Perspectives | Correspondence

Concepts of Nanoparticle Dose Metric and Response Metric

Wittmaack (2007) did not agree with our suggestion (Oberdörster et al. 2005) that particle surface area is a more appropriate dose metric than particle mass or particle number when evaluating dose–response relationships of nanoparticle-induced pulmonary inflammation. According to his understanding of nanotoxicology and based on his calculations, he found particle number to work best as a dose metric. Throughout our review we pointed out that the surface area concept should be considered in the context of nanoparticle surface properties such as chemistry, charge, coating, crystallinity, porosity, and reactivity. For example, nano-titanium dioxide (TiO_2) or nano-copper particles, very distinct from one another, will predictively create separate well-fitting surface area dose–response relationships. Yes, particle number is of importance as well, as we indicated in our review, but not as a direct dose metric.

We would like to address some of the issues Wittmaack (2007) raised in his article. First, Wittmaack suggested that when expressing a pulmonary inflammatory response, a response metric is better done using the ratio of lavaged neutrophils (PMN; polymorphonuclear leukocytes) to macrophages instead of using the fraction of PMNs. Because the purpose of our review (Oberdörster et al. 2005) was not to describe these responses in mathematical terms (whether threshold, linear, or nonlinear) but rather to illustrate that dose–response relationships on a mass basis—but not on a surface area basis—are very different, the choice of the response metric is irrelevant. To demonstrate this, we present our data again (Figure 1), expressed as absolute numbers of elicited PMNs and as PMN/macrophage ratios as a function of administered mass (Figure 1A,B), number (Figure 1C,D), or surface area (Figure 1E,F) of fine and ultrafine (nanosized) TiO_2. The dose–response relationships based on mass and surface area are essentially the same as those shown in our review (Oberdörster et al. 2005) using the percentage of elicited neutrophils.

Second, regarding the issue of particle number being the best dose metric, the particle number dose–response relationships (Figure 1B) are several orders of magnitude apart for fine and ultrafine TiO_2, whereas the surface area plot (Figure 1C) shows a good fit for the combined particle sizes. The reviewers of Wittmaack's article (2007) apparently overlooked this flaw in his argument.

Finally, Wittmaack (2007) calculated that the surface area for ultrafine TiO_2 should be 77 m^2/g and not 50 m^2/g, as we reported (Oberdörster et al. 2005). He derived his value on the basis of the specific density of TiO_2 (anatase) and a spherical primary particle size of 20 nm. BET surface area for this TiO_2 (Degussa P25) has been measured independently by a number of investigators, including our group (Jwo et al. 2005; Long et al. 2006; Wahl et al. 2005), and ranges between 48 and 55 m^2/g. There is no reason to mathematically manipulate this number to a value that is completely at odds with actual measurements. In contrast to the well-established surface area, the average primary particle size of TiO_2 has not been firmly established, with values of 20–30 nm. Indeed, a size of 30 nm (calculated surface area, 51.2 m^2/g) conforms best to the measured BET surface. Thus, we added particle number dose–response data for 30 nm TiO_2 to Figure 1C and 1D; the order of magnitude difference of the dose response between fine and ultrafine particles is obvious, regardless of whether the ultrafines are considered to be 20 or 30 nm in size.

We have concluded that of the three dose metrics discussed, particle number is the worst to describe nanoparticle-induced pulmonary inflammatory effects.

The authors declare they have no competing financial interests.

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Inflammatory Response to TiO_2 and Carbonaceous Particles Scales Best with BET Surface Area

In an attempt to identify the proper dose metric for particle toxicity, Wittmaack (2007) reanalyzed our dose–response data (Stoeger et al. 2006) and that of Oberdörster et al. (2005) on acute lung inflammation in rodents after instillation of various particle types. Out of particle BET surface area (S_{BET}), particle number, joint length, and "geometric" surface area, Wittmaack concluded that particle number tends "to work best" as dose metric. We disagree with his conclusion.

First, we wonder why Wittmaack (2007) used our data but ignored the data of Oberdörster et al. (2005) for the identification of the best dose metric. Figure 1 shows our dose–response data (in mice) for
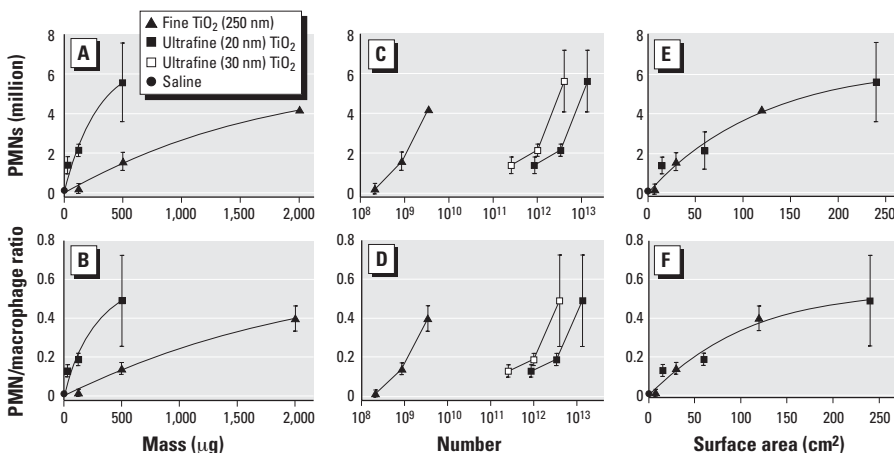

Figure 1. Inflammatory cell response in lung lavage 24 hr after intratracheal instillation of fine (~ 250 nm) and ultrafine (20–30 nm) TiO_2 expressed by different dose metrics [particle mass (*A*,*B*), number (*C*,*D*), and surface area (*E*,*F*)] and different response metrics [number of PMNs (*A*,*C*,*E*) and PMN/macrophage ratio (*B*,*D*,*F*)].

six different types of ultrafine carbonaceous particles (10–50 nm) and the data of Oberdörster et al. (2005) for fine (~ 250 nm) and ultrafine (~ 20 nm) TiO_2 particles; we present the data for rats, which was reanalyzed by Wittmaack, and also the mouse data from Oberdörster et al. (2005). In Figure 1 the inflammatory response after 24 hr is expressed as the ratio of the polymorphonuclear leukocytes (PMNs) to lavaged cells, and the instilled dose is normalized to lung weight, because this facilitates interspecies comparison (Oberdörster et al. 2005). As suggested by Wittmaack (2007), we limit our discussion to the linear response regime [analogous to his Figure 3 (Wittmaack 2007)]. For this data set, the linear correlation coefficient R^2 is 0.46, 0.51, 0.67, and 0.72 for particle number, joint length, "geometric" surface area, and S_{BET}, respectively. Particularly, the response to the fine particles, as represented by the red fit line (almost identical to the y-axis in Figure 1A), is not adequately described by particle number (Figure 1A), whereas S_{BET} works well for all particle sizes (Figure 1B). Although we do not suggest S_{BET} as a "universal" dose metric (chemistry, charge, etc., are also relevant), we conclude that for the dose metric examined here, S_{BET} is the most relevant dose parameter. Wittmaack's preference for particle number appears to be the result of an unsubstantiated restriction of his analysis to our data, which is dominated by particles in
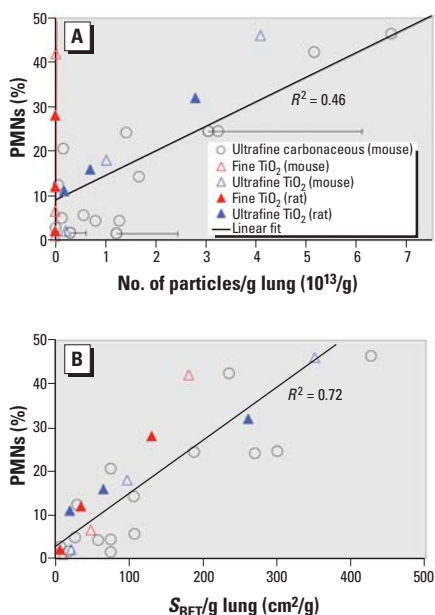

a relatively narrow size regime between about 10 and 25 nm.

Second, all investigated dose parameters (except S_{BET}) depend on accurate determination of the mean particle diameter, $<d>$, requiring tedious and potentially uncertain single particle analysis. Wittmaack (2007) acknowledged potentially large errors in $<d>$ for particles below about 20 nm [i.e., for four out of our six (carbonaceous) particle types]. Being aware of these limitations, we intentionally reported only a range of observed particle diameters (not $<d>$) in our article (Stoeger et al. 2006). Unfortunately, Wittmaack did not discuss his conclusions in light of these methodologic limitations. Especially for the smallest particle type (here spark-generated carbon particles with $<d>$ = 9.8 nm), preferential particle selection is likely to result in an overestimation of $<d>$. Assuming a 25% sizing error, this yields a systematic error of + 100% in particle number (~ $<d>^{-3}$), which shifts these data points far away from the linear fit line (see error bars in Figure 1A). In contrast, S_{BET} requires only a single measurement on an aliquot of the administered particles; that is, it is not adversely affected by problems associated with single particle analysis, and it adequately accounts for potentially important particle characteristics such as particle morphology and surface porosity.

In summary, we do not agree with the dose–response interpretation of our data by Wittmaack (2007). We conclude that S_{BET} (and not particle number) is the best dose parameter, accounting for 72% (R^2 = 0.72) of the observed inflammatory response for both data sets spanning a size range of 10–250 nm.

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Figure 1. Acute pulmonary inflammatory response (PMNs) to TiO_2 [Oberdörster et al. 2005; Figure 4 and Figure S-2 (Supplemental Material available online at http://ehp.niehs.nih.gov/members/2005/7339/supplemental.pdf)] and carbonaceous particles (Stoeger et al. 2006; Figure 1) in rats and mice, with particle number (A) and S_{BET} (B) as the dose metric.

Dose and Response Metrics in Nanotoxicology: Wittmaack Responds to Oberdoerster et al. and Stoeger et al.

In their letters, Oberdörster et al. and Stoeger et al. present some comments on a few out of many issues that I addressed in my reanalysis of literature data on lung inflammatory response to nanoparticle exposure (Wittmaack 2007). I appreciate the opportunity to strengthen and expand my arguments.

I argue that results of nanoparticle toxicology studies should not be interpreted on the basis of the reasoning that the number of surface atoms, relative to all atoms in a (spherical) particle, increases as the inverse of the diameter, D (Oberdörster et al. 2005). If the toxicity of an insoluble particle scales with the number of surface atoms, it is the surface area (A) that counts, not its ratio to the mass (M). Figure 1 shows the size dependence of the specific surface area ($S = A/M = 6/\rho D$) for TiO_2 particles [mass density, ρ(anatase) = 3.9 g/cm^3]. Also presented is an example for the cumulative surface area (ΣA_{ae}) calculated from the mean number concentration of an ambient aerosol (Wittmaack 2002), including extrapolated data for $D < 10$ nm. ΣA_{ae} decreases rapidly with decreasing D, notably for $D < 100$ nm. In contrast, $S_{ae} = \Sigma A_{ae}/\Sigma M_{ae} = \Sigma A_{ae}/\rho \Sigma V_{ae}$ (ρ = 1.5 g/cm^3) increases as $1/D$, for $D < 200$ nm, where V is the particle volume. If toxicity is assessed by reference to S_{ae} rather than to A_{ae}, the danger of exposure to nanoparticles (e.g., for D = 30 nm), compared to fine particles (D = 1 μm), is overestimated by a factor of 1,130. By taking the ratio A/M, we compare apples (the surface area of insoluble particles) and oranges (the mass of soluble particles).
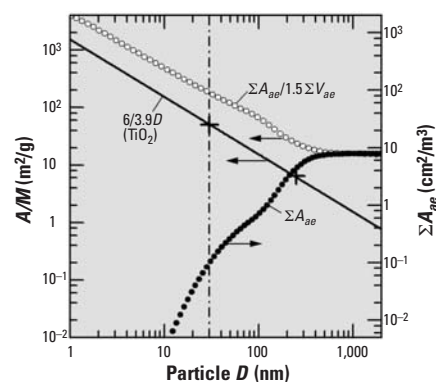

Figure 1. Particle-size dependence of the A/M and the ΣA_{ae}. The straight line relates to TiO_2 particles, the open and solid circles indicate ambient aerosol particles, and the crosses indicate two BET data. According to Oberdoerster et al.'s letter, the so-called 20-nm TiO_2 particles may well have been 30 nm in size.

This type of reasoning in terms of S_{ae} (Oberdörster et al. 2005) has been used often (Kreyling et al. 2006; Nel et al. 2006); Gwinn and Vallyathan (2006) even characterized ultrafine particles (UFPs; i.e., particles with $D \leq 100$ nm) as "UFPs with larger surface area."

In their Figure 1, Oberdörster et al. (2005) reproduced some of their own data in two ways: as the number (n_{PMN}) of lavaged polymorphonuclear leukocytes (PMNs) and as the ratio ($r_{P,m}$) of n_{PMN} to the number (n_{ma}) of macrophages ($r_{P,m}$ $= n_{PMN}/n_{ma}$). To demonstrate that the particle number is not an appropriate dose metric in the special case of TiO$_2$, the data could have been presented in a single graph. I found that particle number is a suitable dose metric for differently prepared carbon nanoparticles (Wittmaack 2007). In their letter, Oberdörster et al. use the comparison between n_{PMN} and $r_{P,m}$ to argue that "the choice of the response metric is irrelevant." Data analysis shows that in their study n_{ma} was essentially constant $(10.9 \pm 0.5) \times 10^6$. Hence, if n_{PMN} is divided by $n_{ma} \cong$ constant, on appropriate scales, the ratio $r_{P,m}$ looks essentially the same as the n_{PMN}. Clearly, this result is not proof of the cited assertion.

To explore this issue further, Figure 2 shows a direct comparison of $r_{P,m}$ with the corresponding fractions $f_{P,m} = n_{PMN}/(n_{PMN} + n_{ma}) = r_{P,m}/(1+r_{P,m})$ for the 250-nm TiO$_2$ data, according to Oberdörster et al.'s letter. The solid line in Figure 2, derived by linear regression analysis of the $r_{P,m}$ data, agrees well with previous results (Wittmaack 2007). Further evaluation provided the clue to the issue in question. By converting the $r_{P,m}$ regression data to fractions $f_{P,m}$, I obtained the curve (dashed line), which is clearly nonlinear. Hence, using the $f_{P,m}$ approach, Oberdörster (2000) converted an existing linear dose–response relationship
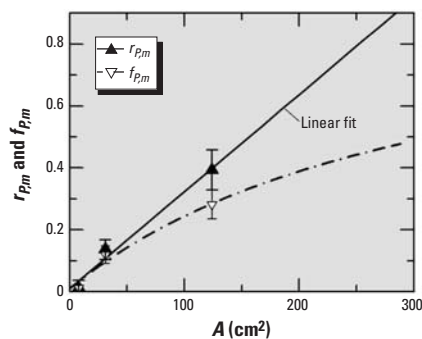
(for n_{PMN} or $r_{P,m}$) artificially to a dependence that feigns the onset of saturation effects. Therefore, the choice of the response metric is not irrelevant.

Preparing Figure 1 of their letter, Stoeger et al. changed from the right (n_{PMN}) (Stoeger et al. 2006) to the wrong ($f_{P,m}$) response metric. For mice exposed to different types of carbon particles except for those with high carbon content (SootH), I derived from their Figure 1B rather high mean lung masses of 0.287 ± 0.047 g, and even higher values (0.469 ± 0.028 g) for the SootH-exposed animals. The ratio of these two masses (0.61) is the same as that of the ratio S_{BET}(SootH)/S_{BET} (SootL). This means that their data were erroneously permuted. Also, the $f_{P,m}$ carbon particle data are poorly correlated with the original n_{PMN} data (Stoeger et al. 2006) because the numbers of "lavaged cells," presumably macrophages, derived from the n_{PMN} and $f_{P,m}$ data, differ vastly (i.e., between about 2×10^5 and 3×10^6. Hence, either the $f_{P,m}$ data in the letter of Stoeger et al. were miscalculated, or n_{ma} exhibited a biologically unreasonable spread. Furthermore, they include 15 response data for carbon in their letter, but the linear dose–response region contains only 13 (Wittmaack 2007).

In their effort to show that the surface area constitutes a proper all-particle dose metric, Stoeger et al. (2006) discredited their own transmission electron microscopy analysis. Their argument is irrelevant because the spark-generated particles contributed only one data point to a total of 13. Finally, Stoeger et al. do not accept one of the most important points of my article: Carbon particles of different origin exhibit large differences in surface toxicity and, therefore, they cannot be used to identify the best dose metric. Moreover, combining TiO$_2$ and carbon data in one graph is not an appropriate comparison.

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Questioning Sources and Cardiovascular Effects of Nickel

Lippmann et al. (2006) attempted to identify subtle deleterious effects in fine airborne particulate matter (FPM), which is laudable. Nevertheless, the authors' claim (Lippmann et al. 2006) that on 14 of 103 days studied in the fall of 2004, concentrated air pollutants (CAPs) at Tuxedo, New York [near New York City (NYC)], contained "greatly elevated concentrations of nickel attributable to the Ni smelter at Sudbury, Ontario" is unsubstantiated. The Ni concentrations to which they referred (174 ng/m^3) on these 14 days were concentrated 10-fold from ambient air. In other words, the Ni in ambient air at Tuxedo was actually only 17.4 ng/m^3, the same as NYC (19 ng/m^3).

Lippmann et al. (2006) assigned the "elevated" Ni to Inco's 381 m stack in Sudbury based on back trajectory analyses. The authors failed to account for vertical components of air parcel movement; also, by singling out one specific trajectory from the "NW wind" days, they implied much more accuracy to the back trajectories than is justified. Because meteorological data are available at 3-hr intervals, three back trajectories could be developed for each daily exposure period. Such back trajectories using the internet-based HYSPLIT model (National Oceanic and Atmospheric Administration 2006) indicate that for the 14 NW wind days, elevated Ni in CAPs on those days was more likely due to sources other than the Sudbury stack > 800 km distant. Furthermore, Inco's stack emissions are characteristic and distinct from the CAPs composition reported by Lippmann et al. (2006). Concentrations of aluminum, chromium, and iron are all 100-fold less than the concentration of Ni in Inco's emissions, whereas in CAPs on the NW wind days, the ratios of Cr:Ni and Fe:Ni, as well as those of Al:Ni and V:Ni, are similar to those of New Jersey air (Reinfelder et al. 2004). The Ni in ambient air at Tuxedo, even on the 14 NW wind days, could be easily assigned to sources surrounding NYC. Given that Tuxedo is near NYC, it should be no surprise that local sources could be large contributors to Ni in

Figure 2. Response of rats to the instillation of 250 nm TiO$_2$ particles shown as the $r_{P,m}$ as reported by Oberdörster et al. in their letter, and the derived $f_{P,m}$ corresponds to the linear fit through the $r_{P,m}$ data.

ambient FPM in Tuxedo. Although the atmospheric Ni emissions from the Sudbury stack can be transboundary and have been significant historically, the incremental contribution of Ni from Sudbury to ambient air at Tuxedo in 2004 would have been dwarfed relative to local sources. Significant reductions in emissions have been made at Inco's Sudbury operations, and air emissions from the Inco stack will diminish further as new pollution control measures are implemented.

Lippmann et al. (2006) presented two lines of evidence that Ni is the major cause of cardiovascular effects of FPM. First, exposures of ApoE$^{-/-}$ mice to CAPs led them to conclude that unusually high heart rate (HR) occurred in response to elevated Ni on the NW wind days. Although the largest sustained apparent difference in HR occurred through most of December, only three NW wind days occurred in that month. Other changes in HR and heart rate variability (HRV) are either due to changes in control animals or occurred when there were no elevated Ni concentrations [see Figure 4 of Lippmann et al. (2006)]. There appears to be an error in the key of Lippmann et al.'s Figure 4 compared with the original manuscript published online: the solid lines now denote filtered air (control) instead of CAPs, and the dashed line indicates CAPs instead of control data. Given that the authors referred to the elevated HR in exposed mice, the key in the print version must be incorrect.

Considering that 2-year inhalation exposures of rodents to nickel sulfate at levels 600 times higher than those used by Lippmann et al. (2006) were without effect on mortality, the relevance of the "subtle" changes in HR and HRV requires further thought. Second, the authors "wondered if Ni may have been responsible for the notably high daily mortality" in NYC. Although it is true that NYC has a cardiovascular and respiratory (CVR) mortality coefficient that is above the national average, 34 of the 90 National Mortality and Morbidity Air Pollution Study (NMMAPS) cities have CVR mortality coefficients greater than those of NYC. Furthermore, there is no statistical relationship between NMMAPS CVR mortality rates and Ni emission rates (U.S. Environmental Protection Agency 2002).

The conclusions of Lippmann et al. (2006) contrast with the recent assessments of the Agency for Toxic Substances and Disease Registry (ATSDR 2005) and the European Union (European Chemicals Bureau 2005) that did not identify human cardiovascular risk factors for Ni. Historical monitoring within the Ni industry identified the link between high occupational exposure of certain Ni species and respiratory cancer, but no such cardiovascular risk factors have been identified after decades of occupational health monitoring.

Further research to evaluate the impacts of the constituents of FPM on cardiovascular health is justified and should continue. Nevertheless, researchers with appropriate expertise work should cooperatively in studies such as these. In this instance, Lippmann et al. (2006) would have benefitted greatly from the inclusion of atmospheric scientists on their research team.

The author is employed by CVRD Inco Limited, the subject of the article by Lippmann et al.

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Cardiovascular Effects of Nickel: Lippmann et al. Respond

It is readily understandable that Dutton of the International Nickel Company (INCO) would like to separate the nickel emissions from the 381-m INCO smelter stack from the highly statistically significant Ni-associated effects on heart rate and heart rate variability that we observed on 14 of 103 consecutive weekdays of exposure in our laboratory (located within the Sterling Forest State Park) in a mouse model of atherosclerosis (Lippmann et al. 2006). Indeed, it is possible that some closer source of Ni could have been responsible for the effects. However, as we noted in our article, the back trajectories on the 14 days with unusually elevated Ni concentrations did not pass over any known industrial sources or large urban areas, but did pass over or near the distant point source of Ni at the INCO smelter in Sudbury, Ontario, Canada. It is also noteworthy that the

14 back trajectories, illustrated in Figure 2 of our article (Lippmann et al. 2006), approached Sterling Forest from a variety of directions, ranging from the NW to the NNE, making it highly unlikely that that their metals compositions were influenced by a significant source within a 100-mi radius. Furthermore, both the directions of the incoming winds and the combination of unusually high Ni and lower than normal vanadium on those 14 days, as compared with the other 89 days of observation, seemed to preclude the major sources of Ni being the Port of New York, the New York City metropolitan area, or other coastal regions where residual oil is used to generate heat and electrical power. It is well known that residual oil combustion effluents are high in both Ni and V.

We commend Dutton on identifying a mislabeled key in Figure 4 of our article (Lippmann et al. 2006) that occurred during the preparation of the print version. As he noted, the original manuscript published online was correctly labeled. (See the Erratum on p. A294.)

Dutton provided no supporting reference for his comment that "2-year inhalation exposures of rodents to nickel sulfate at levels 600 times higher than those used by Lippmann et al. (2006) were without effect on mortality …." Based on the 600× concentration difference, we assume he was referring to a National Toxicology Program (NTP) report (NTP 1996). It should be noted that healthy B6C3F$_1$ mice were exposed in this study, and that healthy B6 mice had much greater survival times than seven other inbred mice strains when exposed to nickel sulfate by Prows et al. (2003).

Dutton also states that "there is no statistical relationship between NMMAPS [National Mortality and Morbidity Air Pollution Study] CVR [cardiovascular risk] mortality rates and Ni emission rates." Again, no reference was cited. Even if his statement was supported by a negative study, it relates to emissions and not concentrations. In our article (Lippmann et al. 2006), we showed that the annual average PM$_{10}$ (particulate matter < 10 μm in aerodynamic diameter) NMMAPS mortality coefficients for 60 NMMAPS cities were significantly associated with annual average ambient Ni and V concentrations in those same cities.

Finally, we take exception to Dutton's comment that implies that we lack sufficient expertise in atmospheric science. The only issue in our article that relates to atmospheric science is our use of HYSPLIT back trajectories, and we fail to see how we misused them.

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ERRATUM

In Figure 4 of Lippmann et al. [Environ Health Perspect 114:1662–1669 (2006)], the key was correct in the original manuscript published online but was incorrect in the final version. The dashed lines should indicate filtered air, and the solid lines should denote CAPS. The corrected figure appears below.
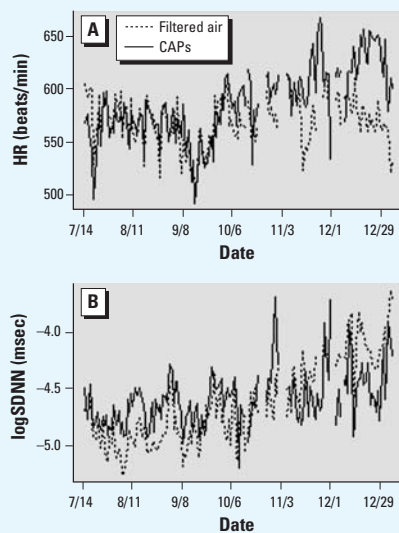

Figure 4. Daily group averaged HR (*A*) and HRV (logSDNN) (*B*) in mice exposed to CAPS or filtered air.

EHP regrets the error.