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to
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My name is Milton Marshall, and I am here to speak at the request of the American Dental Association on the safety of dental amalgam. I received a PhD in Biomedical Sciences from the University of Texas Health Science Center at Houston Graduate School of Biomedical Sciences. I am also certified in toxicology from the American Board of Toxicology, and I have been certified in General Toxicology since 1992. I hold adjunct appointments at the University of Texas Dental Branch in Houston, TX and the University of Texas Medical Branch in Galveston, TX. I am currently employed by Baylor College of Medicine in Houston, TX as the Director of Quality Assurance and Compliance in the Division of Molecular Imaging, Department of Radiology. My background includes regulatory and safety of product development (drugs, devices, biologics, and combination products). I have experience in both preclinical and clinical safety testing.

Key criteria to be considered in associating an effect with exposure are degree and length of exposure. Most adverse health effects have been identified as a result of occupational exposure, which is typically higher than that in the general population. Epidemiological studies typically identify an effect then look at exposures that may have contributed to the observed effect. Another approach is to look at an exposed population and identify problems associated within the exposed group, then attempt to link the problem with a specific exposure. This latter approach has generally been used in considering health effects associated with use of dental amalgam.

I would like to emphasize the fact that the form of mercury used in the formation of dental amalgam is elemental mercury, also referred to as Hg^0. Because of the sensitivity of mercury detection instrumentation, volatile (elemental) mercury can be measured in exhaled air, and the amount of volatile mercury measured in the oral cavity is increased with chewing in persons with amalgam restorations. The total inhaled dose of mercury is small, though, because of the small volume of the oral cavity, and the amount of volatile mercury released depends on the number of amalgam restorations present. After inhalation, the majority of the mercury vapor diffuses across the alveolar membrane and is retained by red blood cells in the pulmonary system. The catalase-peroxidase system in the red blood cells oxidizes elemental mercury to divalent mercury species that is retained by the red blood cells. Human red blood cells have a half-life of 120 days, and the majority of the red blood cells and trapped mercury is excreted in feces via the biliary

system on removal of red blood cells from the circulation by the liver. Thus, only the small amount of mercury that is not trapped in the red blood cells is available to interact with other tissues. Chronic exposure to elemental mercury is best measured by monitoring urine mercury levels.[1]

Occupational exposure to elemental mercury provides the majority of information available on exposure levels that are associated with adverse health effects. Multiple studies have been conducted that correlate elemental mercury levels in air, urinary mercury, and adverse health effects associated with this exposure. From data obtained on workers in the chloralkali industry, a threshold level for subclinical effects was established at 50 μg elemental mercury/g creatinine in urine.[2] Although exposure to elemental mercury can be documented by monitoring urine mercury levels[3], toxicity occurs at levels far above those seen from persons with amalgam restorations who typically have 2-4 μg Hg/g creatinine. Although it is a good practice to correct urine mercury levels for creatinine content to account for hydration status, creatinine concentration in urine is typically 0.5-3.0 g/L[4], and an average value of 1 g/L has been reported[5,6] which enables a direct extrapolation between values in μg/g creatinine and μg/L. Urinary mercury levels of dentists and dental assistants who are occupationally exposed to mercury from placing and/or removing amalgam fillings have shown a steady decrease over time, with the latest 5-year average of urinary mercury levels at or below those in the general population, <4 μg/mL. Further analysis of urinary mercury levels in dentists who participated in five different years of screenings at the annual ADA Health Screening Program indicates a downward trend in urinary mercury over time when the values are averaged from initial to final values. The urinary mercury levels in dentists with both occupational exposure to dental amalgam and to some extent from amalgam restorations, are much lower than those seen in persons with occupational exposure in the chloralkali industry.[5,6]

I would like to provide an overview of several recent reports on dental amalgam, including one published by the Life Science Research Organization, or LSRO, in 2004[5]. The LSRO report is, "Review and Analysis of the Literature on the Health Effects of Dental Amalgam". For this report, an expert panel was convened to identify and review the scientific literature between January 1, 1996 and December 31, 2003 on health effects associated with dental amalgam, and more than 950 scientific articles were reviewed by the expert panel. The quality of literature reports within this time frame was assessed and reviewed to determine if it supported hypotheses relating to adverse health effects associated with dental amalgam. The U.S. EPA General Assessment Factors were considered for determining scientific merit of the literature reviewed. The literature was reviewed for soundness, applicability and utility, clarity and completeness, uncertainty and variability, and evaluation and review (independent verification, validation, and peer review). Evidence regarding adverse outcomes in humans was evaluated from the perspective of epidemiological studies, secular trend data, animal toxicity studies, dose-response relationship, and biological plausibility. A summary of the LSRO report appeared in *Toxicology Reviews* in 2005.[7]

The LSRO expert panel recognized that a number of expert panels had previously reviewed the safety of amalgam for dental use, including the USPHS (1993, 1997), World Health Organization (1997), European Commission (1998), Australia (1999), and Health Canada (2004). Overall, the conclusion from these panels was that no adverse health effects were associated with amalgam use other than occasional allergic reactions.

In reviewing studies on exposure to elemental mercury and urinary mercury levels, the LSRO expert panel drew the following conclusions from their literature review:

- Within the time frame of the review, 1996-2003, mean urinary mercury levels in the general population were <2 μg/L, and 95% of individuals in the general population had urinary mercury levels at or below 4-5 μg/L.
- Long-term use of nicotine gum, intense chewing, and >20 amalgam surfaces resulted in urinary mercury levels that approached occupational exposure.
- Two consistent results were seen with occupational exposure: decreased Tumor Necrosis Factor-α at urine mercury levels ≥6 μg Hg/L and elevated urine N-acetyl β-D-glucosaminidase in the urinary mercury range of 25 μg Hg/L. These observations were deemed to be indicators of elemental mercury exposure and not indicators of adverse health effects.
- Neither occupational exposure nor dental amalgam studies provided sufficient information to support the hypothesis that mercury exposure at levels absorbed from amalgam restorations causes an adverse effect on renal function.
- There was insufficient evidence to support an association between dental amalgam and development of autoimmune diseases, including multiple sclerosis. This same conclusion has been reached by the Multiple Sclerosis Society.
- Case reports and studies of immune function demonstrated a localized allergic response to mercury in some individuals.
- Insufficient evidence was published between 1996 and 2003 to support or refute the hypothesis that elemental mercury contributed to adverse pregnancy outcomes.
- When self-reported complaints were evaluated, there was no evidence to attribute the effects to dental amalgam.
- Chelation therapy as advocated by some has not been shown to be an effective therapy and furthermore, it does not provide a cumulative measure of previous exposure to elemental mercury.
- There were conflicting reports on the effect of dental amalgam on antibiotic resistance in bacteria.
- Research gaps were identified to determine the effects of elemental mercury exposure at <25 $\mu g/m^3$ or urinary mercury levels <35 μg/L produced neurotoxic or reproductive or developmental effects, to determine any effects of co-exposure between elemental mercury and methylmercury, and to conduct well-controlled studies of dental professionals to determine if neurologic or renal effects could be attributed to occupational Hg^0 exposure.

A 20-year retrospective cohort study of New Zealand Defense Force Personnel was published by Bates, et al. in 2004.[8] In this large study, 20,000 people were in the final cohort and groups were analyzed in 5-year intervals over a 20-year period, from 1977-1997. There was no association between dental amalgam and kidney disorders in this study population. Overall, there was no evidence of an association between dental amalgam and neurologic dysfunction.

The conclusion that there was no correlation between amalgam exposure and neurological dysfunction was also drawn from a study of 1,663 male U.S. military personnel by Kingman, et al.[9] In this study, amalgam exposure levels were assigned to one of four groups based on the number of amalgam surfaces present. Although urine mercury levels were not reported for this study population, an earlier publication showed a positive correlation between urine mercury levels and the number of amalgam surfaces present in a military population.[10] From this report, Kingman, et al. estimated that 10 amalgam surfaces would result in an increase in urinary mercury of 1 μg /L.[10] In the recent study[9], no significant trends between the total number of amalgam surfaces and neurological signs were observed, except for a positive trend in abnormal reflexes at the knees of non-diabetic subjects. The clinical significance of this observation was unclear since a bilateral abnormality of ankle reflexes is a more sensitive indicator of neuropathy, and this trend was not observed in these non-diabetic subjects. The neuropathy tests employed were validated and sufficiently sensitive to detect neuropathies in diabetics and dioxin-exposed participants. The overall conclusion from this study was that there was no evidence to support the hypothesis that exposure to dental amalgam causes adverse, clinically-evident neurological effects.

Although fewer subjects (550 adults, 30-49 years of age) were evaluated in a study by Factor-Litvak, et al. in an article that was reviewed in the LSRO report[5,7], there was no association between dental amalgam and cognitive or fine motor functioning in this study.[11] This study was well-designed in that it looked at the correlation between total amalgam and urinary mercury as well as the number of occlusal amalgam restorations and urinary mercury. As expected, urinary mercury levels increased with the total number of amalgam surfaces or with the number of occlusal amalgam surfaces. In persons with amalgam restorations, mean urinary mercury levels varied between just over 1 μg Hg/g creatinine to just under 3 μg Hg/g creatinine; the overall mean urinary mercury level was 1.7 μg Hg/g creatinine.

The conclusions drawn from these articles of the lack of neurological or renal effects from amalgam restorations are also consistent with results from a study by Bellinger, et al. that looked at neuropsychological and renal effects of amalgam in children over a 5-year period.[12] Another study by De Rouen, et al. looked at neurobehavioral effects of dental amalgam in children[13] and found no neurobehavioral or nerve conduction effects during the 7-year period of the study.

In summary, my review of the scientific literature of health effects associated with dental amalgam supports the conclusions from the studies discussed in my presentation that demonstrate the lack of an association between elemental mercury in dental amalgam and adverse health effects other than a mild, localized allergic response in some individuals. These conclusions are also consistent with conclusions from previous studies that also do not show an adverse effect between dental amalgam and renal or neurologic function. Exposure levels to elemental mercury from dental amalgam are below the subclinical threshold level that can be seen in occupationally-exposed individuals in the chloralkali industry. As a toxicologist, my opinion is that the overwhelming body of scientific evidence supports the safety of dental amalgam, and there are no adverse effects in children or in adults after long-term exposures other than a mild, localized allergic response in some individuals.

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