Appendix 2. FAN submission to NRC 2006 on cancer [Grandjean 2004]

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Submission to:
National Research Council Committee:
Toxicologic Risk of Fluoride in Drinking Water; BEST-K-02-05-A
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Fluoride & Cancer: New Report + Background

New study:

> Grandjean P, Olsen J. (2004). Extended Follow-up of Cancer Incidence in Fluoride-Exposed Workers. *Journal of the National Cancer Institute* 96: 802-803.

Excerpt:

> "These findings amplify our previous observation of increased bladder cancer rates among cryolite workers... We therefore believe that fluoride should be considered a possible cause of bladder cancer and a contributory cause of primary lung cancer."

Background:

This study is a 12-year follow-up study to two previous studies conducted by Dr. Philippe Grandjean and colleagues.

No PAH exposure among cryolite workers

A critically important fact for the NRC panel to consider about Grandjean's findings is that the cryolite workers were *not* exposed to Polycyclic Aromatic Hydrocarbons (PAH).

On October 2, 2002, I emailed Dr. Grandjean and asked: "At the cryolite plant, was there any exposure to PAH?"

In response to this question, Dr. Grandjean stated:

> "Thank you for asking this question, which is highly relevant since we found an increased incidence of bladder cancer. All cryolite plant processes were at room temperature, and there was no source of PAH other than some machinery and trucks entering and leaving the plant. **We therefore concluded that there was no increased exposure to PAH among these workers**. I realized too late that we should have included this information in the paper."

In their recent report, Grandjean and Olsen explicitly mention the absence of other carcinogens in the cryolite work place. To quote:

> **"Workers at the cryolite mill in Copenhagen, Denmark, are unique because of their exposure to high levels of fluoride dust and their virtual lack of exposure to other occupational toxicants or carcinogens."**

The absence of PAH exposure among the cryolite workers is extremely important.

For instance, numerous studies have documented an increased cancer risk among workers in the aluminum industry (see references below). The two main cancers reported among the aluminum workers are *bladder and lung cancers* – which are the two main cancers found in the cryolite workplace.

While aluminum workers are heavily exposed to fluorides, the studies reporting increased cancer incidence in the aluminum industry, have assumed that PAH is the main agent causing the cancer.

Dr. Grandjean's research, however, suggests that the airborne fluorides in the aluminum industry are, at the very least, a contributing factor to the increased incidence of these 2 cancers, and that it is misleading to put the blame solely on PAH.

Interestingly, the evidence for increased risk of lung and bladder cancer in the aluminum industry has become so strong that even ALCOA - the world's largest producer of aluminum – recently warned its workers of the problem.

In December of 1999, ALCOA sent a memo to its workforce across the globe, informing them that they were at increased risk of developing cancer – namely *lung and bladder cancer*. According to a December 17, 1999 report from *The Associated Press*:

> "Aluminum manufacturer Alcoa is warning thousands of past and present employees that they may face a greater risk than previously believed of developing *lung or bladder cancer*" (emphasis added). See: http://fluoridealert.org/pollution/1375.html

Additional Evidence that Fluoride May Cause Cancer

Grandjean's and Olsen's observation of a possible fluoride/cancer link gains further support from recent studies examining fluoride's mutagenicity in *humans*.

Since 1994, 3 studies have been published which report an increased incidence of mutagenic damage in humans exposed to airborne fluorides (*Meng 1995, 1997; Lazutka 1999*), while 3 other studies have reported an increased incidence of mutagenic damage in humans drinking elevated levels of fluoride (1.9 - 2.2 ppm; 4 - 15 ppm; & 1.6 –3.5 ppm) in water (*Sheth 1994; Wu 1995; Joseph 2000*). Two studies, however, have reported no increase in mutagenic damage, or a decrease in damage among humans drinking excess fluoride in water *(Li 1995; Jackson 1997).*

Among the studies reporting an increase in mutagenic damage, the most common observed effect has been increased sister-chromatid exchange (SCE) (see: *Sheth 1994; Meng 1995, Wu 1995; Lazutka 1999; Joseph 2000*).

Wu (1995), who found an increase of SCE among humans drinking water with 4 – 15 ppm F, described the significance of SCE as follows:

> "In recent years, SCE analysis has been considered to be a sensitive method for detecting DNA damage. There is a clear relationship between a substance's ability to induce DNA damage, mutate chromosomes, and cause cancers. The SCE frequency in the human body in peripheral blood lymphocytes is very steady, and does not vary with age or sex. Any increase of the SCE frequency is primarily due to chromosome damage. Thus using a method to detect SCE for exploring the toxicity and harm caused by fluoride is of great importance."

The finding of increased SCE in fluoride-exposed humans has reinforced the possibility – as suggested by numerous *in vitro* studies – that fluoride is a mutagenic agent. (See references below)

In regards to the *in-vitro* research on fluoride's mutagenicity, I'd like to draw particular attention to the study by Kishi (1993).

Kishi compared the mutagenicity of fluoride in cells taken from rodents with the mutagenicity of fluoride in cells taken from great apes and humans. The conclusion of the study was that the *ape and human cells showed greater susceptibility to fluoride's mutagenic effects than the rodents*.

These findings suggest that humans may be more susceptible to fluoride's mutagenic properties, and consequently, more susceptible to a potential carcinogenic effect. They may also explain the findings of mutagenic damage in humans drinking water with relatively low fluoride concentrations (1.9 – 2.2. ppm and 1.6 – 3.5 ppm – *Sheth 1994; Joseph 2000*).

Relevance of Grandjean's Findings to Fluoridation & MCL

In their 1992 paper, Grandjean and colleagues discussed the possible significance of their findings of increased cancer risk in fluoride-exposed workers to people drinking fluoridated water. To quote:

> "Should one assume that heavy occupational exposures to fluoride could cause an increased carcinogenic risk, an important question is whether such risk would also pertain to the universal exposure to fluoride at lower intake levels."

In addressing this question, Grandjean stated that the cryolite workers were exposed to roughly 10 times the level of fluoride (ca. 35 mg/day) ingested on a daily basis in fluoridated communities. "However," as he noted,

> "the occupational exposure lasted only for a limited proportion of the workers' lifetime and would therefore correspond to a much lower daily uptake as an average for a lifespan... [I]t is not known whether any fluoride-associated cancer risk would be related to a long-term average uptake rather than to peak doses occurring at critical points of time."

While Grandjean doesn't state this point himself, a margin of 10 (between the dose associated with an increased incidence of cancer and the dose people receive in 1 ppm communities) is actually quite *small*, and far smaller - I believe - than a safety standard for fluoride would allow if it was accepted that fluoride was the cause of the increased cancer.

The margin is even smaller when comparing the dose (ca. 35 mg/day) with the expected doses in 4 ppm communities. For an individual drinking 3 liters of 4 ppm water (= intake of 12 mg/day), the margin would be as low as 3, while for someone drinking 4 liters of 4 ppm water (= intake of 16 mg/day) the margin would be as low as ~2.

Summarizing Recent Evidence Supporting a Fluoride/Cancer Link

As noted above, the evidence supporting a link between fluoride and cancer includes:

> 1. An increased incidence of bladder and lung cancer among fluoride-exposed cryolite workers who were not exposed to PAH, the chemical assumed to be the cause of the increased rates of bladder and lung cancer in the aluminum industry (*Grandjean 1985, 1992, 2004*).
> 2. Increased incidence of mutagenic damage in humans exposed to elevated fluoride in air or water (*Sheth 1994; Wu 1995; Meng 1995, 1997; Lazutka 1999; Joseph 2000*).

3. Evidence of mutagenicity in *in vitro* studies. (*Caspary 1987; Scott 1987; Kishi 1993; Khalil 1995; Mihashi 1996*).
4. Evidence that human cells are more susceptible to fluoride-induced mutatenic damage than rodent cells (*Kishi 1993*).

Additional evidence – not discussed above – also supporting a link between fluoride and cancer includes:

1. Dose-dependent increase of cancer (osteosarcoma) in target organ for fluoride accumulation (bone) in fluoride-treated male rats (*NTP 1990*). According to a recent review by the World Health Organization (*WHO 2002*): "Such a (dose-dependent) trend associated with the occurrence of a rare tumour in the tissue in which fluoride is known to accumulate cannot be casually dismissed."
2. An initially reported increase in non-bone tumors (oral and liver tumors) among the fluoride-treated animals of the NTP study. This conclusion was made by Battelle Laboratories which had conducted the study for the NTP. However, a panel, appointed by the NTP, (which did not include any of the Battelle pathologists) downgraded all of the non-bone tumors. (*Sibbison 1990*).
3. Dose-dependent increase in rare bone tumors (albeit non-malignant) in the fluoride-treated rats in Proctor & Gamble's own animal bioassay, and the occurrence of 4 malignant bone tumors (albeit without statistical significance) (*Maurer 1990; DHHS 1991*).
4. Elevated bone cancer (osteosarcoma) rates among young males in fluoridated versus unfluoridated areas (albeit unrelated to the duration of fluoridation), based on *national data* from the National Cancer Institute (*Hoover 1991*) and a smaller survey by the New Jersey Health Department (*Cohn 1992*). Some epidemiological studies, however, have not found this relationship (*Mahoney 1991; Freni 1992*).

Grandjean's comments on using fluoridation epidemiology to determine fluoride's carcinogenicity

Finally, this is what Grandjean and colleagues had to say about using comparisons of cancer rates in fluoridated vs. unfluoridated to answer the question of whether fluoride causes cancer:

> "[S]everal studies have shown that cancer mortality is similar in communities with or without water fluoridation. With regard to such cancer incidence data, however, the limitations of geographic comparisons must be acknowledged; the significance of individual risk factors is unknown, as is the level of individual fluoride exposure, including occupational exposures. With the distribution of processed food and beverages across fluoridation boundaries and with the widespread use of fluoride-supplemented dentrifices, the relative difference in daily fluoride absorption between fluoridated and nonfluoridated communities is likely to be small, thus further limiting the power of such epidemiological comparisons. Further, these ecological studies cannot exclude an increased cancer risk associated with occupational fluoride exposures" (*Grandjean 1992*).

Grandjean's comments here highlight the importance of utilizing occupational studies, and animal studies, in determining whether fluoride is a carcinogen - especially when considering the diminishing difference in fluoride intake between fluoridated and unfluoridated communities. As such, Grandjean's findings of cancer among fluoride-exposed workers should be taken as a serious red flag.

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