'Total metals … the sum of the concentrations of metals in both the filterable and suspended fractions. Total metals include all metals inorganically and organically bound, both filterable and particulate.'

Information Sheet 2.1 states, 'It is generally advisable to collect two samples, one for total metals and one for dissolved metals.' Consistent with Table 10.10 based elimination method (above), only one sample was taken per sub-location (AEA7, p. 70). However, it might be the case that some patterns or trends may arise from a two-sample consideration.

- **Chemistry**
Barium and calcium, being in the same periodic table column, are expected to have similar drinking water chemistry generally. Both elements contribute to water hardness (NHMRC 2004, Hardness fact sheet). Coprecipitation of barium with calcium (as in drinking water lime softening) is known, and there are a number of insoluble salts of barium including carbonate (NHMRC 2004, Barium fact sheet). Modest corrosion inhibiting calcium carbonate precipitation is not unknown in drinking water supplies and depends on 'pH, temperature, the availability of calcium (hardness) and carbon dioxide' ($CO_2$) (NHMRC 2004, pH fact sheet). There were therefore would-be 'trace' barium oral exposures, with the general reaction:

$$Ca^{2+}, \ Ba^{2+}(aqueous) \leftrightarrow Ca, \ Ba(salt)$$
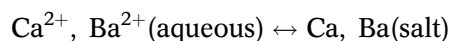
Supporting this presumed reaction, elemental calcium and barium are soluble in 95% ethyl alcohol (ethanol); all other AEA7 metals (p. 70) are not soluble, i.e. arsenic, cadmium, chromium, lead, mercury, and nickel (Perry 1997, Table 2-1). This ties to breast cancer alcohol risk factor generally (AEA7, p. 26, Table 5) and alcohol consumption of affected women (pp. 3, 16, and 36).

## METHODS

### Laboratory data

Using laboratory data of AEA7 (p. 70), two methods were used, per common, chemistry mass balance approaches:

- *Method 1, Barium, suspended metal*: If a suspended barium fraction had been determined to have existed, then the suspended barium fraction was non-settled, non-dissolved barium. This may have

been available for consumption directly or after precipitation (latter possibly not picked up due to sample timing). In the absence of the two-sample protocol, with no formally filtered samples, advantage was made of point of use 'Kitchen-filtered' samples.

• *Method 2, Barium, settled precipitate*: If there had been a fully settled precipitation, then a sub-location total barium reading would have been obtained that was lower than the site-incoming total barium level, and the difference between the two was settled, non-dissolved barium, which had built up on inner surfaces of the on-site pipes and had been available for consumption assuming suitable flow regimes. In the absence of site-incoming sampling, estimation for the same was conducted by judgement of on-site samples generally.

## Chemistry

On-site drinking water chemistry regimes were assessed and compared between the cluster and comparison locations. Again, this was a common chemistry-based approach, in this case, primarily quantitative with back-up qualitative assessment. However, it may be uncommon that such an approach, including 'Methods 1–2' above, has been applied, and rigorously, to metals data of a breast cancer cluster investigation.

## Carcinogen profiling

A new approach, cancer slope factor (CSF) emerging carcinogen profiling, was developed based on established carcinogen knowledge generally. Also new, CSF was used for exposure via a chemical reaction and developed for a reversible reaction, as required for this application with AEA7's data.

CSF risk-dose plots are used for known carcinogens (Khan 2010, pp. 8–10). Barium is not a known carcinogen including mammary carcinogenicity (earlier). In this review, CSF plots were used as a platform to test if barium profiles as a carcinogen, using human IBC SIR (standardised incidence ratio) as the y-axis risk measure and non-dissolved barium determinations as the x-axis, with dose units of mg/L (convertible to the usual, $mg \cdot kg^{-1} \cdot day^{-1}$).

The intention of this process was to force the data to bear out a CSF plot if applicable. This does not depart from the USEPA position (earlier), which sets zero MCLG for carcinogenic chemicals in drinking water, itself based on CSF, but parallels it, though from a reverse direction. The premise was that if barium was an IBC carcinogen, its AEA7 data should somehow manifest CSF.

The development of data presumed a relationship between general population IBC and cluster IBC that the relevant chemistry was the same though more highly exacerbated in the cluster. This meant, since two unknowns were related, that an iterative numerical method was applied, which was examined pictorially (the CSF, non-threshold toxicity platform). In the absence of other data, some judgement was required to estimate general population barium from amongst AEA7 data. This then formed an x–y low exposure base around which the likely culprit (high exposure) barium level could be manipulated for various cases. The cases were medical primary scope; biostatistics error; and upper and lower 95% confidence interval (CI) bounds.

The evaluation was made between the cluster and comparison locations, for conformance to standard CSF.

Microsoft (MS) Excel 2010 plots were used with CORREL, SLOPE, and INTERCEPT functions for the correlation coefficient, slope, and y-intercept. This allowed a fine comparison of the various cases.

## Primary toxin

To confirm that barium was indeed the primary IBC toxin, the presumed chemistry was CSF tested to back-calculate the number of affected women. This was done for both cluster and comparison locations to ensure a comprehensive elimination; a number line pictorial demonstration was used.

### Supplementary assessment

The discussion here gave rise to a number of preliminary, confirmatory matters including the following:

- comparison metals,
- consideration of established drinking water carcinogen risk levels published by the USEPA, and
- biostatistics-based assessment of cluster proper affected women and sensitivity between city-based and state-based.

## RESULTS

### Sampling clarification

The laboratory report (AEA7, p. 70) denoted locations 'Newscaff' or 'New Media.' However, neither term was in textual sections of AEA7. 'Newscaff' was an abbreviation of 'News and current affairs,' also not in textual sections, but an alternate term, 'Newsroom,' was used 18 times, e.g. p. 3. This was the cluster location. The term, 'New Media' (New as adjective) was described as the 'Digital group' twice (pp. 61–62); it was the comparison location.

Brisbane Water supplied the ABC Toowong, and samples were collected from 10 different on-site drinking water outlets (AEA7, p. 19): five from each of the cluster and comparison locations; with sub-locations – cooler, kitchen, kitchen filtered, ladies' toilet, and men's toilet.

### Reaction regime

The full spectrum of the barium exposure reaction (earlier) occurred across the site per examples below (barium data, Table 1, herein).

### Suspended barium fraction

In the absence of the two-sample protocol, a kitchen-filtered sample and its respective kitchen sample (unfiltered) were used and, moreover, covered both the cluster and comparison locations.

In the cluster location, the calculation per NHMRC (2004) Sheet 2.1 (earlier) and Method 1 (earlier) was

'Total metals' – 'Filterable fraction'
= Newscaff kitchen – Newscaff kitchen filtered
= 0.031 – 0.028
= 0.003 mg/L barium, suspended fraction.

In the comparison location, it was

'Total metals' – 'Filterable fraction'
= New media kitchen – New media kitchen filtered
= 0.031 – 0.030
= 0.001 mg/L barium, suspended fraction.

**Table 1** | Drinking water barium (mg/L) from the Brisbane Australia IBC cluster investigation

| Location | Cooler | Kitchen | Kitchen filtered | Ladies' toilet | Men's toilet |
|---|---|---|---|---|---|
| Cluster 'Newscaff' | 0.009 | 0.031 | 0.028 | 0.031 | 0.030 |
| Comparison 'New Media' | 0.032 | 0.031 | 0.030 | 0.031 | 0.030 |

*Note*: Data from AEA7 (p. 70); there were no formally filtered samples.

### Settled precipitated barium

As discussed earlier, to determine settled precipitate, an assessment first had to be made of site-incoming total barium. In the absence of site-incoming samples: if the cooler samples and filtered samples were eliminated, based on their subjection to on-site engineered conditions, four of six samples read 0.031 mg/L with the other two at 0.030 mg/L; and since, as above, 0.030 mg/L was obtained to express 0.001 mg/L non-dissolved fraction within original 0.031 mg/L total metals, then all six samples gave site-incoming total barium as 0.031 mg/L.

For the cluster location cooler sample, Method 2 (earlier) was

Ba (settled precipitate, sub-location) = Ba (site-incoming) − Ba (sub-location)
Ba (settled precipitate, Newscaff cooler) = 0.031 − Ba (Newscaff cooler)
= 0.031 − 0.009
= 0.022 mg/L (maximum on-site barium settled precipitate)

### Settled precipitated barium redissolved

For the comparison location cooler sample, Method 2 (earlier) was

Ba (settled precipitate, sub-location) = Ba (site-incoming) − Ba (sub-location)
Ba (settled precipitate, New Media cooler) = 0.031 − Ba (New Media cooler)
= 0.031 − 0.032
= −0.001 (with minus interpreted as a reverse reaction direction)

This sample represented as 0.001 mg/L barium settled precipitate transported and resuspended/redissolved. This was confirmed by a lead level of 0.007 mg/L for that sample only; with all others, <0.005 mg/L (AEA7, p. 70).

Unlike barium, drinking water lead can be caused by corrosion of plumbing systems and 'will depend on a number of factors including pH, water hardness and the standing time of the water' (NHMRC 2004, Lead fact sheet).

Therefore, since lead had dissolved uniquely higher in this one sample only, of the 10, this represented a non-precipitating, dissolving chemistry generally to explain the higher barium reading qualitatively. The reversible barium reaction (earlier) was tending to the reverse direction, as written, in that one sub-location; there was no direct production of non-dissolved barium – it had precipitated, settled, and built up elsewhere on site, then transported, and resuspended/redissolved.

A partial explanation for the increased lead concentration derives from $CO_2$ availability for calcium carbonate corrosion inhibition (earlier); there was presumably a reduction in water system static pressure with the increased height of the upper floor comparison location relative to the 'lower floor' cluster location (AEA7, pp. 14, 66), accordingly having released, a minimal but a significant, $CO_{2(g)}$ (Perry 1997, Table 2-125, $CO_2$ solubility data).

### Full-site determinations

Barium laboratory data, from AEA7, p. 70, in order of report, are transcribed in Table 1. As far as the data reasonably allowed, this review determined barium-suspended fractions in Table 2. This was followed by the determination of precipitated barium in Table 3. All non-dissolved barium is then summarised in Table 4, the oral exposures.

From the results in Table 4, a detailed comment was made on the chemistry regimes in Table 5.

**Table 2** | Suspended barium[a] fraction (mg/L), kitchen filtered used in the absence of formal filtration

| Location | Cooler | Kitchen | Kitchen filtered | Ladies' toilet | Men's toilet |
|---|---|---|---|---|---|
| Cluster | Insufficient data | 0.003 Suspended | 0 Suspended removed | Insufficient data | Insufficient data |
| Comparison | Insufficient data | 0.001 Suspended | 0 Suspended removed | Insufficient data | Insufficient data |

*Note*: Kitchen samples' example calculations earlier under 'Reaction regime'; suspended barium was non-settled, non-dissolved barium.
[a]Likely together with calcium.

**Table 3** | Settled precipitated barium[a] (mg/L) = site-incoming total barium − sub-location total barium

| Location | Cooler | Kitchen | Kitchen filtered | Ladies' toilet | Men's toilet |
|---|---|---|---|---|---|
| Cluster | 0.022 Settled precipitate | 0 No precipitate | 0 per kitchen | 0 No precipitate | 0.001 Settled precipitate |
| Comparison | −0.001 Settled precipitate transported resuspended/redissolved | 0 No precipitate | 0 per kitchen | 0 No precipitate | 0.001 Settled precipitate |

*Note*: Cooler samples' example calculations earlier under 'Reaction regime.'
[a]Likely together with calcium.

**Table 4** | Summary of calculated non-dissolved barium[a] (mg/L); the oral exposures

| Location | Cooler | Kitchen | Kitchen filtered | Ladies' toilet | Men's toilet |
|---|---|---|---|---|---|
| Cluster | 0.022 Settled precipitate | 0.003 Suspended | 0 Suspended removed | 0 No precipitate | 0.001 Settled precipitate |
| Comparison | − 0.001 Settled precipitate transported resuspended/redissolved | 0.001 Suspended | 0 Suspended removed | 0 No precipitate | 0.001 Settled precipitate |

[a]Likely together with calcium.

**Table 5** | Detail – drinking water barium chemistry regime

| Location | Average non-dissolved barium (mg/L) | Range non-dissolved barium (mg/L) | Comment on the status of reaction $Ca^{2+}$, $Ba^{2+}$ (aqueous) ↔ Ca, Ba (salt) |
|---|---|---|---|
| Cluster | 0.0052 (17% of site-incoming total barium) | 0–0.022 (0–71% of site-incoming total barium) | Both average and range expressed the reaction not having moved in the reverse (dissolving) direction at all: the average had expressed solid formation generally; the range, equilibrium through to high solid formation |
| Cluster cooler sub-location | | 0.022 | Most exacerbated solid formation |
| Comparison | 0.0002 (0.6% of site-incoming total barium) | −0.001 to 0.001 (−3 to 3% of site-incoming total barium) | Both average and range expressed near equilibrium conditions generally, neither highly dissolving nor highly solids forming but some solids resuspended/redissolved |
| Comparison cooler sub-location | | −0.001 | Most exacerbated the reverse of solid formation |

### Carcinogen profiling

#### Biostatistics risk assignment

Data points were generated to plot biostatistics risk versus barium oral exposure of Table 4. The risk was assigned, Table 6, to each of the sub-location concentrations as follows:

**Table 6** | SIR assignment for non-dissolved barium[a] (mg/L)

| Location | Cooler | Kitchen | Kitchen filtered | Ladies' toilet | Men's toilet |
|---|---|---|---|---|---|
| Cluster | 0.022<br>Settled precipitate | 0.003<br>Suspended | 0<br>Suspended removed | 0<br>No precipitate | 0.001<br>Settled precipitate |
| Risk assignment, biostatistics SIR | 6.02[b]<br>Brisbane IBC SIR, medical primary scope (AEA7), i.e. for the likely culprit water sample | 1<br>Judged as all Brisbane domestic equivalent where IBC could have occurred | 0 | 0 | 0.33 |
| Comparison | −0.001<br>Settled precipitate transported resuspended/redissolved | 0.001<br>Suspended | 0<br>Suspended removed | 0<br>No precipitate | 0.001<br>Settled precipitate |
| Risk assignment, biostatistics SIR | −0.33<br>Minus sign reflects the reverse of the precipitation reaction | 0.33 | 0 | 0 | 0.33 |

[a]Likely together with calcium.
[b]Adjustment of the above, 6.02 only was required for the development of other cases, below.

- An estimate of Brisbane onefold IBC risk, non-dissolved barium was necessary to 'standardise' the exposure, similar to the IBC SIR. That is, IBC had not occurred in every domestic location – if barium was causal, it could only have been where the water chemistry was similarly exacerbated. In the absence of other data, this was not going to be found in the comparison location since it had no IBC; only in the cluster location, if at all; the commercial cooler was not common domestically; the filter was not generally common domestically; the commercial ladies' and men's toilet on-site piping was not common domestically; however, the kitchen sub-location conditions, albeit in a commercial site, were not dissimilar to ambient temperature piped domestic kitchen sink water supply generally. Therefore, from it, non-dissolved barium of 0.003 mg/L was assigned an SIR of 1.
- Following from immediately above, assignment of all non-dissolved barium of 0.001 mg/L was assigned an SIR of ⅓ (i.e. 0.001/0.003) = 0.33. The comparison cooler was assigned an SIR of minus ⅓; the minus reflected, compared with all other samples, a reverse reaction direction with the result to resuspend/redissolve transported precipitated barium (above).
- Assignment of all non-dissolved barium of 0 mg/L was assigned an SIR of 0.
- The likely culprit sub-location barium concentration of the cluster cooler, 0.022 mg/L, was assigned, from AEA7, Table 2, p. 13, an SIR of 6.02 (for Brisbane IBC, medical primary scope, 10 women (p. 10)). Brisbane (city) SIR was chosen, not all-Queensland (state) SIR of 6.25, because water was supplied by Brisbane Water (p. 19).

#### CSF conformance test – 10 women

Does the data set from Table 6 conform generally to a CSF plot? If it did, then that would confirm that the IBC cluster was associated with barium and that barium profiles as a carcinogen. The data set, Table 6 (all 10 points), is plotted in Figure 1(a).
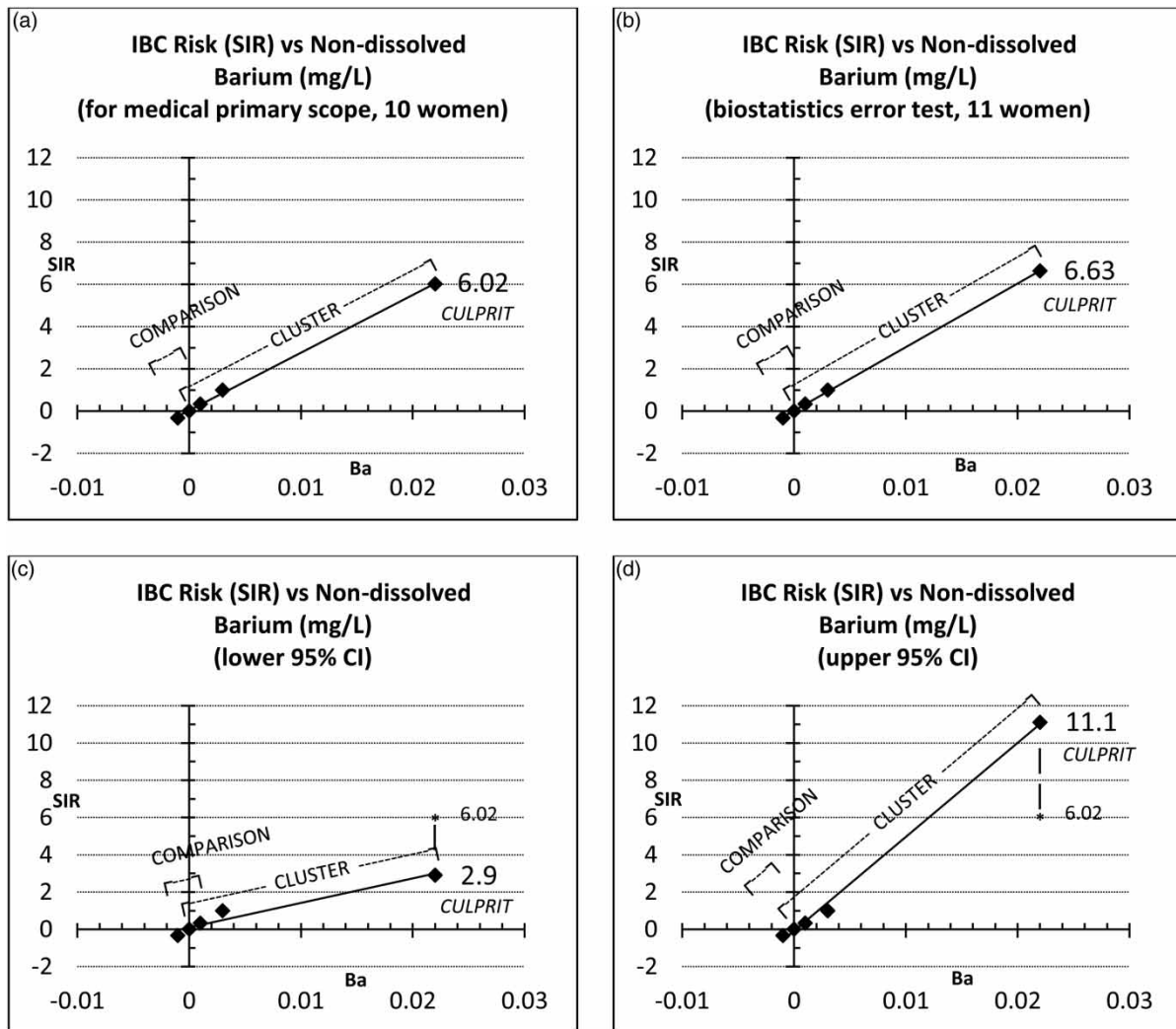
**Figure 1** | CSF conformance tests (some data points overlapped).

As required, Figure 1(a) satisfied a CSF plot – it intimated a straight line (a correlation coefficient of 0.99943, close to 1); with a slope, 274 (mg L$^{-1}$)$^{-1}$, positive in direction; and a *y*-intercept of 0.029, close to 0 (the zero exposure–zero risk condition).

From Khan (2010), 'Figure 3. Illustration of a Cancer Slope Factor (CSF) for carcinogenic chemicals' (p. 8) was in the positive-only quadrant; it did not have negative exposure-negative risk. However, that was chemically meaningful here because the exposure dose was generated by a reversible reaction with the positive-only quadrant representing non-dissolved barium formation and the negative-only quadrant representing resuspended/redissolved barium. The cluster and comparison data sets are marked in Figure 1(a) to show that the cluster data set conformed fully to a CSF plot by the quadrant location, but the comparison data set did not.

It is important to note that there was no correlation here of IBC with dissolved barium; only non-dissolved barium (salt), but produced from part of the site-incoming dissolved barium. This drinking water, barium salt phenomenon is not noted in the ADWG (NHMRC 2004, 2011, Barium fact sheet).

### CSF conformance test – 11 women

From AEA7 (p. 35), the biostatistics error could only ever have been an undercount of breast cancer cases and produced a falsely low SIR, not a falsely high SIR. In AEA7 (Table 2, p. 13), the SIR of 6.02

was obtained from 10 women divided by an expected number of 1.66, i.e. 10/1.66 = 6.02. The SIR for a total of 11 women was then 11/1.66 = 6.63. To test if the overall methodology here was correct, a better CSF conformance should generally be obtained if the 6.02 above was displaced by this 6.63.

The CSF conformance for 11 women is plotted in Figure 1(b) and results compared to those for 10 women in Table 7; a better correlation coefficient and *y*-intercept were obtained for 11 women, as required. The slope was positive in direction.

### CSF conformance tests – 95% CI

The CSF methodology was applied using the bounds of lower and upper 95% CI, 2.9–11.1, from AEA7 (Table 2, p. 13), Brisbane women.

The lower CI data were plotted (6.02 above displaced by 2.9) and upper CI (6.02 above displaced by 11.1) in Figure 1(c) and 1(d), respectively. The CSF conformance is compared in Table 7; satisfactory slopes, correlation coefficients, and *y*-intercepts were obtained.

### Summary of CSF conformance findings

**Table 7** | Conformance to CSF – IBC risk versus non-dissolved barium

| Test case (Figure 1(a)–1(d)) | SIR – assigned risk to culprit sub-location | Positive slope (mg·L$^{-1}$)$^{-1}$ required | Correlation coefficient = 1 ideal | *y*-Intercept = 0 ideal |
|---|---|---|---|---|
| Test measure → | – | Yes/no | $\approx 1/ \neq 1$ | $\approx 0/ \neq 0$ |
| 1a. Unadjusted – 10 women | 6.02 | 274 Yes | $0.99943 \approx 1$ | $0.029 \approx 0$ |
| 1b. Biostatistics error – 11 women | 6.63 | 301 Yes | $0.99987 \approx 1$ | $0.015 \approx 0$ |
| 1c. Lower SIR 95% CI bound | 2.9 | 132 Yes | $0.9724 \approx 1$ | $0.10 \approx 0$ |
| 1d. Upper SIR 95% CI bound | 11.1 | 505 Yes | $0.9986 \approx 1$ | $-0.09 \approx 0$ |

### Back-calculated number of women

If barium had been a known IBC toxin, with CSF of 1/0.003 (refer Table 6, cluster kitchen) = 333 (mg L$^{-1}$)$^{-1}$, what back-calculated IBC number of women is obtained from the likely culprit concentration (cluster cooler) of 0.022 mg/L?

From Khan (2010), p. 9, 'Equation (3): calculated risk from exposure to carcinogenic contaminants

Risk (R) = CSF (mg·kg$^{-1}$·day$^{-1}$)$^{-1}$ × Exposure dose (mg·kg$^{-1}$·day$^{-1}$).'

Using alternative units, this gave

SIR = 333 (mg·L$^{-1}$)$^{-1}$ × 0.022 (mg·L$^{-1}$) = 7.3.

Multiplying by the Brisbane-based expected number, 1.66 (AEA7, Table 2, p. 13), the chemically determined, cluster location IBC number of women was

7.3 × 1.66 = 12.1, say 12.

If the 0.003 and 0.022 mg/L above were replaced by the respective comparison sub-locations' non-dissolved barium (Table 4, herein), this gave CSF = 1/0.001 = 1,000 (mg·L$^{-1}$)$^{-1}$

Risk (R) = CSF × Exposure dose
SIR = 1,000 × −0.001 = −1
−1 × 1.66 = −1.66, a null number of women (say −1.7).

If only 0.003 was replaced

Risk $(R) = CSF \times$ Exposure dose
$SIR = 1,000 \times 0.022 = 22$
$22 \times 1.66 \approx 37 \gg 14$ women, also null.

If only 0.022 was replaced

Risk $(R) = CSF \times$ Exposure dose
$SIR = 333 \times -0.001 = -0.333$
$-0.333 \times 1.66 = -0.55$, a null number of women (say $-0.6$).

The results were compared against a number line in Figure 2.
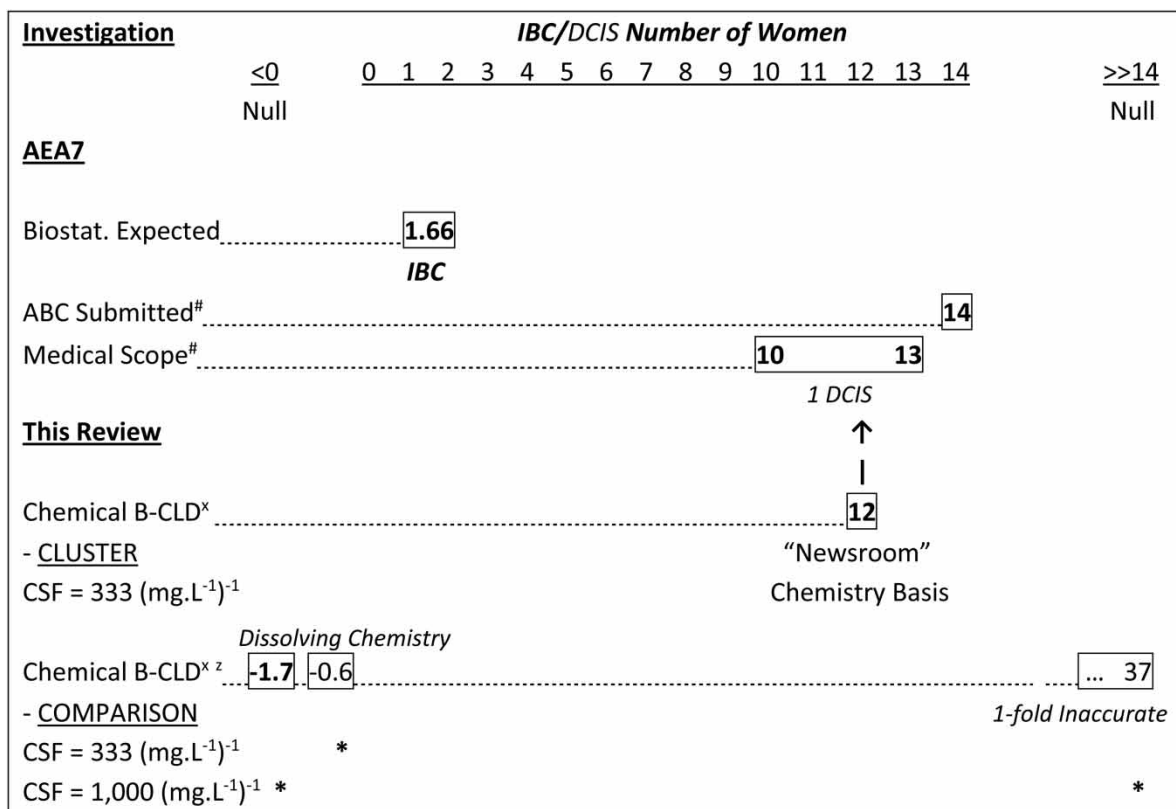


# in medical primary scope 10 IBC; out of medical primary scope 2 IBC, 1 DCIS; 1 unconfirmed "fourteenth" AEA7 p. 10

x  B-CLD (back-calculated);   z  "-1.7" is strictly from comparison location data only

**Figure 2** | Chemically derived number of women.

## DISCUSSION

### Underlying chemistry

From Table 5, there was a distinct difference in the barium chemistry regime between the cluster and comparison locations! Non-dissolved barium dominated in the cluster location, by over 20-fold in average and maximum, against the comparison location. Redissolved solids did not occur in the cluster location, but only in the comparison location. The most extreme and opposite conditions occurred in corresponding sub-locations, the (engineered) coolers of the cluster and comparison locations.

## Comparison metals

AEA7 comparison metals were arsenic, cadmium, chromium, lead, mercury, and nickel (p. 70). Except for one comparison location lead reading, 0.007 mg/L, discussed earlier, all results across the site were prefixed with '<' and unremarkable. (None read, ND – not detected.)

This, of course, is not a comprehensive quantitative elimination of comparison metals. Accordingly, future studies may benefit from lower detection limits.

In this case, preliminary qualitative elimination does derive from alcohol solubility (earlier).

## New methodology

From Table 7, satisfactory slope direction, correlation coefficient, and y-intercept were obtained for the unadjusted 10 women case. CSF conformance was achieved; a carcinogen profile match for barium has been obtained. Confirmation derived from (i) a better correlation for 11 women, consistent with biostatistics error and (ii) satisfactory correlations for lower and upper 95% CI bounds.

All four cases, Figure 1(a)–1(d), showed that the cluster data set conformed to a standard CSF plot, including positive-only quadrant location. By contrast, the comparison location only partly conformed on quadrant location and was below the onefold SIR non-dissolved barium level of 0.003 mg/L. Therefore, the CSF conformance contrast was consistent with the chemical regime contrast (above) between the cluster and comparison locations.

## Existing carcinogens

Dividing the onefold 0.003 mg/L non-dissolved barium, above, by the (onefold) expected number of 1.66, gave 0.0018 mg/L, the one-woman IBC dose. This was close to the USEPA's 0.002 mg/L $10^{-4}$ cancer risk for arsenic in drinking water, and in log order of the same for bromate, 0.005 mg/L (USEPA 2018). Atomic weight adjusted, 0.0018 mg/L barium is 0.0010 mg/L as arsenic and 0.0017 mg/L as bromate. Therefore, the one-woman IBC-barium level resolved in consistent magnitude of established inorganic carcinogen risk levels (and with a methodology not informed of the same established levels).

This is not asserting that barium necessarily shares similar carcinogenicity to arsenic and bromate. It confirms the potential departure from the 0.7–2 mg/L order of magnitude of the (non-cancer, cardiovascular) barium ADWG figures (earlier); informing the guideline fact sheet of cancer-related evidence at a more sensitive level.

## Primary toxin

It is clear from Figure 2 that the cluster location chemistry gave an in range (with AEA7) number of women, 12, which contrasted against those of the comparison location, grossly out of range. This 12 was within the 10–14 women range (in medical primary scope 10 IBC; out of medical primary scope 2 IBC, 1 DCIS; 1 unconfirmed '14th') of AEA7 (p. 10) and was consistent with the IBC medical primary scoped, 10 women have been a possible undercount (p. 35).

Therefore, concluded by this numerical match, it is put that barium has been confirmed as the primary IBC toxin, under the chemistry described in this review, with general population SIR onefold concentration of 0.003 mg/L (CSF = 333 $(\text{mg·L}^{-1})^{-1}$), and the cluster location cooler as the culprit sub-location. (It possibly has included the 1 DCIS case (SIR 5.38 AEA7, Table 2, p. 13) in the newsroom, '…NEWS OPERATIONS ASSISTANT…it was non-invasive…' (ABC 2007, witness, transcript lines 62–64).)

**Biostatistics**

Alternatively to the chemically derived number of women, from the biostatistics, the general population expected IBC number of women was 1.66, above, which estimated to 2, of the 14, to have been exposed off-site and/or by on-site non-culprit sub-locations. Therefore, the biostatistics confirmed the same reconciliation; $14 - 2 = 12$ women in the cluster proper.

Substituting with all-Queensland-based biostatistics (AEA7, Table 2, p. 13), this replaced 1.66 and (earlier) 12.1, respectively, with 1.60 and 11.7. It still estimated 2 and 12, as above, but not as close. The conclusion on barium held. However, the sensitivity favoured Brisbane, consistent with a Brisbane-based water supply (p. 19).

**Comparison IBC cluster**

Garland (2008) investigated a two- to fivefold (p. 8), IBC cluster (p. 7) at the UCSD (University of California San Diego), USA. This states, 'The domestic water comes mainly from the Torrey Pines Reservoir, but may at times be connected to other reservoirs operated by the City of San Diego' (p. 10). The associated report, Thaung & Woodard (2007), states '… An additional water sample collected on April 5, 2007… The drinking water was negative for mercury, arsenic, nickel, and lead. … copper and barium were detected well below the Environmental Protection Agency's maximum contaminant levels (MCL). '

However, this barium elimination did not complete with consideration of the USEPA MCLGs for carcinogenic chemicals in drinking water set as zero (earlier).

AEA7 did not test for copper (p. 70); Garland (2008) did not test for cadmium or chromium. Of arsenic, lead, mercury, barium and nickel, barium was therefore the only metal found common to both Brisbane and San Diego IBC investigations; on this matter, San Diego was not inconsistent with Brisbane.

This was based in the absence of the laboratory's report: (i) there were two measurement descriptors for San Diego, 'negative' and 'detected,' with barium given the latter; (ii) the approximate barium limit of determination was 0.01 mg/L (NHMRC 2004, 2011, Barium fact sheet, citing the American Public Health Association 1992); (iii) northern, Torrey Pines/UCSD were served by Alvarado and/or Miramar drinking water treatment plants, with 2007 effluent barium having ranged up to 0.11 mg/L, above the California Department of Public Health (CDPH), 0.1 mg/L detection limit for reporting (DLR) (The City of San Diego 2007); and (iv) Brisbane barium readings were typically 0.03 mg/L (earlier).

With copper now added to the metals' test list, the alcohol solubility preliminary comparison metals elimination (earlier) continues to stand (Perry 1997, Table 2-1). The San Diego results have eliminated from six metals to two with a preliminary copper elimination regards alcohol solubility, leaving barium isolated. That is a significant, stand-alone finding.

Also, three-total drinking water treatment plants served San Diego, with defined sub-city service zones. The other, Otay, serving the south, had 2007 effluent barium as ND – not detected (The City of San Diego 2007). Therefore, of the three sub-city zones, the IBC cluster did not occur where barium was not detected.

Garland (2008) reported '… no evidence of heavy metal contamination …' (p. 10) and Thaung & Woodard (2007) 'Negligible amounts … barium.' However, both positions were a USEPA MCL-only perspective, an established knowledge assessment, and did not reflect an attempt at aligning barium levels with a sub-MCL carcinogen MCLG position or similar. This was comparable to the AEA7 approach.

Therefore, from all the above, the San Diego USA IBC cluster findings supported those of the Brisbane Australia IBC cluster, in relation to barium exposure generally and water supply exposure specifically.

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Neither medical study specified drinking water testing for anions, disinfection by-products, pesticides' residuals, or radionuclides. AEA7 (p. 67) directly declined organochlorine pesticides and Garland tested for coliforms (Thaung & Woodard 2007).

### Practical application

The likely IBC-barium exposure identified in this review was barium in the presence of calcium: though from drinking water, it was not dissolved in the aqueous matrix, with barium and calcium ions mixed throughout; it was coprecipitated, with the barium intimately bound with calcium, in a crystal matrix, transported generally as miniscule slurry.

If the IBC-barium evidence here is ever raised to causative or precautionary status, by relevant agencies, then it is of remedial note that a (managed site) point of use kitchen filter was not ineffective at removing the SIR onefold correlated 0.003 mg/L (measured as suspended solids).

### Additional supporting research

Coprecipitated calcium–barium, above, has immediate bearing on cellular breast cancer research. Bi et al. (2013), without mentioning barium, touches on the known barium health end point (non-cancer) cardiovascular (earlier); this is in relation to the regulation of vascular smooth muscle cell proliferation by the calcium-activated potassium channel ($K_{Ca}$) $K_{Ca}$3.1. This same $K_{Ca}$3.1 is one of three $K_{Ca}$ implicated in breast cancer (Huang & Jan 2014, Table 1. Potassium channel expression in cancer, p. 153). Barium is a physiological antagonist for potassium channels (Poddalgoda et al. 2017, p. 304).

Huang & Jan (2014, Table 1), above, similarly assigned bone cancer with two channels. Only one is $K_{Ca}$. However, both comprise a subset of 13 breast cancer channels. That is worth holding in mind because 'after absorption, barium is deposited in bone and teeth' (NHMRC 2011, Barium fact sheet). That may indicate initiating channel(s) for breast cancer.

This review recommends, in the first instance, in vitro mammary (IBC/DCIS) cell biochemistry testing using high dose barium calcium carbonate. The hypothesis is that (i) exposure to drinking water barium by itself will not cause cancer per status quo (earlier) but (ii) exposure to drinking water coprecipitated calcium–barium will cause breast cancer initiated by an erroneous $K_{Ca}$ trigger ('Ba$_{Ca}$'), refer Huang & Jan (2014), 'Figure 2. Proposed mechanisms for potassium channels to regulate cell proliferation, 3 Regulating calcium signalling,' p. 155. The Brisbane data here have considered a modified barium exposure not previously assessed in public drinking water health studies.

Poddalgoda et al. (2017, p. 304) also state that 'The toxicity of barium is mediated by the free cation through substitution for calcium …' In this special case of a calcium–barium coprecipitate, is this behaviour modulated since barium has undergone pre-exposure 'substitution' for calcium?

## CONCLUSIONS

The main conclusions, from this review of the Brisbane Australia IBC cluster investigation, were

- *Consistent with drinking water exposure*: (i) a barium chemistry, number of women calculation sensitivity preferred Brisbane (city) biostatistics over all-Queensland (state) and (ii) the San Diego IBC cluster occurred in a sub-city service zone where barium levels had triggered the CDPH DLR, not in another zone where barium was not detected.
- *Metals elimination*: (i) a confirmed, reversible barium reaction was identified for Brisbane; (ii) of five metals, tested by both investigations, barium was the only metal found common to both Brisbane Australia and San Diego USA IBC clusters; and (iii) alcohol solubility isolated barium.

- *On-site location elimination*: Consistent with barium chemistry regimes, the cluster location data set conformed fully to a CSF plot; the comparison location data set did not. Against a medically scoped, observed range of 10–14 women, a cluster location barium CSF back-calculation gave 12 women, and possibly covered the IBC–DCIS link; the comparison location gave null women numbers of <0 or 37. Biostatistics confirmed the '12' figure.
- *IBC-barium evidence*: There is now environmental evidence, for a wider review, that barium causes IBC and possibly DCIS. A correlation was obtained between IBC–DCIS and oral exposure drinking water barium, $CSF \approx 330$ $(mg \cdot L^{-1})^{-1}$. This was not with dissolved barium; it was with non-dissolved barium, though produced from part of the site-incoming, sub-guideline dissolved barium. USEPA cancer risk levels confirmed on the magnitude. The culprit barium was likely crystalline with calcium.
- *Further work*: Probing a sub-guideline regime has produced a demonstrable quantitative outcome in this case. Accordingly, sensitive water metals detection limits need to be considered for future cancer cluster studies generally. For IBC/DCIS, cell biochemistry testing has been put forward.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this paper is available at https://dx.doi.org/10.2166/h2oj.2019.016.

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