International Academy of
IAOMT
Oral Medicine & Toxicology

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August 23, 2006

VIA E-MAIL

Michael Adjodha
Center for Devices and Radiological Health (HFZ-480),
Food and Drug Administration,
9200 Corporate Blvd., Rockville, MD 20850

Re: *Joint Meeting of the Dental Products Panel of the Medical Devices Advisory Committee of the Center for Devices and Radiological Health and the Peripheral and Central Nervous System Drugs Advisory Committee of the Center for Drug Evaluation and Research*

Dear Mr. Adjodha:

This letter is written on behalf of the International Academy of Oral Medicine and Toxicology ("IAOMT") and is submitted as a comment on the neuro-toxicity of dental amalgam fillings, the subject of discussion at the joint meeting scheduled for September 6-7, 2006. The IAOMT is an organization of dentists, physicians, and research professionals devoted to the examination, compilation, and dissemination of scientific research relating to the biocompatibility of oral/dental materials. The fundamental mission of the IAOMT is to promote the health of the public. It also:

- Accumulates and disseminates scientific information;
- Promotes relevant research and education;
- Promotes funding for relevant research;
- Promotes education of the public, professional organizations, and other groups, by providing scientific information;
- Promotes non-invasive scientifically sound therapies;
- Provides advisory services if/when required;
- Promotes mercury-free dentistry.

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As this Panel knows, mercury is a very toxic substance--more toxic than lead, cadmium, or arsenic.[1] The mercury is not locked into the amalgam matrix, but is continuously released as a vapor and inhaled into the lungs of the dental patient. On average, eighty percent of the mercury inhaled into the lungs is absorbed into the bloodstream.[2] Elemental mercury is continuously emitted from dental amalgam fillings and absorbed by the patients in whom the fillings are implanted. At least seventeen separate studies have assessed the extent to which dental patients are exposed to mercury contained in mercury fillings.[3] While the authors of these studies disagree concerning the precise quantity of mercury being absorbed from mercury fillings, none have argued that dental amalgam fillings are not a source of mercury exposure. Studies demonstrate that two-thirds of the mercury absorbed by non-occupationally exposed populations is derived from amalgam fillings.[4] Other studies

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[1]Sharma, RP; Obersteiner, EJ. *Metals and Neurotoxic Effects: Cytotoxicity of Selected Metallic Compounds on Chick Ganglia Cultures*. J Comp Pathol, 91(2):235-44 (1981).

[2]Kudsk, F.N., *Absorption of Mercury Vapour from the Respiratory Tract in Man*, Acta Pharmacol. et Toxicol. 23:250-262 (1965).

[3]These studies were recently summarized in the following paper: Richardson, G.M., *Inhalation of Mercury-Contaminated Particulate Matter by Dentists: An Overlooked Occupational Risk*, Human and Ecological Risk Assessment, 9:1519-1531 (2003).

[4]Aposhian, H.V., et al., *Urinary mercury after administration of 2,3-dimercaptopropaane-1-sufonic acid: correlation with dental amalgam score,* FASEB J, vol. 6 (April 1992), pp. 2472-2476. *See also*, Sandborgh-Englund, et al., *Mercury in Biological Fluids After Amalgam Removal*, J Dent Res, 77(4): 615-24 (Apr. 1998); World Health Organization, *Environmental Health Criteria 118: Inorganic Mercury* (1991) p. 36; Clarkson, T.W.; et al., *Biological Monitoring of Toxic*

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have confirmed a correlation between the number of fillings and the mercury found in cadaver brains.[5]

In 1995, an important review article summarized some of the scientific documentation concerning dental amalgam was published in the highly prestigious scientific publication, the FASEB Journal.[6] The authors detailed the scientific data and conclusions from scores of peer-reviewed articles documenting the deleterious effects of mercury vapor on the immune, renal, reproductive, and central nervous systems. The authors noted that "[r]esearch evidence does not support the notion of amalgam safety." In their conclusion, the authors admonished that:

> The collective results of numerous research investigations over the past decade clearly demonstrate that the continuous release of Hg° from dental amalgam tooth fillings provides the major contribution to Hg body burden. The experimental evidence indicates that amalgam Hg has the potential to induce cell or organ pathophysiology. At the very least, the traditional

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Metals: The Prediction of Intake of Mercury Vapor From Amalgams (1988) p. 256. ("The release of mercury from dental amalgams makes the predominant contribution to human exposure to inorganic mercury including mercury vapor in the general population."); Lorscheider, FL; et al. *"Mercury Exposure from Silver Tooth Fillings: Emerging Evidence Questions a Traditional Dental Paradigm."* FASEB J., 9:504-8 (1995). ("[D]ental amalgam tooth fillings are the major source of Hg exposure for the general population.")

[5]Eggleston, et al., *Correlation of dental amalgam with mercury in brain tissue*, J Prosth Dent, 58(6), 1987.

[6]Lorscheider, FL; et al. *"Mercury Exposure from Silver Tooth Fillings: Emerging Evidence Questions a Traditional Dental Paradigm."* FASEB J., 9:504-8 (1995).

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dental paradigm, that amalgam is a chemically stable tooth restorative material and that the release of Hg from this material is insignificant, is without foundation. One dental authority states that materials are presently available that are suitable alternatives to Hg fillings.

* * * *

It would seem that now is the time for dentistry to use composite (polymeric and ceramic) alternatives and discard the metal alchemy bestowed on its profession from a less enlightened era. Although human experimental evidence is incomplete at the present time, the recent medical research findings presented herein strongly contradict the unsubstantiated opinions pronounced by various dental associations and related trade organizations, who offer assurances of amalgam safety to dental personnel and their patients without providing hard scientific data, including animal, cellular and molecular evidence, to support their claims.

A number of studies demonstrating neurobehavioral deficits in dental personal have been published.[7] Standard medical

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[7]Ngim, CH; et al., *Chronic Neurobehavioral Effects of Elemental Mercury in Dentists*, Brit J Indust Med, 49:782-90, 1992. Gonzalez-Ramirez, D; et al. *Sodium 2,3-Dimercaptopropane-1-Sulfonate Challenge Test for Mercury in Humans: II. Urinary Mercury, Porphyrins and Neurobehavioral Changes of Dental Workers in Monterrey, Mexico*. J Pharmocol Exper Therap, 272(1):264-74 (1995); Echeverria, D; et al., *Behavioral Effects of Low-Level Exposure to Hg° Among Dentists*. Neurotoxicol Teratol, 17(2):161-8 (1995); Shapiro, I.M., et al., *Neurophysiological and neuropsychological function in mercury-exposed dentists*. The Lancet 1, 1147-1150 (1982); Uzzell, B.P., et al., *Chronic low-level mercury exposure and neuropsychological functioning*. J of Clin and Exper Neuropsych. 8, 581-593.

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textbooks also recognize this phenomenon.[8] Dentists with occupational exposure to mercury score below normal on neurobehavioral tests of motor speed, visual scanning, verbal and visual memory, and visuomotor coordination.

Scientific investigators have detected "significant [central nervous system] effects" among dentists and dental assistants at very low levels of Hg° exposure (i.e. urinary Hg° ‹ 4 µgs/liter). They concluded that "[t]he pattern of results, comparable to findings previously reported among subjects with urinary Hg° › 50 µgs/liter, presents convincing new evidence of adverse CNS effects associated with low Hg° exposures within the range of that received by the general population."[9] This finding demonstrates adverse neurobehavioral deficits in dentists and dental assistants at urine mercury levels essentially equivalent to the urine mercury levels of those people in whom amalgam has been placed.

Risk assessment studies for mercury demonstrate that the quantity of mercury absorbed by people with amalgam exceeds the mercury doses established as safe by the Environmental Protection Agency, the Agency for Toxic Substances & Disease Registry, and Health Canada. The U.S. and Canada have developed minimum risk levels for mercury through government sponsored risk and exposure assessments. Through the development of formal toxicological profiles, the ATSDR establishes "Minimal Risk Level (MRL)" exposure standards for the general population in the United States. The ATSDR has also published its Toxicological Profile for Mercury, in which it established a "minimum risk level" for mercury. The MRL for mercury established in this publication set the chronic inhalation

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[8]*See* Harrison's Principles of Internal Medicine (14th Edition) at 2567.

[9]Echeverria, et al., *Neurobehavioral Effects from Exposure to Dental Amalgam Hg°: New Distinctions Between Recent Exposure and Hg Body Burden,* FASEB J. 12, 971-980 (1998).

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MRL for mercury at 0.0002 mg/m³. The daily dose resulting from such an exposure would be 2.4 µgs/day. In Canada, Health Canada commissioned its own risk assessment to evaluate general population exposure to amalgam mercury. This formal assessment was presented to Health Canada in August of 1995[10] and was later published in a peer-reviewed risk assessment journal.[11] This report established a tolerable daily intake (a/k/a reference dose) for mercury 0.014 ugs/kg/day, which would equal 1.4 ugs/day. Americans with amalgam fillings are receiving doses of mercury from all sources that exceed these limits, and the primary source of mercury for the general population is amalgam fillings, which contribute far more mercury than all other sources of mercury combined.

The EPA has also conducted a formal risk assessment for mercury and determined a sub-chronic (short-term) reference dose of 0.3 µgs/m³ with an equivalent absorbed daily dose of 3.84 µgs.[12] Absorption of mercury in excess of these doses presents increasing risk of neurological harm. A dental patient with amalgam fillings absorbs mercury in excess of these published toxicological thresholds.[13]

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[10]Health Canada, *Assessment of Mercury Exposure and Risks From Dental Amalgam: Final Report*, Medical Devices Bureau, Environmental Health Directorate.

[11]Richardson, G.M., et al., *A Monte Carlo Assessment of Mercury Exposure and Risks from Dental Amalgam,* Human and Ecological Risk Assessment, 2(4):709-761(1996).

[12]U.S. EPA. "Health Effects Assessment Summary Tables: FY-1997 Update" (1997).

[13]*See, e.g.*, World Health Organization, *Environmental Health Criteria 118: Inorganic Mercury* (1991) p. 36, concluding that 3 to 17 micrograms are absorbed daily by persons with mercury fillings. This document reflects that the concensus average estimate is 10 µgs absorbed per day, an uptake

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Mercury is of even greater concern where the patient is a child or a woman of child-bearing age. "The developing fetus and young children are thought to be disproportionately affected by mercury exposure, because many aspects of development, particularly brain maturation, can be disturbed by the presence of mercury. Minimizing mercury exposure is, therefore, essential to optimal child health."[14] Mercury in all of its forms is toxic to the fetus and children, and efforts should be made to reduce exposure to the extent possible to pregnant women and children as well as the general population.[15]

About eight percent of U.S. women of child-bearing age have enough mercury in their blood for their children to be at risk. The National Academy of Sciences estimates that 60,000 newborns a year could be at risk of learning disabilities because of mercury their mothers absorbed during pregnancy. Significantly, mercury in the tissues of fetuses and infants (11-50 weeks of life) correlates significantly with the number of dental amalgam fillings of the mother.[16] "From the nephrotoxicity point of view, dental amalgam is an unsuitable filling material, as it may give rise to mercury toxicity. In these exposure conditions,

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corroborated by a more recent daily estimate of 12 µgs/day. Skare, I, et al., *Human Exposure to Mercury and Silver Released from Dental Amalgam Restorations*, Archives of Environmental Health, vol. 49, no. 5, pp. 384-394 (Sept.-Oct. 1994). Levels for some individuals may be as high as 100 µgs/day. Lorscheider, FL; et al. *"Mercury Exposure from Silver Tooth Fillings: Emerging Evidence Questions a Traditional Dental Paradigm."* FASEB J., 9:504-8 (1995).

[14]Goldman LR, Shannon MW, *Technical Report: Mercury in the Environment: Implications for Pediatricians.* American Academy of Pediatrics: Committee on Environmental Health. Pediatrics (2001) Jul;108(1):197-205.

[15]*Id.*

[16]Drasch et. al., "*Mercury Burden of Human Fetal and Infant Tissues,*" European Journal of Pediatrics (August 1994).

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renal damage is possible and may be assessed by urinary excretions of albumin, NAG, and gamma-GT."[17]

Scientific studies have demonstrated associations between mercury and neurological disease. These studies justify avoiding unnecessary mercury exposure. For example, one epidemiologic study correlates body mercury levels with increased risk of idiopathic Parkinson's disease.[18] Animal studies demonstrate exposure to mercury vapor and autoimmunity.[19] One such study showed that dental silver amalgam and silver alloy implanted in the physiological milieu of the peritoneal cavity released enough metals to adversely effect the immune system.[20]

Mercury has even been linked to Alzheimer's disease ("AD").[21] Professor Boyd Haley, Chairman of the Department of

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[17]Mortada WL, Sobh MA, El-Defrawy MM, Farahat SE. Urology and Nephrology Center, Mansoura University, Faculty of Science, Egypt. J Nephrol 2002 Mar-Apr;15(2):171-6.

[18] Ngim, C., *Epidemiologic Study on the Association between Body Burden Mercury Level and Idiopathic Parkinson's Disease*, Neuroepidemiology, 8:128-141 (1989).

[19]Warfvinge, et al., *Systemic Autoimmunity Due to Mercury Vapor Exposure in Genetically Susceptible Mice: Dose-Response Studies*, Toxicol Appl Pharmacol, 132:299-309 (1995).

[20]Hultman, P; et al., *Adverse Immunological Effects and Autoimmunity Induced by Dental Amalgam and Alloy in Mice*, FASEB J, 8:1183-90 (1994).

[21]Ehmann, et al., *Brain Trace Elements in Alzheimer's Disease*, Neurotoxicology, 7(1):195-206 (Spring 1986); Thompson, et al., *Regional Brain Trace-element Studies in Alzheimer's Disease*, Neurotoxicology, 9(1):107 (Spring 1988); Vance, *Trace Element Imbalances in Hair and Nails of Alzheimer's Disease Patients*, Neurotoxicology, 9(2):197-208 (Summer 1988); Wenstrup, et al., *Trace Element Imbalances in Isolated Subcellular Fractions of*

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Chemistry at the University of Kentucky, concludes that "mercury and other blood-brain permeable toxicants that have enhanced specificity for thiol-sensitive enzymes are the etiological source of AD. Included in this category are other heavy metals such as lead and cadmium that act synergistically to enhance the toxicity of mercury and organic-mercury compounds."[22]

Material safety data sheets distributed by Kerr Corporation and other amalgam manufacturers reflect, *inter alia*, that mercury is a skin sensitizer, a pulmonary sensitizer, a nephrotoxin, and a neurotoxin. Kerr does not qualify its warnings by informing the user (i.e. dentists) that such toxic properties are ameliorated by

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Alzheimer's Disease Brains, Brain Res, 12;533(1): 125-31 (Nov. 1990); Cornett, et al., *Imbalances of Trace Elements Related to Oxidative Damage in Alzheimer's Disease Brain*, Neurotoxicology, 19(3):339-45 (June 1998); Mutter, *Alzheimer Disease: Mercury as a Pathogenetic Factor and Apolipoprotein E as a Moderator*, Neuroendocrinol Lett. 2004; 25(5):275-283. ("Inorganic mercury [found in dental amalgam] may play a major role [in the pathogenesis of Alzheimer's Disease."]) Pendergrass, J. C., et al., *Mercury Vapor Inhalation Inhibits Binding of GTP to Tubulin in Rat Brain: Similarity to a Molecular Lesion in Alzheimer's Disease Brain.* Neurotoxicology 18(2), 315-324 (1997); Pendergrass, J.C., *Inhibition of Brain Tubulin-Guanosine 5'-Triphosphate Interactions by Mercury: Similarity to Observations in Alzheimer's Diseased Brain*, Metal Ions in Biological Systems V34, *Mercury and Its Effects on Environment and Biology*, Chapter 16. Edited by H. Sigel and A. Sigel (1996); Duhr, E.F., et al., *HgEDTA Complex Inhibits GTP Interactions With The E-Site of Brain b-Tubulin*, Toxicology and Applied Pharmacology 122, 273-288 (1993); Leong, CCW, et al., *Retrograde Degeneration of Neurite Membrane Structural Integrity of Nerve Growth Cones Following In Vitro Exposure to Mercury*, Neuroreport, vol.12, pps. 733-737 (2001).

[22]Haley, B., *The Relationship of the Toxic Effects of Mercury to Exacerbation of the Medical Condition Classified as Alzheimer's Disease*, The Nordic Journal of Biological Medicine (June-July 2003).

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mixing mercury with the other amalgam constituents. Kerr successfully argued that its warnings were legally adequate to notify a dentist of the dangers associated with mercury ***and*** mixed dental amalgam.[23] This argument convinced the Sixth Circuit Court of Appeals to dismiss a lawsuit brought by a dentist who alleged personal injuries caused by Kerr's failure to warn of the dangers associated with mixed dental amalgam. *See*, *Barnes v. Kerr Corp.*, 418 F.3d 583 (6th Cir. 2005). The *Barnes* Court concluded that "[r]easonable minds... could not differ as to the sufficiency of the warnings given to Barnes." *Id.* at 591.[24]

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[23]Kerr's position is particularly important to this issue. Kerr claims to maintain 46% of the national market for dental amalgam.

[24]Kerr has shielded itself from liability by successfully arguing that its warnings adequately notify dentists of the hazards of mixed dental amalgam. Meanwhile, the ADA has shielded itself from liability by successfully arguing that it owes no legal duty to dental patients. In response to a lawsuit brought by a plaintiff who alleged he was injured by the mercury in his fillings, the ADA was named as a defendent, the ADA argued: "The ADA owes no legal duty of care to protect the public from allegedly dangerous products used by dentists. The ADA did not manufacture, design, supply or install the mercury-containing amalgams." *Tolhurst v. Johnson & Johnson Consumer Products, Inc.*, Superior Court of Santa Clara County, State of California, Case No. 718228, October 22, 1992.

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Ironically, dentists across the country are forbidden by their state dental boards from disclosing such information.[25] Dentists who desire to communicate with their patients or with the public face professional discipline for engaging in such communications. Therefore, manufacture warnings are not disseminated to the public.[26]

The IAOMT submits that the U.S. FDA cannot assure the public of the safety and effectiveness of dental amalgam where

- The largest U.S. manufacturer of dental amalgam openly warns (without qualification or limitation) that amalgam is a potent neurotoxin capable of inducing a myriad of adverse health effects;

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[25]*See, e.g.*, the published admonishments of the North Carolina Board forbidding North Carolina dentists from engaging in any communications "that you practice 'Mercury-free Dentistry,' 'Metal-free dentistry,' or that you should 'Eliminate your exposure to Mercury,' or that 'Silver fillings contain mercury that may leak into your body and cause health problems,' or make any reference that mercury fillings are harmful."

[26]In two separate cases, courts recently considered claims respectively brought by a dental patient and by a dentist alleging injuries caused by exposure to mercury vapor and amalgam aerosols during the placement and removal of amalgam fillings. Expert testimony supported the conclusion that the injuries of the respective plaintiffs was caused by this exposure. The defendants filed pretrial motions challenging the validity and reliability of the plaintiffs' proffered expert testimony pursuant to *Daubert v. Merrill Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993). However, both courts denied these motions and found the plaintiffs' proffered expert testimony valid, reliable, and admissible. *See Barnes v. The Kerr Corporation*, U.S. District Court for the Eastern District of Tennessee, Case No. 4:99-CV-00079; *McReynolds v. Mindrup*, Circuit Court of Jackson County, Missouri, Case No. CV97-1891.

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- The published science demonstrates grim and compelling evidence that the mercury derived from amalgam fillings is ***not*** safe;
- Dental amalgam represents by far the largest source of mercury exposure for the general public;
- Dentists are prevented from warning patients in whom dental amalgam is placed and removed of the potential adverse effects associated with dental amalgam;
- The safety of this dental restorative material has not been investigated in the same manner as other dental and medical implants classified in Class III.[27]

The IAOMT calls on the FDA to immediately ban mercury fillings until such time as reliable proof of safety and effectiveness is demonstrated.

Sincerely yours,

Terrence G. Messerman, DDS

Terrence Messerman, DDS
President, IAOMT

cc: International Academy of
Oral Medicine & Toxicology

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[27]The FDA continues to ignore the fact that its own rules require the classification of dental amalgam in Class III. Dental and medical devices constituting "implants" must be classified in Class III, requiring the products manufacturers to obtain premarket approval prior to marketing the product. In our view, the FDA's position that dental amalgam is not an implant is indefensible and irresponsible.