The correspondence section is a public forum and, as such, is not peer-reviewed. EHP *is not responsible for the accuracy, currency, or reliability of personal opinion expressed herein; it is the sole responsibility of the authors.* EHP *neither endorses nor disputes their published commentary.*

Adverse Health Effects from Combustion-Derived Nanoparticles: The Relative Role of Intrinsic Particle Toxicity and Host Response

doi:10.1289/ehp.0800218

It is widely accepted that airborne pollution causes adverse health effects in humans (Gauderman et al. 2007). In addition to the concentration of particulate matter (PM), these effects have been related to innate particle toxicity. Stoeger et al. (2009) recently showed that, with a slope that significantly depends on particle structure, surface, and organic carbon content, combustion-derived nanoparticles behave in a different manner in *in vitro* systems and when reacting with lung surface (i.e. after particle–lung interaction).

We have stressed that mechanistic linkages between PM and health effects should be investigated in more detail (Cetta et al. 2007, 2008). Here, we would like to comment on the role of the individual response in the occurrence of the clinically evident outcome, that is, how individual characteristics of the host, in the presence of the same (or similar) noxious agents, are responsible for or determine the type and the severity of the response.

Until now, toxicity has been considered mainly as an intrinsic property of each pollutant, depending on size, type, and composition of each particle. Stoeger et al. (2009) focused specifically on structure, BET (Brunauer, Emmett, and Teller) surface area, and oxidative potency. Interestingly, they stressed particle–lung interaction and the ability of some particles rich in organic content, namely, soot with high organic content, to determine a higher than expected inflammatory response due to increased cytochrome P450 1A1 induction; they also introduced a new parameter, inflammatory efficacy, in addition to oxidative potency.

In our opinion, this could be just the top of the iceberg. In fact, "oxidative stress" is a working hypothesis in the search for a common mechanistic linkage between particulate material and adverse health effects. But it is not unique. In particular, in a recent *in vitro* study in which different types of particles were used (PM < 2.5 or ≤ 10 μm in aerodynamic diameter, tire debris), the same concentration of different particles with the same exposure time elicited different effects on sperm cell function (motility, viability, rate of apoptosis) (Collodel G, Geminiani M, Cetta F, Camatini M, Bolzacchini E, Renieri T, unpublished data). However, variability of the observed effects was less than that elicited by changing the host, with lower adverse effects in New Zealand rabbit sperm, more evident effects in human sperm, and very severe effects in humans with previous impaired sperm function (e.g., varicocele). Sperm cell function is easy to quantify and compare not only among different pollutants but also among different host species or subgroups. These findings are in accordance with recent epidemiologic data showing more pronounced respiratory and cardiovascular effects in patients with previous respiratory and cardiovascular impairment or specific susceptibility, respectively (Gauderman et al. 2007).

The results of these studies will also have relevant implications for policy makers (Cetta et al. 2007). In fact, until now, contrast measures have mainly been directed to reduce PM concentration. Curent evidence suggests that—more important than reducing the overall PM concentration—it is of paramount importance to reduce selectively the concentration of those pollutants that are more toxic or more strictly related with adverse health effects, such as traffic-related particles. In the future, because of the better knowledge of the host response and of the variability of individual susceptibility in the occurrence of these effects, a major goal for policy makers will be the proper and early recognition—by means of sensible and specific tests—of at-risk subpopulations.

This early recognition of at-risk subpopulations could facilitate better prevention or reduction of negative effects of host–pollutant interactions.

The present work has been supported by The PROLIFE Research Project, City of Milan, Italy.

The authors declare they have no competing financial interests.

Francesco Cetta
Armand Dhamo
Laura Moltoni
Department of Surgery
Research Doctorate in Oncology and Genetics
University of Siena
Siena, Italy
E-mail: cetta@unisi.it

Ezio Bolzacchini
Department of Environmental Science
University of Milan-Bicocca
Milan, Italy

References

Cetta F, Dhamo A, Schiraldi G, Allegra L. 2008. Comment on "Emissions from brake linings and tires": case studies of Stockholm, Sweden 1995/1998 and 2005 [Letter]. Environ Sci Technol 42:2708–2709.

Cetta F, Dhamo A, Schiraldi G, Camatini M. 2007. Particulate matter, science and European Union policy [Letter]. Eur Respir J 30:805–806.

Gauderman WJ, Vale H, McConnell R, Berhane K, Gilliland F, Thomas D, et al. 2007. Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. Lancet 269:571–577.

Stoeger T, Takenaka S, Frankenberger B, Ritter B, Karg E, Maier K, et al. 2009. Deducing *in vivo* toxicity of combustion-derived nanoparticles from a cell-free oxidative potency assay and metabolic activation of organic compounds. Environ Health Perspect 117:54–60.

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

Prenatal Lead Exposure and Schizophrenia: Further Evidence and More Neurobiological Connections

doi:10.1289/ehp.0800484

In 2004, Opler et al. published a study in *Environmental Health Perspectives* (*EHP*) suggesting an association between prenatal lead (Pb^{2+}) exposure and schizophrenia (Opler et al. 2004). In the November 2008 issue of *EHP*, Opler et al. (2008) further supported this association using a different cohort of subjects. In a letter published in *EHP* in 2004 (Guilarte 2004), I indicated that a plausible neurobiological connection between prenatal Pb^{2+} exposure and schizophrenia may be that Pb^{2+} is a potent antagonist of the *N*-methyl-D-aspartate (NMDA) receptor (NMDAR), and NMDAR hypofunction is thought to be involved in the pathophysiology of the disease. Since then, another plausible neurobiological connection has surfaced, and this relates to hippocampal neurogenesis. Neurogenesis occurs not only during development but is also prominent in the adult brain (Laplagne et al. 2006). A well-characterized neurogenic zone in the adult brain is the subgranular zone of the dentate gyrus (DG) in the hippocampus (Zhao et al. 2008). Although the significance of newly born neurons in the adult hippocampus is currently under investigation, the overwhelming evidence supports a role in hippocampus-dependent learning (Dupret et al. 2008; Imayoshi et al. 2008).

Schizophrenia patients express cognitive deficits that may be related to hippocampal dysfunction (Gothelf et al. 2000; Sweatt 2004). So, what is the new neurobiological connection between Pb^{2+} exposure and schizophrenia? Recent evidence indicates that neurogenesis is decreased in schizophrenia patients, and this decrease may contribute to their cognitive dysfunction (Kempermann et al. 2008; Reif et al. 2006). In an animal model using the NMDAR antagonist phencyclidine (PCP) to induce schizophrenia-like symptoms in mice, Maeda et al. (2007) observed reduced DG neurogenesis that was reversed by the atypical antipsychotic drug clozapine. Co-administration

of D-serine and glycine also inhibited the PCP-induced decrease in neurogenesis. PCP, like Pb^{2+}, is an NMDAR antagonist, and D-serine and glycine activate NMDAR; this suggests that chronic NMDAR hypofunction decreases neurogenesis in the hippocampus, an observation consistent with my comments in 2004 (Guilarte 2004). Models of developmental Pb^{2+} exposure have also shown decreased DG neurogenesis and are associated with deficits in learning (Jaako-Movits et al. 2005; Verina et al. 2007). Therefore, reduced DG neurogenesis appears to be a common factor in schizophrenia and in animal models of schizophrenia and developmental Pb^{2+} exposure.

Schizophrenia is a neurodevelopmental disorder that is expressed later in life. Pb^{2+} is a neurotoxicant that is known to cause developmental abnormalities. Animal models of developmental Pb^{2+} exposure express a behavioral phenotype with features that overlap with those in animal models of schizophrenia, including increased spontaneous activity, decreased social interaction, and learning deficits (Moreira et al. 2001; Nihei et al. 2000). Also, some of the behavioral effects described in adolescents with early-life Pb^{2+} exposure are similar to those expressed in schizophrenia patients (Opler and Susser 2005). Thus, although the environmental causes of schizophrenia have not evaluated environmental toxicants, the emerging evidence from the human studies by Opler and colleagues and animal studies suggest that prenatal Pb^{2+} exposure may be an environmental risk factor for schizophrenia.

The author declares he has no competing financial interests.

Tomás R. Guilarte
Environmental Health Sciences
Johns Hopkins Bloomberg School of Public Health
Baltimore, Maryland
E-mail: tguilart@jhsph.edu

References

Dupret D, Revest J-M, Koehl M, Ichas F, De Giorgi F, Costet P, et al. 2008. Spatial relational memory requires hippocampal adult neurogenesis. PloS One 3(4): e1959; doi:10.1371/journal.pone.0001959 [Online 9 April 2008].

Gothelf D, Soreni N, Nachman RP, Tyano S, Hiss Y, Reiner O, et al. 2000. Evidence for the involvement of the hippocampus in the pathophysiology of schizophrenia. Eur Neuropsychopharmacol 10:389–395.

Guilarte TR. 2004. Prenatal lead exposure and schizophrenia: a plausible neurobiologic connection [Letter]. Environ Health Perspect 112:A724.

Imayoshi I, Sakamoto M, Ohtsuka T, Takao K, Miyakawa T, Yamaguchi M, et al. 2008. Roles of continuous neurogenesis in the structural and functional integrity of the adult forebrain. Nat Neurosci 11:1153–1161.

Jaako-Movits K, Zharkovsky T, Romantchick O, Jurgenson M, Merisalu E, Heidmets L-T, et al. 2005. Developmental lead exposure impairs contextual fear conditioning and reduces adult hippocampal neurogenesis in the rat brain. Int J Devl Neurosci 23:627–635.

Kempermann G, Krebs J, Fabel K. 2008. The contribution of failing adult hippocampal neurogenesis to psychiatric disorders. Curr Opin Psychiatry 21:290–295.

Laplagne DA, Esposito MS, Piatti VC, Morgenstern NA, Zhao C, van Praag H, et al. 2006. Functional convergence of neurons generated in the developing and adult hippocampus. PloS Biol 4(12): e409; doi: 10.1371/journal.pbio.0040409 [Online 21 November 2006].

Maeda K, Sugino H, Hirose T, Kitagawa H, Nagai T, Mizoguchi H, et al. 2007. Clozapine prevents decrease in neurogenesis in mice repeatedly treated with phencyclidine. J Pharmacol Sci 103:299–308.

Moreira EG, Vassilieff I, Vassilieff VS. 2001. Developmental lead exposure: behavioral alterations in the short and long term. Neurotoxicol Teratol 23:489–495.

Nihei MK, Desmond NL, McGlothan JL, Kuhlmann AC, Guilarte TR. 2000. *N*-Methyl-D-aspartate receptor subunit changes are associated with Pb^{2+}-induced deficits of long-term potentiation and spatial learning. Neurosci 99:233–242.

Opler MGA, Brown AS, Graziano J, Desai M, Zheng W, Schaefer C, et al. 2004. Prenatal lead exposure, δ-aminolevulinic acid, and schizophrenia. Environ Health Perspect 112:548–552.

Opler MGA, Buka SL, Groeger J, McKeague I, Wei C, Factor-Litvak P, et al. 2008. Prenatal exposure to lead, δ-aminolevulinic acid, and schizophrenia: further evidence. Environ Health Perspect 116:1586–1590.

Opler MGA, Susser ES. 2005. Fetal environment and schizophrenia. Environ Health Perspect 113:1239–1242.

Reif A, Fritzen S, Finger M, Strobel A, Lauer M, Schmitt A, et al. 2006. Neural stem cell proliferation is decreased in schizophrenia, but not in depression. Mol Psychiatry 11:514–522.

Sweatt JD. 2004. Hippocampal function in cognition. Psychopharmacol 174:99–110.

Verina T, Rohde CA, Guilarte TR. 2007. Environmental lead exposure during early life alters granule cell neurogenesis and morphology in the hippocampus of young adult rats. Neuroscience 145:1037–1047.

Zhao C, Deng W, Gage FH. 2008. Mechanisms and functional implications of adult neurogenesis. Cell 132:645–660.

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.

Plant Food Allergens: Another Climate Change–Public Health Link

doi:10.1289/ehp.0900670

The recent article titled "Rising CO_2, Climate Change, and Public Health: Exploring the Links to Plant Biology" (Ziska et al. 2009) is an interesting and useful commentary on this important topic. Although some aspects of the article have been considered in some detail previously, such as the impacts of climate change and elevated carbon dioxide on aerobiology (e.g., Beggs 2004; Confalonieri et al. 2007) and the human health implications of this (e.g., Beggs and Bambrick 2005; Shea et al. 2008), the broader review of links between climate change, plant biology, and human health, particularly the examination of toxicology and pharmacology, is timely and brings together a number of somewhat distinct areas of research.

In their article, Ziska et al. (2009) mentioned the potential impacts of elevated atmospheric CO_2 concentration on ragweed pollen allergenicity and poison ivy toxicity, and therefore considered respiratory allergies and contact dermatitis, respectively. Surprisingly, however, these authors did not recognize that there is a third major mechanism for human contact with plant allergens: ingestion. In an article published in *Air Quality, Atmosphere & Health*, I (Beggs and Walczyk 2008) proposed, for the first time, a link between climate change and plant food allergens, such as peanut, and the rise of associated diseases. There is potential for such impacts in the future, but they may have already occurred (Beggs and Walczyk 2008).

I agree that the plant biology aspect of climate change and human health is underappreciated, and I also strongly support Ziska et al.'s (2009) highlighting of the many key questions that remain to be addressed and the urgent need to find answers to these questions. Studies should also investigate the impacts of climate change, particularly elevated CO_2, on plant food allergens, especially their relative concentrations.

The author declares he has no competing financial interests.

Paul John Beggs
Environmental Science
Department of Environment and Geography
Faculty of Science
Macquarie University
New South Wales, Australia
E-mail: paul.beggs@mq.edu.au

References

Beggs PJ. 2004. Impacts of climate change on aeroallergens: past and future. Clin Exp Allergy 34:1507–1513.

Beggs PJ, Bambrick HJ. 2005. Is the global rise of asthma an early impact of anthropogenic climate change? Environ Health Perspect 113:915–919.

Beggs PJ, Walczyk NE. 2008. Impacts of climate change on plant food allergens: a previously unrecognized threat to human health. Air Qual Atmos Health 1:119–123.

Confalonieri U, Menne B, Akhtar R, Ebi KL, Hauengue M, Kovats RS, et al. 2007. Human health. In: Climate Change 2007: Impacts, Adaptation and Vulnerability. Contribution of Working Group II to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change (Parry ML, Canziani OF, Palutikof JP, van der Linden PJ, Hanson CE, eds). Cambridge, UK:Cambridge University Press, 391–431.

Shea KM, Truckner RT, Weber RW, Peden DB. 2008. Climate change and allergic disease. J Allergy Clin Immunol 122:443–453.

Ziska LH, Epstein PR, Schlesinger WH. 2009. Rising CO_2, climate change, and public health: exploring the links to plant biology. Environ Health Perspect 117:155–158.

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

Clarification

On p. A155 of the April Focus article [*Environ Health Perspect* 117:A150–A156 (2009)], a statement reads, "The primary global impact of oil sands comes through the release of greenhouse gases created when about 800 million cubic feet of natural gas (approximately 10% of Canada's total natural gas consumption) is burned daily to create heat for extraction and upgrading, says Stringham." To clarify: This statement refers to the global impact of oil sands *production*. As noted in the preceding paragraph of the article, most of the greenhouse gas emissions related to oil sands overall come from burning the fuel derived from these reserves.