Perspectives | Correspondence

Prenatal Lead Exposure and Schizophrenia: A Plausible Neurobiologic Connection

In their article in the April issue of *EHP*, Opler et al. (2004) raise the intriguing possibility that prenatal exposure to the ubiquitous developmental neurotoxicant lead (Pb^{2+}) may be associated with schizophrenia, an adult psychiatric disease. Although the study has certain limitations that the authors discussed, it brings to light the possibility that prenatal Pb^{2+} exposure may be a risk factor for the expression of schizophrenia later in life. If an association between developmental Pb^{2+} exposure and schizophrenia exists, then identifying plausible neurobiologic substrate(s) would be useful in future studies. A common and potentially critical link between developmental Pb^{2+} exposure and schizophrenia is the disruption of glutamatergic synaptic activity—specifically, hypoactivity of the N-methyl-D-aspartate subtype (NMDAR) of glutamatergic receptors.

The "glutamatergic hypothesis" of schizophrenia originated from observations that administration of NMDAR noncompetitive antagonists exacerbates psychotic symptoms in schizophrenics and mimics schizophrenia in nonpsychotic subjects (Coyle et al. 2003; Konradi and Heckers 2003). Further, the administration of such antagonists in animals models certain aspects of the disease. There is experimental evidence that Pb^{2+} is a potent and selective inhibitor of the NMDAR, and the NMDAR plays an important role in neuronal development, synaptic plasticity, and learning and memory (Nihei and Guilarte 2001). Similar to rats exposed to Pb^{2+} during development, several lines of evidence have implicated NMDAR hypofunction in the pathophysiology of schizophrenia (Coyle et al. 2003; Konradi and Heckers 2003).

Developmental exposure to Pb^{2+}, in the same concentration range as implied in the work by Opler et al. (2004), alters gene and protein expression of NMDAR subunits in the rat brain (Nihei and Guilarte 2001). A consistent change in NMDAR subunits measured in young adult Pb^{2+}-exposed rats is a decrease in NR1 subunit gene expression (Nihei and Guilarte 2001). These findings resemble some of the changes in NMDAR subunit expression described in the brain of schizophrenic patients (Konradi and Heckers 2003; Tsai and Coyle 2002). Further, there is compelling evidence for a common molecular target, the glycine modulatory site of the NMDAR. A proposed mechanism by which Pb^{2+} inhibits NMDAR function is by binding to a divalent cation site associated with the glycine site and allosterically inhibiting glycine binding (Hashemzadeh-Gargari and Guilarte 1999). The significance of the antagonistic action of Pb^{2+} at the glycine site of the NMDAR is that studies have identified abnormalities associated with schizophrenia that interfere with the activation of the glycine modulatory site of the NMDAR (Coyle and Tsai 2004a). Further, the use of NMDAR glycine site agonists such as glycine, D-serine, or D-cycloserine in clinical trials has demonstrated some efficacy in ameliorating the negative symptoms and cognitive disabilities in schizophrenics (Coyle and Tsai 2004a, 2004b).

Although an environmental component to the etiology of schizophrenia has been proposed (Tsuang 2000), developmental Pb^{2+} exposure has not been considered a potential risk factor for schizophrenia until the article by Opler et al. (2004) was published. It is possible that in susceptible individuals, the presence of Pb^{2+} during the development of the central nervous system may be directly related or may contribute to the expression of schizophrenia later in life.

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Editor's note: In accordance with journal policy, Opler et al. were asked whether they wanted to respond to this letter, but they chose not to do so.

Activities and Organophosphate Exposures: Need for the Numbers

The article "Agricultural Task and Exposure to Organophosphate Pesticides among Farmworkers" (Coronado et al. 2004) seems to be founded on an erroneous premise and presents virtually no data to estimate levels of worker or child exposure. Useful data generated in conjunction with this research probably exists, but they were not published.

In the abstract, Coronado et al. (2004) state that

Little is known about pesticide exposure among farmworkers, and even less is known about the exposure associated with performing specific tasks.

The investigators open weakly by ignoring the substantial exposure (amount per person) data available related to work tasks of handlers [Pesticide Handlers Exposure Database; U.S. Environmental Protection Agency (EPA) 1995] and harvesters (U.S. EPA Transfer Coefficients) in the open literature and regulatory files of registrants and the U.S. EPA (U.S. EPA 1998).

We commend Coronado et al. (2004) for their use of a very large random sample of 213 farmworkers from 24 communities. The sensitive metabolite analyses of urine were reported as "percent detectable dimethyl metabolites" without reference to the total amounts measured in the various urine specimens. This is unacceptable for exposure assessment if their intent was, as they stated, to "examine the association between specific agricultural tasks and levels of exposure among adult workers and children living in the same household." Failure to report urine metabolite levels deprives readers of the opportunity to transform percentages to dose, a measure of exposure. Dose (micrograms per person) defines the relationship of agricultural task to organophosphate (OP) exposure. Coronado et al. (2004) must have calculated the metabolite levels, but their failure to present those data seriously devalues the contribution and the cooperation of their subjects.

Coronado et al. (2004) reported the percentage of detectable dimethyl urinary metabolites in children ($n = 211$; 2–6 years of age). These data do not permit estimation of dose, and they prohibit full evaluation of the relationship of exposure from parents' work tasks or other sources to the dimethyl metabolites from residential exposures, particularly diet (Krieger et al. 2003). It seems that the urine OP metabolite levels of children are more likely linked to dietary exposure (Zhang and Krieger 2004) than to environmental sources (Lowenhurz et al. 1997) proposed by Coronado et al. (2004). Meaningful discussion is again prohibited by the lack of metabolite urine levels presented.

The data presented by Coronado et al. (2004) are not adequate. We believe that the metabolite levels in urine should be published in *EHP* or otherwise made available to investigators.

The authors declare they have no competing financial interests.

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Activities and Organophosphate Exposures: Response

In their letter, Krieger and Zhang note that our article (Coronado et al. 2004) is "founded on an erroneous premise" and that it "presents virtually no data to estimate levels of worker or child exposure." Our analyses show that the children of workers who reported thinning plants had significantly higher proportions of detectable urinary metabolites of organophosphate (OP) pesticides than the children of workers who reported that they did not perform this task. We concur that no urinary metabolite dose estimates were presented. However, we cited Curl et al. (2002), whose analyses using the same data set show significant correlations between pesticide exposure levels (geometric means and percentiles) between adult farmworkers and children who live in the same household, and high correlations between pesticide residues in house and vehicle dust. When our research team embarked upon investigating the relationship between job task and pesticide exposure, we agreed that calculating the percent detection of metabolites in the urine samples of workers who did and did not perform a given task would permit exploration of this issue. Thus, we noted that the analyses were exploratory in nature (see "Methods"; Coronado et al. 2004). This meant that significant findings would offer directions for further inquiry and investigation.

Krieger and Zhang also state that there is "substantial … data available related to work tasks of handlers," and they specifically cite the Pesticide Handlers Exposure Database and the U.S. Environmental Protection Agency (EPA) Transfer Coefficients. The Pesticide Handlers Exposure Database aims to determine how much residue (as a percentage of pesticide applied) ends up as external exposure to workers (Van Hemmen 1992). These data are used in worker risk analysis, taking an activity, translating it to external exposure, then translating it to a body burden or toxicologic risk (e.g., using a dermal absorption rates). The database generates hypothesized toxicologic risk estimates and relies on no biomonitoring data, such as testing for pesticide residues in urine or blood. Transfer coefficients estimate the amount of treated foliage with which a worker comes in contact while performing a given task (Knaak et al. 1996). A formula based on fixed assumptions about the clothing that a worker wears and the rate of dermal exposure is used to calculate the body burden of pesticide exposure when a worker performs a given task on a given crop.

We agree that these databases represent important sources of data on both exposure and body burden. However, because formulas used in the calculations of exposure rely on fixed values for protection incurred by personal protective equipment, work hours, absorption rates, and spray patterns, they generate hypothesized risk estimates. Various studies have reported that < 100% of workers routinely use personal protective equipment while applying pesticides, and many may enter recently treated fields (before the expiration of the reentry interval), resulting in potentially higher exposures than estimated in these databases.

Our data are unique in that they provide real-world data on differences in proportion of detection of dimethyl urinary metabolites of adult workers. Moreover, by documenting differences in proportions of detection of urinary metabolites among children of farmworkers, our analyses begin to answer the question of whether or not pesticide residues are being brought into homes where children may be exposed. Because it is widely believed that pesticide residues accumulate in home environments, that they degrade more slowly than pesticides in fields, and that children have unique susceptibilities to and frequencies of exposure (given their propensity for hand-to-mouth behaviors and their frequent contact with floors), such a question merits investigation. Moreover, the relationship between workers' job task and pesticide residues in collected house dust and vehicle dust samples provide compelling evidence that the take-home pathway is an important source of exposure.

Krieger and Zhang argue that urinary OP metabolite levels of children are more likely linked to dietary exposure than to environmental sources. The findings of Curl et al. (2002)—showing a significant correlation between adult and child urinary metabolite levels and showing lower median total dimethyl urinary metabolite concentrations among children adhering to an organic diet compared to children consuming conventional diets—support the claim that dietary sources contribute to children's pesticide exposure (Curl et al. 2003). However, there is a growing body of evidence that supports the claim that environmental sources contribute to children's pesticide exposure. Data from Curl et al. (2002) might also support the take-home pathway because it argues that children are affected by the residues brought home by their parents. McCauley et al. (2001) showed that home pesticide residues in dust are associated with home practices such as changing out of work clothing within 2 hr of returning home. Further research by McCauley et al. (2001)—showing that greater numbers of agricultural workers who live in a house and in close proximity to treated fields is associated with elevated residues of pesticides in house dust—offers additional support for the nondietary pathway of exposure. Our analyses (Coronado et al. 2004) show that the proportion of detectable pesticides residues in home and vehicle dust are greater for workers who thin plants than for workers who do not perform this task (home dust *p*-value = 0.003; vehicle dust *p*-value = 0.001). Although in our analyses we did not assess the associations between dust levels and urinary metabolite concentrations, our results do suggest that contamination of the home environment varies by occupational characteristics (Coronado et al. 2004).

In the next 5 years we will explore the take-home pathways as well as other pathways of pesticide exposure among children, including the dietary pathway. It is our hope that continued research will help clarify the important pathways involved in children's exposure to pesticides. We believe that the most meaningful and relevant scientific

discoveries result from hypotheses that are controversial. We look forward to further research and discovery on this topic.

The authors declare they have no competing financial interests.

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Electromagnetic Fields and Free Radicals

The article "Magnetic-Field–Induced DNA Strand Breaks in Brain Cells of the Rat" by Lai and Singh (2004) is interesting. The possibility that exposure to anthropogenic nonionizing radiation and/or electromagnetic fields (EMFs) might increase oxidative potential and free radical burden in cells may be a unifying theme for possible adverse biological consequences. Two articles published in *EHP* in the past explored two ideas in this regard. In the first article, we (Stevens and Kalkwarf 1990) pointed out *a*) that ferritin has a stable magnetic moment of 3.8 Bohr magnetons, and *b*) that on the basis of reports from Bawin and Adey (1976) and others that EMFs could alter calcium homeostasis, increases in free radicals could be expected. In the second article, I postulated

specifically that "EMF-induced loss of iron from its intracellular storage protein, ferritin, might increase oxidative stress" (Stevens 1993).

This is an intriguing area of inquiry at the scientific level that may also have health implications.

The author declares he has no competing financial interests.

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Electromagnetic Fields: Lai's Response

I agree with Stevens that free radicals and changes in oxidative state in cells could play an important mediating role in some biological effects of nonionizing electromagnetic fields (EMFs), such as DNA damage. Certainly, cellular iron metabolism affects these processes. Genetic damage in cells can lead to malignancy and cancer. However, excessive cumulative genetic damages could also result in cell death. One possibility is that EMFs may be useful in treating cancer.

The author declares he has no competing financial interests.

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Complexity of Factors Involved in Human Population Growth

We would like to thank Bob Weinhold (2004) for his informative article documenting the issues facing humans in regard to infectious disease and the growing concern within the medical community that traditional thinking, approaches, and methods may well be inadequate to face the challenges ahead. We would also like to thank Steven Salmony (2004) for his thoughtful letter regarding Weinhold's (2004) article, in

which he presents another extremely important issue: that of human population growth and its interconnection with food resources. Both of these articles report the results of good science, and both describe well some of the critical issues facing humans at this time. We would like to present another viewpoint that we believe is both more helpful and more accurate for describing the problems we face and for setting research and decision-making goals that will involve the health of all systems.

Our approach (Fowler and Hobbs 2002, 2003) stems from systemic thinking as a paradigm that is emergent from modern systems theory, cybernetics, and information theory from their beginnings in the late 1940s. Basically, this way of thinking posits that all things are intricately interconnected in very complex ways, so that any action (or inaction, for that matter) will always result in a variety of consequences. Some of these we can predict and some we cannot; some will be evaluated as positive and some will be evaluated as negative in human value systems. Examples of these systemic reactions can be given for any field of inquiry (e.g., environmental, social, political, religious, personal) and at any level of organization (e.g., individual, species, ecosystem, biosphere); what we find is that there is never a single cause or a single outcome. It is always more complex than that. As humans, we have been able to ignore this complexity until very recently because simple cause-and-effect models were accurate enough to help us deal with the problems we faced.

However, as we have become more sophisticated with our technologies, we are experiencing unprecedented success at altering our world. The resulting changes are so profound that simple models no longer adequately describe the problems or define goals and guidelines to solve these problems. Certainly, as Hopfenberg (2003) so clearly pointed out, humans are biological organisms, and food availability is one of the factors that contribute to the wealth of factors that determine population size. It is, however, also true that the number of other factors that influence human population size is beyond human capacity to list, comprehend, and synthesize. We cannot measure them all nor can we accurately weigh the relative importance of each factor's influence on the actual number of humans (e.g., disease, parasites, social upheaval, religious viewpoints, economics).

Each such factor is, in turn, influenced by other factors. For example, weather patterns influence the amount of food available. Ocean currents influence weather patterns; the orbiting of the earth and moon influence ocean currents; the orbits of other planets

and the gravitational forces of the sun and other celestial bodies influence the orbits of the earth and moon; and so on. In each case, there are multitudes of other factors involved. The amount of food available is dependent on, or influenced by, microbes, other consumers, and predators and prey at all levels. A huge variety of physical forces is also at play in influencing primary and other levels of production, including volcanoes, hurricanes, floods, forest fires, and various human influences such as the use of pesticides and fertilizers and increased carbon dioxide production.

Human population numbers are also dependent on an enormous number of factors beyond food, including disease and all the other factors that were listed by Weinhold (2004). Had we been unable to curtail the effects of smallpox, for example, the human population would probably be smaller than it is today, as is the case for so many wildlife species whose populations are regulated, in part, by the effects of disease. However, when considering human population numbers, human value systems, economics, politics, and religion, all factors over which we have some limited measure of control, must also be taken into account.

We believe that any approach to dealing with human problems must take into account all of this complexity or it will lead to more problems. A systemic approach, such as we propose in our work (Fowler and Hobbs 2002, 2003), takes into account all of this complexity and also gives empirical guidelines for how to deal with the problems. It not only allows us to deal with how much food can be sustainably extracted from the various resource systems to feed ourselves but addresses the deeper and, we believe, more important question: how many of us should there be to feed?

The authors declare they have no competing financial interests.

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Past and Future Considerations for Heavy-Duty Diesel Engine Emissions

In her Commentary in the June issue of *EHP*, "Diesel Exhaust: A Moving Target," Janet Arey (2004) makes a strong point for standardizing diesel exhaust reference material for future research due to the changes in diesel technology and resulting emissions.

Arey (2004) appropriately recognized that diesel exhaust particulates are a small category of emissions in what is truly a complex mixture of ambient particles. According to the U.S. Environmental Protection Agency's (EPA's) most recent emissions inventory (U.S. EPA 2003), emissions from all diesel sources (on-road light and heavy-duty, off-road, marine and rail) in 2001 accounted for 4.37% of the nation's fine particle inventory.

Recognizing the shift toward dramatically lower emissions and potential changes in the composition of those emissions, diesel engine manufacturers have initiated a unique broad-ranging stakeholder project known as the Advanced Collaborative Emissions Study, or ACES (French 2003). The objective of this collaborative government, academic, and industry research program is to develop the necessary data to assess and characterize in a timely manner (i.e., in the 2007–2008 timeframe) the emissions and any potential health effects from real-world exposures to exhaust from advanced prototype 2007–2010 heavy-duty engines, aftertreatment systems, and reformulated fuels. This effort includes 794 emissions characterizations, chronic animal exposure studies, and short-term studies on allergic responses, and it is expected to publish findings in 2009–2010 (Warren 2004).

In further noting Arey's appeals on the "need to understand the atmospheric chemistry of diesel and other vehicle exhaust" (Arey 2004), alternative fuels should also be evaluated. Now, more than ever, this is of particular significance as the use of alternative-fueled vehicles has increased, but the understanding and research of these emissions in the atmosphere have not kept pace.

A number of recently published studies have assessed the emissions from alternative-fueled heavy-duty vehicles. In a study of school buses running on diesel and compressed natural gas (CNG), low-emitting clean diesel technology had the lowest level of both U.S. EPA regulated emissions and toxic air compounds as defined by the California Air Resources Board (Ullman et al. 2003).

Similarly, the California Air Resources Board conducted a small-scale research project comparing transit buses using CNG to buses using advanced clean diesel technology (cleaner diesel fuel and particulate traps) (Ayala et al. 2002). This limited study found that the clean diesel bus had fewer emissions of toxic compounds than the CNG bus, and that both types of buses (CNG and those using filters and cleaner fuel) were superior to conventional diesel fuel and engines (Holmean and Ayala 2002). Even though the CNG bus was not equipped with an oxidation catalyst, the higher emissions of air toxics (1,3-butadiene, formaldehyde, etc.) could be expected by similar technology configurations currently in use around the country. For some areas that have aggressively promoted the use of so-called clean alternative fuels such as CNG without a complete understanding of their emissions profiles, these findings call for an additional consideration by Arey and other atmospheric chemists.

As the subtitle on the cover of the June issue of *EHP* appropriately suggests, diesel technology is a moving target—moving rapidly toward very low emissions across the board in all engine types and categories, with clearly defined pathways and time frames. For highway vehicles, 2004 model heavy-duty diesel engines have only one-eighth the level of emissions of nitrogen oxides and particulate matter compared to those built a dozen years ago, with 90% in additional reductions of particulate matter on track beginning in 2007 (U.S. EPA 2001). The U.S. EPA recently issued final rules for the fourth round of new lower emissions standards for off-road machines and equipment in the farming, construction, and industrial sectors, along with proposed rules for cleaner fuel requirements for marine vessels and locomotives (U.S. EPA 2004). Taking effect beginning in 2008 and at full implementation in 2014, these standards will converge at virtually the same low levels as highway engines.

Finally, an additional consideration, which was not identified by Arey (2004) but is significant, is the future impacts of applying new reformulated lower-sulfur diesel fuels and emissions filters on existing engines and equipment of various ages and types, an effort increasingly under way at the state and federal levels. Given this level of rapid change, establishing standardized reference materials will be particularly challenging.

The author declares he has a competing financial interest because he is the executive director of the Diesel Technology Forum, a not-for-profit educational organization representing the interests of the diesel industry.

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Heavy-Duty Engine Emissions: Response

In his letter, Schaeffer concludes that because of the ongoing changes in diesel technology, "establishing standardized reference materials [of diesel exhaust particles (DEPs)] will be particularly challenging." As amply illustrated by the work of DeMarini et al. (2004) and Singh et al. (2004), which prompted my commentary (Arey 2004), the effort is worth making because multidisciplinary studies on representative DEP samples are needed if meaningful assessments of the health hazards associated with DEPs are to be made. DeMarini et al. (2004) and Singh et al. (2004) highlighted the chemical, physical, and biological differences between two widely used DEP samples, one mainly studied for pulmonary toxicity and the other for genotoxicity; before their studies, the chemical composition and biologic activity of the samples had not been compared.

In his letter, Schaeffer describes the Advanced Collaborative Emissions Study (ACES), an important diesel assessment project currently in the planning stage by the Health Effects Institute (Boston, MA). Perusing Warren's presentation on the project (Warren 2004) cited by Schaeffer, I found that the utility of standard reference materials that allow for collaborations and exhaustive characterization of DEPs is reinforced by several issues Warren highlighted; for example, which of the "794 measurements under consideration" should be made; what should the results be compared to; and what health effect testing should be conducted? Until we fully understand the mechanisms of action of diesel and ambient particles that are involved in their adverse health effects, we need more multidisciplinary, collaborative efforts to study samples that can be shared among researchers.

The author declares she has no competing financial interests.

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Monitoring for Asbestos: U.S. EPA Methods

I would like to correct a misimpression about the methods used by the U.S. Environmental Protection Agency (EPA) in monitoring for asbestos in the air following the collapse of the World Trade Center in "Health and Environmental Consequences of the World Trade Center Disaster" (Landrigan et al. 2004). The authors state that

> More than 10,000 ambient air samples from lower Manhattan were tested for asbestos by the U.S. EPA using phase-contrast light microscopy (PCM) to identify fibers > 5 mm in length; more than 8,000 of these samples were also examined by transmission electronic microscopy (TEM) to identify fibers of ≥ 0.5 mm in length.

This suggests that the U.S. EPA placed more emphasis on the analysis of asbestos in air samples using phase-contrast light microscopy (PCM) than those examined by transmission electron microscopy (TEM). This is not the case.

Recognizing the potential asbestos hazard, the U.S. EPA initiated its asbestos environmental sampling on the afternoon of September 11, employing TEM analysis as the primary method of recording the presence of asbestos fibers. The agency relied more heavily on the TEM data because PCM analysis cannot distinguish asbestos from other mineral fibers and would therefore not provide as accurate a measure of airborne asbestos concentrations as TEM.

As directed in the procedures outlined in the Asbestos Hazard Emergency Response Act (AHERA) (U.S. EPA 1987), TEM counts were recorded for both short (0.5–5 mm) and long (> 5 mm) asbestos fibers. The U.S. EPA's World Trade Center website (U.S. EPA 2004) summarizes the results of 9,604 asbestos samples from 22 monitoring stations in lower Manhattan that were analyzed by TEM, not the 8,000 samples cited in the article (Landrigan et al. 2004).

Most of the asbestos samples were also analyzed by PCM. The PCM analysis was performed to provide ancillary information about total fiber counts and data for the Occupational Safety and Health Administration.

Because there has been much public confusion about the use of the two analytic methods in the World Trade Center response, I felt it was especially important to correct and clarify that the U.S. EPA used the most accepted and appropriate method to protect the health of residents and response workers in the aftermath of the disaster.

The author declares she has no competing financial interests.

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Editor's note: In accordance with journal policy, Landrigan et al. were asked whether they wanted to respond to this letter, but they chose not to do so.

Evaluating the Toxicity of Chemical Mixtures

Tinwell and Ashby (2004) provided a detailed evaluation of the joint action of a mixture of estrogenic chemicals using the immature rat uterotrophic assay. The researchers demonstrated that a mixture of estrogenic chemicals in which each individual chemical was present in the mixture at levels approximating the no observed effect level (NOEL) elicited a mea-

surable response. This work advances our understanding of the toxicity of endocrine-active substances, and Tinwell and Ashby are to be commended for providing detailed results of their experiments suitable for evaluation by others.

The analysis of the data, however, stopped short of providing insights into the joint action of mixtures of endocrine disruptors. Tinwell and Ashby (2004) proposed three avenues for the analysis of the joint

action of chemicals. The first, a simple addition-of-effects approach, is overly simplistic and unrealistic, as demonstrated by the authors. The second, graphic isobole analysis, was rejected by the authors for any mixture in excess of three chemicals. We concur that isobole analysis poses limitations for more complex mixtures of chemicals. The third, concentration addition, was deemed impractical by Tinwell and Ashby due to the requirement of detailed characterization of

Corrections

In "Cause-Specific Mortality and the Extended Effects of Particulate Pollution and Temperature Exposure" by Goodman et al. [Environ Health Perspect 112:179–184 (2004)], Figures 2–4 were incorrect; the corrected figures appear below. *EHP* regrets the errors.
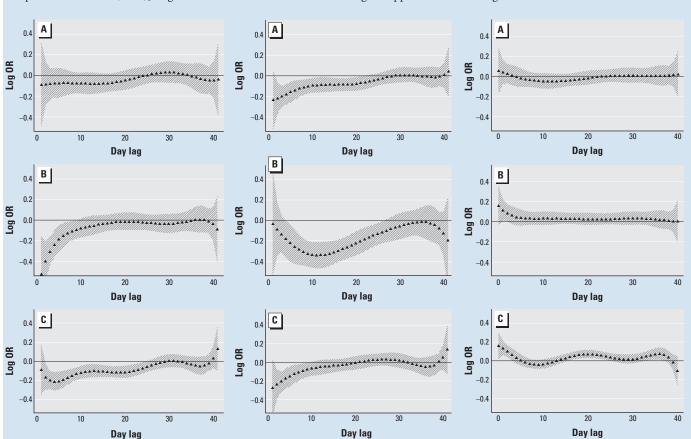

Figure 2. Polynomial distributed lag analysis of total nontrauma mortality versus minimum temperature adjusted for same-day minimum temperature for ages (*A*) 0–64, (*B*) 65–74, and (*C*) ≥ 75 years. Percent increase in total mortality for each 1°C decrease in minimum daily temperature for lags 1–41 days fitted with a sixth-degree polynomial.

Figure 3. Polynomial distributed lag analysis of (*A*) cardiovascular, (*B*) respiratory, and (*C*) other mortality versus minimum temperature adjusted for same-day minimum temperature. Percent increase in cause-specific mortality for each 1°C decrease in daily minimum temperature for lags 1–41 days fitted with a sixth-degree polynomial.

Figure 4. Polynomial distributed lag analysis of total nontrauma mortality versus BS adjusted for minimum temperature for ages (*A*) 0–64, (*B*) 65–74, and (*C*) ≥ 75 years. Percent increase in total mortality for each 10-μg/m³ increase in mean BS for lags 0–40 days fitted with a sixth-degree polynomial.

The April 2004 news article "Reaching across the Border with the SBRP" [Environ Health Perspect 112:A278–A279 (2004)] listed an incorrect URL for the University of Arizona website where visitors may download a Spanish-language environmental toxicology textbook. The correct URL is http://superfund.pharmacy.arizona.edu/outreach.html.

In the May 2004 toxicogenomics news article "Diet and DNA" [Environ Health Perspect 112:A404 (2004)], the European Nutrigenomics Organisation (NuGO) was described as "a network of 22 scientists" when in fact it is a network of 22 organizations.

EHP regrets the errors.

the concentration–response relationship of each chemical within the mixture. We agree that analysis of mixtures toxicity using concentration addition requires an understanding of the toxicity of the individual constituents within a mixture. However, we disagree that such a data requirement should discourage efforts to model and predict toxicity of chemical mixtures using this approach. Results reported by Tinwell and Ashby (2004), along with published data cited by the authors, provided sufficient information on the toxicity of the individual chemicals for us to accurately model the joint action of the mixture based upon concentration addition.

The authors' recommendation that toxicity of chemical mixtures be directly assessed on a case-by-case basis (Tinwell and Ashby 2004) would provide a Band-Aid but not a cure to the dilemma of characterizing the hazards of chemical mixtures. Chemical mixtures are ever varying with respect to constituents and to concentrations of those constituents. Granted, the individual toxicity of many, if not most, chemicals has not been adequately evaluated to provide the concentration–response information required for the joint evaluation of toxicity. Rather than avoid such endeavors, the scientific community should mobilize to generate such data; the data should be made available in the public domain; and, alternative approaches (i.e., *in vitro* analyses of ligand–receptor interactions) should be explored as means to rapidly generate surrogate data for use in mixtures toxicity assessments. Thanks to the efforts of investigators such as Tinwell and Ashby, who are generous with the data they have generated, a growing database exists for estrogenic chemicals. Hopefully, key agencies (i.e., the National Institute of Environmental Health Sciences, the U.S. Environmental Protection Agency) will take the initiative to generate public-domain databases on chemicals harboring other mechanisms of toxicity. With such data resources, we may someday have the ability to routinely model the toxicity of chemical mixtures.

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Editor's note: In accordance with journal policy, Tinwell and Ashby were asked whether they wanted to respond to this letter, but they chose not to do so.