March 31, 2013

Comments by Kristin Homme on Goldhaber statement for April 4, 2013, CEAC meeting (attached)

I appreciate the effort by this commissioner to read and comment on one of the recent journal articles related to amalgam. I hope he and others will continue this effort. Science is by nature skeptical in its search for reliable knowledge, and it is the job of a scientist to attack studies and to find flaws. On the other hand, the policymaker has a harder job -- to weigh the totality of the evidence on all sides, and to consider the risks and benefits of the status quo as well as the proposed action/s. I hope the commission will take its policymaking responsibilities seriously.

Goldhaber makes several points that are at least partially true, but he overlooks the larger picture, described below.

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<th>Goldhaber points:</th>
<th>Response:</th>
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<td>The Woods et al., 2012, reanalysis is about urinary mercury levels, not dental amalgam. (Goldhaber states: “...the [Woods et al., 2012] paper does NOT claim to demonstrate a significant relationship between dental mercury amalgam and ... urinary Hg [mercury]...”)</td>
<td>True, this reanalysis used urinary mercury levels as the exposure/risk variable, -- and it found significant associations between urinary mercury levels and neurobehavioral deficits in boys with a common genetic variant. However, some background on the Children’s Amalgam Trials, described later, is worth considering. In brief, many other studies do demonstrate a significant relationship between dental amalgam and urinary mercury -- including the parent study of the same dataset by DeRouen et al. (The authors included Woods.) “Baseline mean creatinine-adjusted urinary mercury levels were 1.8 microg/g in the amalgam group and 1.9 microg/g in the composite group, but during follow-up were 1.0 to 1.5 microg/g higher in the amalgam group than in the composite group (P&lt;.001).” [This p-value means the finding is highly significant, i.e., unlikely to be due to chance.] DeRouen, et al., 2006.</td>
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<td>The children's baseline urinary mercury levels suggest other environmental sources of mercury (which may confound the results).</td>
<td>True, but this problem also existed in the parent study (De Rouen et al., 2006), which has been widely cited by amalgam advocates as providing high-quality evidence of the safety of amalgam. This possible confounding may be moot, because two other reanalyses of this dataset (Geier et al., 2011, and Geier et al., 2012), which used “amalgam score” as the exposure metric, detected two other dose-response relationships of harm. If the unknown exposure were large, these relationships would have been obscured. In addition, since the children were all in an orphanage, their environmental exposures were likely to be similar, so confounding is unlikely.</td>
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<td>Goldhaber states: “Rather, [Woods et al., 2012] assumes other environmental sources of mercury...”</td>
<td>Goldhaber’s point is unclear but may relate to the previous point. Goldhaber seems to imply (incorrectly) that Woods et al. assumed that the unknown, non-amalgam mercury exposures were the source of the harm. In fact, Woods et al. did not specify the sources.</td>
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Goldhaber points: | Response:
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Urinary mercury levels were almost equal between composite and amalgam groups, thus amalgam could not be a significant source. | Although the urinary mercury levels were indeed almost equal between the two groups, the conclusion that amalgam could not be a significant source is false. The amalgam group contained children with a range of amalgams, including children with few amalgams. Consequently, the simple, dichotomous exposure variable -- amalgam versus composite -- was too inexact to reveal associations. It was only after Geier et al. used a more refined exposure metric (“amalgam score”) that a dose-response relationship was revealed.

Goldhaber misidentifies a study in his opening sentence: “…the 2012 Woods, et al., restudy of the Evans, [sic] et al., Portuguese Mercury-amalgam study” | Evens et al., 2001, is an interim study on fish consumption and methylmercury in the Children’s Amalgam Trial population. Goldhaber probably meant to say that Woods et al., 2012, is a restudy of DeRouen et al., 2006.

Goldhaber states: “...[Woods et al., 2012] CANNOT be used seriously to suggest that Hg-amalgam fillings are dangerous.” | Viewed in isolation, this is true. But viewed in the context of the parent study (DeRouen et al., 2006) and other studies that have found a significant association between mercury dental amalgam and increased urinary mercury, it is reasonable to infer from the Woods et al., 2012, study that mercury amalgam fillings may be dangerous, particularly to individuals with the identified genetic variant.

Goldhaber states: “At present there is no serious study that I am aware of that makes such a claim.” | The other two reanalyses of this high-quality dataset, Geier et al., 2011, and Geier et al., 2012, do provide evidence for this claim. In addition, many other studies show an association between amalgam and health effects, but they are retrospective, thus they may be viewed as of lesser quality than the Children’s Amalgam Trial datasets, in which the data were gathered prospectively.

Overview of the mercury and amalgam epidemiological literature and the Children’s Amalgam Trials

It has been established in the literature including the parent study (DeRouen et al., 2006) that amalgam is associated with increased urinary mercury levels. What has been less clear is whether these increased levels cause harm. Within the past decade, several studies have found various types of harm at alarmingly low levels. But none of these studies were of the quality of the Children’s Amalgam Trials.

The Children’s Amalgam Trials are a pair of prospective, randomized, controlled, clinical trials, first published in 2006. The trial in New England lasted five years, and the trial in Portugal lasted seven years. Each trial followed about 500 children. Both trials found no significant harm associated with amalgam, but both found higher urinary mercury levels associated with amalgam. (In both studies, this association had a p-value of p<.001, which means the association was highly significant and was unlikely to be due to chance.)

Both these 2006 analyses used the dichotomous variable, amalgam versus composite, then compared neurobehavioral test results between these two groups and found few significant differences. These results have been widely cited as providing high-quality evidence of the safety of amalgam.
In 2011, Geier et al. reanalyzed the Portugal dataset but used a more refined exposure variable -- an “amalgam score” -- based on the size and duration of the amalgams. This added precision allowed a dose-response relationship to be revealed for elevated porphyrins (a biomarker of enzyme damage in the heme synthesis pathway, associated with toxic metals). (This association between “amalgam score” and the porphyrin biomarkers for damage applied to the entire population, not just the genetically susceptible subgroup identified by Woods, et al.)

Woods et al., which included four members from the original team, then reanalyzed the dataset, this time using an exposure metric that was a mathematical construct based on urinary mercury levels. The authors found a dose-response relationship with neurobehavioral deficits in boys with a common genetic variant that affects 28% of the population. (Note that there is no ideal exposure metric for amalgam-related mercury exposure or body burden.)

Finally, Geier et al., 2012, showed that “amalgam score” is associated with a biomarker for kidney damage in boys with the same genetic variant.

**Significance of the Woods et al., 2012, reanalysis of the Portugal Children’s Amalgam Trial**

The Woods et al. reanalysis is seminal because it removes the cornerstone -- the 2006 findings of no-association -- from the amalgam-is-safe theory. Amalgam proponents must now resort to citing tradition and experience, rather than science, as justification for their position.

In addition, when viewed in the context of the findings of other studies including the parent study, Woods et al. provides evidence that mercury exposures (including amalgam) that cause increased urinary mercury levels are associated with neurobehavioral harm in boys with a common genetic variant.

Finally, what is remarkable about the Woods et al. results is the consistency and significance of the findings of harm. Of the 23 neurobehavioral tests employed, 11 showed deficits that were significant at $p \leq .05$, and of those, 7 were significant at $p \leq .01$. These effects were not apparent year-to-year, but became apparent by the end of the seven-year study, which begs the question about longer-term effects of mercury from any source, including dental amalgam.
Statement: Clearing up a key misunderstanding regarding the 2012 Woods, et al., restudy of the Evans, et al., Portuguese Mercury-amalgam study

Recently, in order to better understand the issues raised by mercury amalgam in dentistry, I carefully examined the 2012 paper by James S. Woods, et al., (Neurotoxicology and Teratology 34 (2012) 513-521 [available online]). To my surprise, the paper does NOT claim to demonstrate a significant relationship between dental mercury amalgam and either urinary Hg (mercury) or behavioral effects. Rather, it assumes other environmental sources of mercury in the study population, and in its main findings it specifically ignores the different kinds of fillings (Hg vs. composite) in the study population. Thus it CANNOT be used seriously to suggest that Hg-amalgam fillings are dangerous. At present, there is no serious study I am aware of that makes such a claim.

Below are two important quotes, at some length, from the paper:

From section 2.1:

"Studies conducted during the course of the clinical trial (Evans et al., 2001) demonstrated that the children had no significant exposure to methylmercury from dietary fish consumption. However, other unidentified sources of environmental mercury exposure may have contributed to baseline urinary mercury concentrations, which were 1.5±1.2 (0.1–7.7) and 1.4±1.1 (0.0–8.6) μg/L for amalgam and composite groups, respectively. Mean urinary mercury concentrations by treatment group and by gender for each year of the clinical trial have been previously published (Woods et al., 2007)."

From Section 2.5:

"Urinary Hg concentrations (HgU) measured at each annual behavioral test session were employed as the measure of Hg exposure instead of the dichotomous assignment to amalgam or composite resin treatment groups as performed in the clinical trial. Treatment assignment from the clinical trial was evenly split among boys (81 from the composite group and 83 from the amalgam group), whereas girls came slightly more frequently from the amalgam group (74 composite and 92 amalgam). However, treatment assignment accounted, at most, for only 17% of the variation in HgU among boys (Year 2 r²=0.171) and 15% among girls (Year 2 r²=0.154)."

Note that urinary Hg levels were almost equal between composite and Hg-amalgam subjects, and thus amalgam could not be a significant source of urinary Hg. The restudy does not anywhere claim to be determining the effects of dental amalgam, but rather, from UNKNOWN environmental sources of Hg.

Naturally, none of this lessens the importance of making sure that Hg released in the process of filling teeth be reclaimed and kept out of the environment, but in my opinion it does make requiring any particular sort of informed consent before amalgam can be used a considerable stretch, without scientific basis.

Michael H. Goldfrank
Berkeley CEAC Commissioner, Council District 6