Letters to the Editor

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Methemoglobinemia: A Novel Way to Noninvasively Measure It by Pulse Oximetry

To the Editor: We read with interest the article by Linz et al[1] regarding methemoglobinemia in rubber molding workers exposed to an adhesive containing dinitrobenzene. Prompt diagnosis and treatment is dependent on a high index of suspicion and an infrastructure that facilitates prompt confirmation of the diagnosis. Blood testing for methemoglobin by cooximetry from arterial or venous samples is not readily available in medical clinics or hospitals and is not available at most workplaces where exposure to substances known to cause methemoglobinemia occurs.

A new pulse oximeter is available that measures methemoglobin noninvasively using a finger probe. It uses eight wavelengths and signal extraction technology to accurately measure methemoglobin,[2] carboxyhemoglobin,[3] and arterial blood oxygenation in a few seconds. The Rad-57 pulse cooximeter has been developed by Masimo (Masimo Corp., www.Masimo.com) and can be a cheap, noninvasive way to screen for methemoglobin, but also carboxyhemoglobin, in the workplace. In addition to being used for quickly identifying workers toxic from exposure to substances causing methemoglobinemia and toxic exposure to carbon monoxide in confined spaces, it may be used to identify smokers as part of an employee wellness program.

Prompt diagnosis of dyshemoglobinemias can be achieved using pulse cooximetry in a noninvasive manner in the field or workplace. This can be lifesaving and decrease the burden of life-threatening toxicities.

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Authors' Response

To the Editor: We appreciate the comments by Drs Mamatha P. Reddy and Sridhar P. Reddy regarding noninvasive measurements of methemoglobinemia (MetHb) by pulse oximetry. We concur with their view that the prompt diagnosis and treatment of an acquired dyshemoglobinemia is dependent on a high index of suspicion and an infrastructure that facilitates prompt identification and treatment when necessary. They go further to discuss using a unique newly patented technology in pulse oximetry involving eight wavelengths of light along with signal extraction technology (not available at the time of our toxic occupational event) to earlier identify and prevent potentially toxic events involving methemoglobin and carboxyhemoglobin (COHb).

An accurate, easy-to-use, yet noninvasive portable monitoring device capable of rapid turnaround time for onsite or point-of-care methemoglobin determinations would seem highly desirable, especially a device that requires no user calibration. The Rad-57 cm pulse oximeter that they discuss offers the additional advantages that it can be used stationary (like in an intensive care unit) or can be moved from person to person (like in an emergency room setting or workplace). The instrument appears well suited for many field or hospital settings because the pulse oximeter can be handheld, is relatively small in size (17.5 cm × 7.6 cm × 3.6 cm), and only weighs 13 oz.[1]

The technology available with the Masimo Rad-57 cm pulse oximetry demonstrates considerable capabilities not available in previous pulse oximeters. In 1995, the company introduced Read-Through Motion and Low Perfusion pulse oximetry, known as SET. In 2005, Masimo introduced the Rad-57 cm pulse oximetry device, which provided for the first time noninvasive monitoring of carbon monoxide and methemoglobin in the blood. In older pulse oximeters, hemoglobin oxygen saturation by pulse oximetry did not correlate with COHb levels and consistently overestimated the fractional arterial oxygen saturation in patients with severe carbon monoxide poisoning.[2]

Comparison of pulse oximetry and arterial blood gas oxygen saturation (measured and calculated values, respectively) in the presence of methemoglobin has displayed significant discrepancies as the methemoglobin levels exceed 9%, whereas oxygen saturation uniformly was lower with pulse oximetry. Because of these findings, Rausch-Madison and Mohsenifar have recommended that when methemoglobin levels exceed 10%, cooximetry be used as a screen for methemoglobinemia and that serial cooximeter measurements are used to guide therapy.[3] Haymond and others studied oxygen saturation (SO_2) measurements by pulse oximetry, cooximetry, and arte-

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rial blood gas analysis, which they observed were often used interchangeably. They found oxygen saturation results from these methods were virtually identical, but in cases of increased dyshemoglobin fractions, including methemoglobinemia, it is crucial to distinguish the specific limitations of these methods. They concluded that SO_2 calculated from pH and PO_2 in blood gas analyzers should be interpreted with caution as the algorithms used assume normal O_2 affinity, normal 2,3-diphosphoglycerate concentrations, and no dyshemoglobins or hemoglobinopathies. They recommended that cooximeter reports should include dyshemoglobin fractions in addition to the oxyhemoglobin fraction. In cases of an increased MetHb fraction, they observed pulse oximeter values trend toward 85%, underestimating the actual oxygen saturation. They also found that hemoglobin M variants may inaccurately yield normal MetHb and increased COHb or sulfhemoglobin (SulfHb) fractions measured by cooximetry.[4] Ralston and others also found several potential sources of error in pulse oximetry investigated resulting from electrical interference, dyes, dyshemoglobins, and various other pigments.[5]

At present, cooximeters are the most frequently used instrument for assessing MetHb, although errors occur when other types of hemoglobin are present such as SulfHb and fetal hemoglobin.[6] Cooximeters use spectrophotometric techniques, yet results vary among different instruments as well as when compared with gas chromatography (considered to be the "criterion" standard).[7] Gas chromatography is used in a variety of situations for determining the number and concentration of components in a volatile mixture or volatile impurities in a substance. The major disadvantages for clinical use of gas chromatography include the need for specialized equipment, measurements are labor- and time-intensive, and analyses require sophisticated technical expertise. We suggest that blood analysis through cooximetry in the hospital setting is the current standard of analysis for the acute and periodic testing of persons who are exposed, work in contact, or must handle products that potentially could induce acquired methemoglobinemia.

Drs. Reddy state that "blood testing for methemoglobin by cooximetry from arterial or venous samples is not readily available in medical clinics or hospitals."[8] A recent study by Hampson and others evaluated the ability of hospitals in the Pacific Northwest to measure COHb levels by surveying the clinical laboratory of every acute care hospital in Washington, Idaho, Montana, and Alaska regarding their ability to measure COHb levels, the method used, and the time required. If they could not measure COHb, they were then asked whether samples were sent elsewhere, the location of the referral laboratory, and time required to obtain a result. In the four states surveyed in 2003 to 2004, only 44% of acute care hospitals have the capability to measure COHb, whereas the remaining 56% send blood samples to other laboratories.[4] In contrast to these findings, all but one of our 10 Northern Ohio community-based acute care and referral center hospitals involved in the Bowling Green State University Respiratory Technology Program have immediate onsite availability of at least one cooximeter for measuring MetHb and COHb. One of our affiliate teaching institutions (Fairview Hospital, Cleveland, OH) indicated a purchase intention for a Rad-57 cm pulse oximeter to be used as a "screening" device in their emergency services department (Frank Sandusky, Manager of Respiratory Care Services, Fairview Hospital, Cleveland, OH, personal communication, July 11, 2006). We have not been able to document similar availability in workplaces in affiliate hospital service areas known to be at risk for causing methemoglobinemia.

In our case series review, five steam press operators were repeatedly exposed at a rubber processing plant (through manual handling) to an adhesive containing dinitrobenzene. Methemoglobin levels in the steam press workers were obtained and processed at our community hospital emergency room by using an IL 282 Cooximeter ranged from 3.8% to 41.2%.[9] The subsequent investigation following the exposure incident uncovered that p-DNB had formed during the manufacture of one of the proprietary substances used as a base chemical in the adhesive. This p-DNB-contaminated chemical was then introduced into the adhesive during its formulation. The National Institute of Occupational Safety and Health recommended that plant workers use butyl rubber gloves to avoid skin contact with the dried adhesive and that plant management institute periodic follow up medical monitoring of all workers exposed to the adhesive.[10] We suggest that mandatory recommendations specifically include either periodic blood cooximetry determinations or specific Masimo Rad-57 cm pulse oximetry for methemoglobin tracking.

Drs. Reddy describe the new Masimo pulse oximetry technology as "cheap noninvasive way to screen for methemoglobin as well as carboxyhemoglobin in the workplace."[8] The Rad-57 cm pulse oximeter has a relatively modest retail price of $4995 and requires minimal technical skills, yet the device until now has been marketed by Masimo to the medical community where "hospitals and EMS providers are now using this device" as well as "being used mainly in ERs and by the RT world" (D. Hunt, Masimo Sales Consultant, written communication, July 06, 2006). Masimo has indicated plans to target nonhospital workplace use of the technology in the near future.

Before extending the use of cooximetry, another population that could benefit from early screening and detection of acquired methemoglobinemia by a noninvasive screening device is infants younger than 4 months of age who are fed formula diluted with water from rural domestic wells. These particular infants are especially at risk for developing acute acquired methemoglobinemia from nitrate exposure.[11] Several factors may contribute to this phenomenon. Because the pH of the upper gastrointestinal tract typically is higher in infants than in older children

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and adults, conversion of ingested nitrate to nitrite is enhanced. Premature or newborn infants may also be more susceptible because of their higher levels of fetal hemoglobin (HbF).[12] Normal HbF fractions at birth are approximately 65% to 80% of total hemoglobin. During the next few months after birth, hemoglobin F production declines and production of hemoglobin A predominates. By the age of 4 months, normal HbF fractions are approximately 10% of total hemoglobin.[13] Infant concentrations of nicotinamide–adenine dinucleotide-dependent methemoglobin reductase (an enzyme responsible for reduction of methemoglobin back to normal hemoglobin) provides only half the reductase activity present in adults,[14] thus resulting in increased methemoglobin that place newborns and young infants fed formula diluted with nitrate-contaminated well water at higher risk for toxicity.[15]

It seems certain that continued advancement will occur in the measurement of dyshemoglobinemias such as methemoglobinemia that can pose life-threatening toxicities. At this time, Masimo is awaiting U.S. Food and Drug Administration (FDA) 510(k) clearance for its new bedside Radical-7 pulse oximeter, which will allow continuous noninvasive measurements of COHb, MetHb, O_2 saturation, pulse rate, and perfusion index. The Rad-57 cm pulse oximeter is the newest FDA-approved advancement in screening devices offering several advantages over older pulse oximetry technology. Additional data in the higher ranges of MetHb and COHb in higher ranges would be helpful in assessing the accuracy of the device as referenced by Drs Reddy.[15,16] This device is likely to be clinically useful in several settings, including occupational and environmental sites where rapid, simple, noninvasive assessments of MetHb, COHb, and oxyhemoglobin are warranted.

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Lung Cancer Mortality in the German Chromate Industry, 1958 to 1998

To the Editor: To put in accurate context the article by Birk et al that concludes that the study's findings suggest "a possible threshold effect of occupational hexavalent chromium exposure on lung cancer,"[1] three points should be considered: 1) these data were withheld from a federal rulemaking proceeding, 2) these data were actually part of a larger study that refutes the authors' conclusion, and 3) after examining the study, the U.S. Occupational Safety and Health Administration (OSHA) rejected the authors' conclusion.

The issue of the carcinogenicity of hexavalent chromium (Cr[VI]) is one of great public health and regulatory interest. In October 2004, OSHA issued a proposed standard that would have greatly reduced workplace exposures to Cr(VI).[2] The proposed rule included a risk assessment that was based on data from workers with generally higher exposure levels than those seen in the Birk et al article. Throughout the rulemaking proceeding, OSHA asked for epidemiologic

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data on workers with lower exposure to Cr(VI), but neither the chromium industry nor the epidemiologists who conducted this study provided it to the agency at the public hearings or during the public comment period.[3]

In fact, the data presented by Birk et al were part of a larger multiplant study done for the chromium industry, completed more than 2 years before OSHA issued its proposed standard, but never published or given to OSHA by its authors.[3] That study, in which workers from four low-exposure facilities (two German facilities and two U.S. ones) were combined into one cohort reported significantly elevated lung cancer risk at both high and intermediate exposure levels, along with a clear dose–effect relationship[4] (see Table 1). Despite repeated emphasis in the study protocol and the final report on the need to maximize statistical power by combining data from the four facilities,[4,5] the investigators subsequently divided this study into two components and published two statistically underpowered studies.[1,6] In their logistic regression in the second of these papers, Birk et al combined the low and intermediate exposure categories from the final report into a single referent category. The result was the disappearance of the finding of greatest regulatory importance: the increased risk of lung cancer among those in the intermediate exposure group whose exposures were well below the OSHA standard in effect at the time and close to the exposure limit OSHA was contemplating. The dose–effect relationship vanished as well, because only a single nonreferent exposure category remained (see Table 2).[3] In comments to OSHA, two industry groups cited the supposed lack of a positive finding at low exposures in the German data as evidence the proposed OSHA standard was unnecessarily stringent.[7,8]

The authors justify their straying from their own protocol and dividing the study into two smaller, underpowered studies by noting that exposure history was estimated using airborne Cr(VI) levels in the U.S. facilities and urinary chromium levels in the German plants. In the final report, provided to the chromium manufacturing companies that paid for the study, these data were combined, using, ironically, a conversion factor[9] that is cited in the present paper when comparing the measured urinary Cr(VI) levels to OSHA's permissible exposure limit.

It is important to note that OSHA has rejected Birk et al's conclusion that "these data suggest a possible threshold effect" of Cr(VI) exposure on lung cancer. The agency's scientists explained in the final standard that the Birk et al study's "small cohort size, few lung cancer cases (eg, 10 deaths in the three lowest exposure groups combined) and limited follow up (average 17 years) severely limit the power to detect small increases in risk that may be present with low cumulative exposures."[10]

The Occupational Safety and Health Act instructs the agency to use the "best available evidence."[11] We believe that failure to provide the original study to OSHA, as well as the decision to bifurcate the study into two separate, underpowered publications, made after the final report was complete and the results were known, are inconsistent with the obligation of scientists to fully and promptly report findings of public health importance, even those that may trouble the sponsors of their study.

TABLE 1
Elevated Lung Cancer Mortality Risk in Intermediate and High Exposure Groups in Original Unpublished Study*

Cumulative Exposure to Cr(VI)	OR†	95% CI
Low (<40 μg/L)	Reference	—
Intermediate (40 μg/L to <200/L)	4.9	1.5–16.0
High (≥200 μg/L)	20.2	6.2–65.4

*Adapted from Table 17 in Final report: collaborative cohort mortality study of four chromate production facilities, 1958–1998.[4]
†Odds ratio from logistic regression analysis.
CI indicates confidence interval.

TABLE 2
Increased Risk of Lung Cancer Mortality Risk Among Workers With Intermediate Exposure Disappears in *JOEM* Publication of German Component of Study*

Cumulative Exposure to Cr(VI)	OR†	95% CI
Low and intermediate (<200 g/L)	Reference	—
High (≥200 μg/L)	6.9	2.6–18.2

*Adapted from Birk et al.[1]
†Odds ratio from logistic regression analysis.
CI indicates confidence interval.

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Authors' Response

To the Editor: Michaels et al attempt to "put in accurate context" our recent paper on an epidemiological study of lung cancer mortality among a cohort of German chromate industry workers.[1] We address each of the three specific points relevant to our research, as well as an overarching policy issue, raised by Michaels et al.

First, Michaels et al claim that "these data were withheld from a federal rulemaking proceeding." We conducted the original study under a contract between Applied Epidemiology, Inc. and the Industrial Health Foundation (IHF) and submitted our 139-page technical report to IHF (dated April 7, 2003) completing our contractual obligation. It is standard in the consulting industry to undertake client assignments on a confidential basis. Although the IHF study was undertaken on such a basis, we had the right to publish the results after considering (without obligation) client comments. Without any further contract with IHF, we began preparing manuscripts long before the Occupational Safety and Health Administration (OSHA) review. At the urging of the U.S. Office of Management and Budget, however, we accelerated this process so that at least the basic results from the U.S. and the German cohorts might be published and available to the OSHA process. The U.S. paper[2] was accepted for publication immediately, whereas the German paper was held up in review by a different journal for many months—ironically until the end of the OSHA comment period—and rejected. We then submitted it to *JOEM* and, after revision (results and interpretations unchanged), it was accepted and provided to OSHA.

Michaels et al's second point is that "these data were actually part of a larger study that refutes the authors' conclusion." That the German paper was part of a larger study effort is of course correct, as described in both the U.S. and the German papers, as well as in a response to Michaels et al's earlier criticisms of the U.S. paper.[3] That the results refute our conclusion that the data suggest a threshold is inaccurate and based on information taken out of context.

Originally, the German cohort was part of a study that combined this group with a cohort of U.S. chromate industry workers to maximize statistical power. However, as explained in both papers and in response to Michaels et al's earlier criticisms, several substantial differences between the cohorts complicated the analyses. Specifically, differences were seen by gender (only the U.S. plants included women), age (U.S. employees were substantially younger at hire and at end of follow up), ethnicity (U.S. plants included black and Hispanic workers, German plants had nearly no minorities), smoking prevalence (U.S. plants had lower rates), and—perhaps most importantly—exposure data (U.S. plants only had air monitoring data, German plants relied mainly on urinalysis). Because of these potentially important differences by country, and the fact that 88% of the lung cancer deaths were observed among the German subcohort, colleagues attending the Epidemiology in Occupational Health Symposium held in Barcelona in 2002, where the study was publicly presented,[4,5] recommended that the results be stratified by country and reported separately. This suggestion had also been made after review of the study protocol by a senior academic epidemiologist who served as an external advisor.

While stratifying the results by country resulted in a U.S. report with low statistical power (fully acknowledged in the paper), it was felt that those results should be made available to the scientific community through a peer-reviewed publication. Consequently, a more straightforward statistical analysis of the German data was possible with statistical power only slightly lower than that of the combined cohorts. Because the risk for the U.S. plants was not elevated, and all U.S. deaths occurred in the lowest exposure category, the resulting lung

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cancer standardized mortality ratio (SMR) for the German plants increased relative to the combined cohorts. SMR analysis by level of cumulative exposure (see Table 4 in the German paper) generated similar results to the combined cohort (also reflected in two additional tables in the client report) leading to our suggestion of a threshold.

We performed logistic regression analyses in the original study and, as described in our article, to investigate simultaneously the influences on the risk estimates of cumulative exposure, peak exposure, and smoking. We do not consider the results presented in Michaels et al's Table 1 to be reliable largely because of the substantial differences between the U.S. and German cohorts. Also, we note the instability of the models as reflected in the wide confidence intervals, the uncertain adequacy of the fit of the model, and the fact that the logistic regression did not take into account the time dependency of the cumulative exposure metric. The results of the logistic regression analysis for the German plants, described in our article and partially included in Michaels et al Table 2, were taken directly from Table 19 of the client report and were not, as suggested by Michaels et al, produced after the decision to report results separately by country. We have explained in both the publication and the client report that a "low" exposure category estimate was technically impossible, because there were no cases with all necessary data available in the "low" category in the German cohort.

Michaels et al's third point largely reiterates (by quoting OSHA) our own words: "Demonstrating a clear (and statistically significant) threshold response in epidemiological studies is difficult especially, as in this study, the number of available cases is relatively small, and the precise estimation of small risks requires large numbers."[1] We hope, however, that by presenting such results—even if only suggestive—we will stimulate additional useful epidemiologic research and expand scientific inquiry.

Finally, although offering no solution, Michaels et al do raise a legitimate regulatory/policy point: how can the regulatory community obtain all scientifically sound and relevant evidence for their deliberations? Policymakers and regulators readily rely on material published in the peer-reviewed scientific journals. It is understood—correctly or incorrectly—that the peer review process imparts some degree of consistency with current standards and therefore quality. Michaels et al previously asserted that "Parties involved in the rulemaking process should also be required to certify that they have submitted all relevant data to the public record, whether or not those data have undergone peer review."[6] They apparently include material that is not published and not subject to rigorous peer review to be among the "best available evidence" that OSHA is to use. We believe that this is not so straightforward and that fuller discussion is warranted.

We are disappointed that Michaels et al have chosen to speculate about (or at least not read carefully and represent accurately) our work for IHF and the publications derived from that work (especially because we did attempt to discuss these very points directly with Michaels during several phone conversations around May 2005). Nevertheless, we are grateful to the editor of *JOEM* for the opportunity (not offered by the journal in which Michaels et al first published their story[6]) to respond and to offer a clearer perspective on our research.

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The Beryllium Occupational Exposure Limit: Historical Origin and Current Inadequacy

To the Editor: We are writing in response to "The Beryllium Occupational Exposure Limit: Historical Origin and Current Inadequacy"[1] by Jonathon Borak. As Assistant Secretary of Energy for ESH, one of us (D.M.) was the federal official responsible for overseeing the Department of Energy's (DOE's) Chronic Beryllium Disease Prevention Program final regulation, which lowered the level triggering protection for beryllium-exposed

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workers in the U.S. nuclear weapons complex from 2.0 $\mu g/m^3$ to 0.2 $\mu g/m^3$.

We share Dr Borak's conclusion that the current Occupational Safety and Health Administration (OSHA) occupational exposure standard (OEL) of 2.0 $\mu g/m^3$ is inadequate to protect workers from chronic beryllium disease (CBD). The scientific literature summarized by Dr Borak, particularly the cases among workers and community residents exposed to levels well below the current standard,[2,3] strongly suggests that there is no safe level of exposure to beryllium.

One clear policy implication of this literature is that the OSHA OEL needs to be dramatically strengthened and that beryllium exposure must be eliminated whenever possible to prevent CBD. Beryllium plays an important role in national security but given the metal's severe and well-established health effects, it is hard to justify using beryllium in golf clubs, bicycle frames, and other consumer products. Even if the workers manufacturing these products could be protected from all beryllium exposure, recent reports of CBD cases among metal recycling workers[4] underscore the need to remove beryllium from commerce.

The primary limitation of Dr Borak's editorial is his failure to recognize that OELs are shaped not only by science, but also by the actions of individuals and corporations, who wield political and economic power. In our view, one of the primary reasons the inadequate OEL for beryllium has remained unchanged is that Brush Wellman, the sole North American beryllium producer, has relentlessly opposed more protective standards for exposed workers.

In 1975, OSHA proposed a comprehensive standard to protect beryllium-exposed workers, including a plan to lower its workplace exposure limit to 1 $\mu g/m^3$, on the basis of beryllium's carcinogenicity.[5] OSHA's effort was foiled, however, by a collaboration of the DOE, the Department of Defense, and the beryllium industry.[6] (Secretary of Energy, Bill Richardson, acknowledged the industry–government intervention, explaining "Priority one was production of our nuclear weapons . . . [the] last priority was the safety and health of the workers that build these weapons."[7])

By the late 1980s, the existence of CBD cases among workers exposed to beryllium at levels below the existing standard led Dr Merril Eisenbud, the author of the Atomic Energy Commission's original (1949) standard, to end his support of the 2 $\mu g/m^3$ OEL.[8] This evidence also prompted the DOE to begin, in 1991, the administrative process of lowering the OEL applied in nuclear weapons facilities. Brush Wellman opposed the change, contending that DOE had no evidence "that the existing standard is unsafe or that the new proposed standard affords any greater degree or [sic] safety."[9]

Despite the compelling and growing evidence, Brush Wellman defended the 2 $\mu g/m^3$ OEL with a tautologic argument, essentially: "We will examine the work history of all workers with CBD; even if we do not find evidence they were exposed to levels above the standard, we will assume they have been, since CBD is only associated with excessive exposure levels." This can be seen in Brush's 1991 talking points, which advised its executives to defend the 2 $\mu g/m^3$ as follows: "(1) Experience over several decades has, in our view, demonstrated that levels of airborne beryllium within the OSHA threshold limit value afford a safe workplace. (2) In most cases involving our employees, we can point to circumstances of exposure (usually accidental), higher than the standard allows. In some cases, we have been unable (for lack of clear history) to identify such circumstances. However, in these cases we also cannot say that there was *not* excessive exposure"[10] (emphasis in original).

Around the same time, Brush Wellman also opposed the American Conference of Governmental Industrial Hygienists's (ACGIH's) efforts to lower the beryllium threshold limit value (TLV), writing "We feel the evidence for retaining the presently adopted TLV is compelling" [and] ". . . there is still no evidence of any diagnosed cases of CBD where the exposure level can be reasonable demonstrated to have been at or below the 2 μg level."[11]

Dr Borak states that in 1996 Brush Wellman (in a notice for customers) "expressed uncertainty that the OSHA PEL was adequately protective."[1] In its communications with regulatory officials, however, the manufacturer retained its traditional opposition. For example, in a meeting on the proposed DOE standard, an executive asserted that the company "is unaware of any scientific evidence that the standard is not protective. However, we do recognize that there have been sporadic reports of disease at less than 2 $\mu g/m^3$. Brush Wellman has studied each of these reports and found them to be scientifically unsound."[12]

By 1999, the ever increasing number of CBD cases rendered the claim that the old standard was safe less and less plausible. Yet, this did not compel Brush to endorse a more protective OEL. Rather, the manufacturer asked DOE to delay issuing a new standard, claiming that "important research is underway which may provide a scientific basis for a revision to the occupational standard for beryllium" and pointing to studies on particle size, particle number, and particle surface area.[13]

In retrospect, it is clear that Brush's interpretation of the evidence supporting the adequacy of the OEL was incorrect; independent experts recognized this inadequacy more than 15 years ago. The beryllium industry had a strong financial incentive to challenge the mounting evidence and to oppose regulatory action that would result in a lower exposure limit. It appears this incentive shaped the interpretation given to scientific evidence by scientists employed by the beryllium industry. A policy lesson here is that regulatory agencies should discount the interpretation of data by parties with financial conflict of interest.

Although the past cannot be changed, much can be done to better protect cur-

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rent and future workers from beryllium exposure.

Now that Dr Borak, with the support of Brush Wellman, has acknowledged the current OSHA standard is inadequate, we sincerely hope that Brush Wellman will devote its resources and political muscle to urge OSHA to strengthen its OEL so that chronic beryllium disease becomes a disease of the past.

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Author's Response

To the Editor: I appreciate this opportunity to comment on the letter submitted by Dr Michaels and Ms Monforton, which was a response to my recent editorial on the occupational exposure limit for beryllium.[1] They do not disagree with my discussion of the science, but fault me for not discussing political and economic issues, particularly with respect to the actions and interests of Brush Wellman. The implication of their letter is that Brush Wellman obstructed lowering the beryllium occupational exposure limit and that their actions were inconsistent with the science.

I do not speak for Brush Wellman. My first contact with Brush Wellman was in 2002; I have no personal knowledge regarding the motivation or behavior of Brush Wellman and its executives during earlier times. When I proposed the literature review that was the basis for this editorial, it was accepted and supported without restrictions, limitations, or editorial control.

To the best of my knowledge, the unrestricted support that I received was not atypical for Brush Wellman. Based on publicly available records, similarly unrestricted support was provided over the past 15 years to researchers at National Jewish Medical and Research Center (National Jewish) and the National Institute of Occupational Safety and Health (NIOSH), which has led to extensive, detailed, and independent evaluations of numerous Brush Wellman facilities and many of its employees.* These do not seem to be the actions of a corporation bent on obstructing scientific progress or concealing its findings.

Perhaps the issues are just a matter of perspective. For example, consider the findings of a recent General Accounting Office (GAO) report on

*Service agreements between Brush Wellman and National Jewish and a Memorandum of Understanding (MOU) between Brush Wellman and NIOSH have been entered into evidence in civil litigation and are available from the author. With respect to its two major facilities in Tucson, Arizona, and Elmore, Ohio, the 1992 and 1994 agreements, respectively, funded National Jewish to develop and administer worker questionnaires, to review all personnel rosters, medical surveillance data, and industrial hygiene data, to estimate historical exposures, and to integrate that information with individual work and job histories. In addition, Brush Wellman paid for BeLPT and other clinical evaluations on a fee-for-service basis. The only restriction imposed by Brush Wellman was that individual confidentiality be protected: "National Jewish may . . . use Brush Wellman data in statistical compilations and researchers shall likewise be able to use the data and the statistical correlations . . . . Brush Wellman does not reserve in any way the right to control, direct or censor conclusions or report dissemination." In its MOU with NIOSH, which was reviewed by the NIOSH Board of Scientific Counselors and judged to be "a model for similar work with industry groups,"[7] Brush Wellman affirmed: "In the event of disagreement regarding interpretation or analyses, each party retains the right to disseminate their work."

†The GAO report provides an interesting perspective because in a letter officially appended to the report, Dr Michaels (then Assistant Secretary of the Department of Energy) wrote: "We found the report to be accurate."

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the response of Federal agencies to "beryllium uses and risks."[2]† That report specifically addressed the proposed 1975 Occupational Safety and Health Administration (OSHA) standard described by Dr Michaels and Ms Monforton as having been "killed . . . by a collaboration of the DOE, the DOD and the beryllium industry." GAO noted that in 1977, OSHA received "about 150 written comments" and heard testimony from 46 individuals "representing business, government, labor, and academia"; in 1978, scientific panels were convened by NIOSH, the Centers for Disease Control and Prevention, and Health, Education, and Welfare to review the scientific evidence; also that year, the Secretaries of Defense and Energy expressed concerns about national security implications and the scientific basis of the proposal; in 1979, further meetings were held among the Department of Defense (DOD), Department of Energy (DOE), and OSHA; and finally, in the early 1980s, OSHA discontinued work on this standard "because of other regulatory priorities." Thus, whether it was actively "killed" or left to die of neglect may be a matter of perspective. OSHA did not officially revisit the beryllium issue until 1998 and a new permissible exposure limit (PEL) still has not been formally proposed.

As for DOE, it expanded its beryllium exposure monitoring and medical surveillance programs during the 1980s to 1990s and in 1999 reduced beryllium exposure among its workers by adoption of an action level lower than the OSHA PEL. On the other hand, DOE did not propose a lower PEL because it found the scientific evidence to be insufficient: "DOE reviewed the scientific evidence suggesting that the current OSHA 8-hour PEL does not sufficiently protect worker health . . . it is difficult to determine from this scientific evidence the exposure levels necessary to eliminate the risk of contracting CBD."[3] That statement, which still correctly describes the scientific evidence, does not differ significantly from conclusions of my editorial.

There are a number of likely reasons that the scientific evidence remains uncertain. Chronic beryllium disease (CBD) is a relatively rare disorder that develops with variable, but sometimes long latency, and is most often found in asymptomatic individuals. Also, historical exposure data (from DOE and others) have limited informational value because exposures were often above the OSHA PEL.[2] In addition, beryllium sensitization and CBD have only recently been studied prospectively in individuals without previous occupational exposures (eg, new hires) and there have been few longitudinal worker studies. Such factors combine to challenge studies of disease onset and frustrate efforts to identify exposure levels necessary to trigger CBD.

Another reason is the relatively inconsistent ways that beryllium sensitization and CBD have been studied. In a review of 19 published studies of beryllium workers, we found 10 different and often incompatible sets of diagnostic criteria for CBD.[4] Likewise, criteria for a positive BeLPT have varied among the five laboratories that perform the test and over time in most of those laboratories. Such inconsistencies make difficult the pooling of data (eg, meta-analysis) that might otherwise address the difficulties posed by the small numbers of reported cases.

In short, there are real deficits of scientific knowledge. Whether it is accordingly appropriate to strictly invoke the Precautionary Principle, as seemingly proposed by Dr Michaels and Ms Monforton, is a philosophical issue of much debate but little certainty.[5,6] Their view that there is "no safe level" of beryllium exposure seems tenuous at best and their assertion that my literature summary implied that conclusion is wrong. In that specific context, they are also wrong to suggest that I had read or relied on their references 2 and 3, both published and/or presented after my manuscript was submitted and accepted by the *Journal*.

Finally, with respect to the need to "discount the interpretation of data by parties with financial conflict of interest," I note in the interest of full disclosure that Dr Michaels has served as a paid plaintiffs' expert in litigation against Brush Wellman.

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Arsenic Exposure and Diabetes Mellitus Risk

To the Editor: Chiu et al[1] have presented the annual (and 3-year moving average) diabetes mellitus (DM) standardized mortality ratios (SMRs) for 1971 to 2000 for males and females from the Blackfoot disease (BFD) endemic area of southwest Taiwan. They have examined the temporal pattern of the data following the transfer by 1975 of the

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population from an artesian well water supply with a median arsenic level of 780 μg/L (ppb) to a reservoir-sourced water system with an arsenic concentration of less than 10 μg/L. The authors concluded from their ecologic analysis that the DM mortality rate showed a significant and causal decline for females but not for males. Our reanalysis of their data suggests that this conclusion is based on an artifactual data analysis and a too-facile interpretation.

In Figure 1, we present a graphing of their 3-year moving average SMRs with data for both males and females on the same graph unlike their presentation of separate graphs. Our examination of this figure suggests that the DM SMR pattern for males and females differ considerably during the 1970s but not during the 1980s and 1990s. In Figure 2, we have included linear regressions (or time-series regressions) for the 1980–2000 data points and find that the DM SMRs for the males and for the females each show a similar significant negative slope of approximately 3% per year. Thus, we dispute the conclusion that there is a gender difference in temporal pattern (at least during the 1980s and the 1990s).

During the 1970s, there is a similar pattern also for males and females; however, the pattern for the females seems to have come 3 years earlier. During the 1970s, both males and females showed a sharp drop in the DM SMR down to near 50 with a sharp rise to approximately 150. The relationship of this pattern to the change in water supply is uncertain, because the change was only complete in 1975.

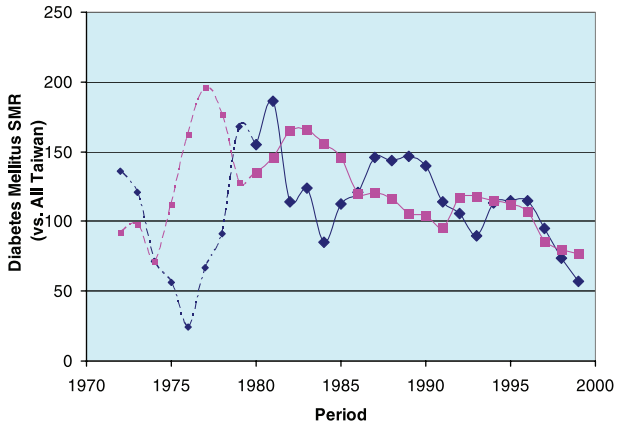

Fig. 1. Time trends for Diabetes Mellitus SMRs (3-year moving averages) for Males (Blue Diamonds) and Females (Red Squares) in Blackfoot Disease area (from Chiu et al., 2006).

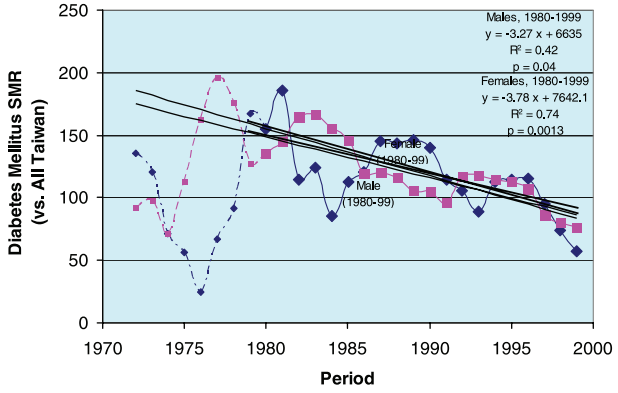

Fig. 2. Linear regression analyses for 1980–1999 data applied to Time trends for Diabetes Mellitus SMRs (3-year moving averages) for Males (Blue Diamonds) and Females (Red Squares) in Blackfoot Disease area (from Chiu et al., 2006).

Certification of DM as the underlying cause of death is quite susceptible to selection and reporting biases, and analyses based on small numbers should be cautious. Over the 30-year observation period, the number of DM deaths expected annually has increased 10-fold, which suggests marked changes in either demography or diagnostic choice. The DM mortality data, themselves, during the 1970s are sparse with approximately two DM deaths per year for males and fewer than six per year for females. In contrast, during the 1990s, there was an average of 17 male and 26 female DM deaths per year, providing much greater stability to the analysis.

Even if the decline in DM mortality was causally associated with the change in water supply, it is unclear that the causal agent is the arsenic in the water. Historically, the most prominent health characteristic of the BFD endemic area is BFD, a condition closely associated with high arsenic level artesian well water use[2] for which no new cases appeared after the cessation of use of the artesian wells.[3] However, BFD never appeared in areas in northeast Taiwan that had similar arsenic levels to those in the BFD area.[4] A number of papers have cited fluorescent compounds (humic substances) in the artesian well water as a potential causative agent for BFD,[5,6] and township stratification of the BFD area cancer mortality data revealed the suggestion of a separate nonarsenic carcinogenic risk factor related to the drinking water.[7] Thus, the decline in diabetes mortality may be the consequence of withdrawal of a water-borne factor, but whether arsenic is that factor is not clear.

Whether arsenic exposure and DM mortality are associated is not yet clear; the literature cited by Chiu et al[1] is incomplete. They have cited a possible association at a Swedish smelter, but not the negative findings from either a U.S. copper smelter (observed/expected = 54/65)[8] or a U.K. tin smelter (observed/expected = 0/3.1).[9] Pooled together, they yield an SMR =

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0.79 (95% confidence interval = 0.60–1.03). Clearly, this is not indicative of an increased DM mortality risk with at least arsenic inhalation exposure. Both of these cohorts had sufficient arsenic exposure to demonstrate a significant increased mortality from lung cancer. Further work is necessary to delineate the causal factors for DM in the BFD area.[10]

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Authors' Response

To the Editor: We thank Lamm et al[1] for responding to our article.[2] They recalculated our data only for the period 1980–2000 (excluding 1971–1979) and this led to an estimate of similar significant negative slope for diabetes mellitus (DM) standardized mortality ratios (SMRs) for males and females. They dispute our conclusion that there is a gender difference in temporal pattern (only during the 1980s and 1990s). Because inorganic arsenic has been reported to be associated with an increased mortality from DM, it is logical to expect that a reduction of arsenic exposure through improvement in the water supply system would lead to a decrease in mortality rates from DM in both males and females living in the Blackfoot disease (BFD) endemic areas. We feel that their argument, however, provides further evidence that the association between arsenic exposure and DM was causal.

Their point of criticism regarding the use of DM listed on the death certificate as the underlying cause of death has already been addressed in the discussion section of our article.

We agree with Lamm et al that small numbers of DM deaths will provide much less stability to the analysis, particularly during the 1970s. To minimize this statistical variability, the 3-year moving averages of the SMR were calculated for this study.

Lamm et al argue that fluorescent compounds (humic substances) in the artesian well water are a potential causative agent for BFD; thus, the decline in diabetes mortality may be the consequence of withdrawal of a water-borne factor, but whether arsenic is that factor is not clear. In our opinion, in the BFD endemic areas, the main exposure to inorganic arsenic is through ingestion of artesian well water containing high concentrations of arsenic. Physical and chemical characteristics of drinking water have been intensively studied in both BFD endemic and nonendemic areas.[3] In artesian well water, the only chemical component exceeding the daily maximum allowable limit was arsenic. Although fluorescent compounds, known as humic substances, have been suggested to exert an initiator role in the development of BFD,[4,5] there has been no epidemiologic evidence to show a correlation between exposure to humic substances and development of DM. The association between humic substances and BFD might be due to the confounding effect of an association between BFD and arsenic exposure.[6] Thus, the reduction in DM mortality in the study area may result from the withdrawal of arsenic exposure through improvements in the water supply system as reflected by a change in water source.

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