(Lead Endnotes)

1 David S. Cloud, "Here's Donny! In His Defense, a Show Is Born," The New York Times, April 19, 2006, http://query.nytimes.com/gst/fullpage.html?res=9A02E6DD143FF93AA25757C0A9609C8B63&scp=4&sq=%22I+decide+what%92s+best.%22&st=nyt

2 Inspired by the declaration, the cable television humor program "The Daily Show" launched the action-packed adventures of "The Decider," featuring Bush as a comic book hero. In Washington City, the corridors of power were menaced by crippling indecision until…The Decider. http://politicalhumor.about.com/od/dailyshow/v/thedecider.htm

3 Hansen, J. et. al. Earth's Energy Imbalance: Confirmation and Implications. Science 3 June 2005: Vol. 308. no. 5727, pp. 1431–1435.

4 Hansen, J. et. al. Earth's Energy Imbalance: Confirmation and Implications. Science 3 June 2005: Vol. 308. no. 5727, pp. 1431–1435.

5 In the United States, the largest methane emissions come from the decomposition of wastes in landfills, ruminant digestion and manure management associated with domestic livestock, natural gas and oil systems, and coal mining. Table 1 shows the level of emissions from individual sources for the years 1990 and 1997 to 2003.

Table 1

U.S. Methane Emissions by Source ($TgCO_2$ Equivalents)

Source Category	1990	1997	1998	1999	2000	2001	2002	2003
Landfills	172.2	147.4	138.5	134.0	130.7	126.2	126.8	131.2
Natural Gas Systems	128.3	133.6	131.8	127.4	132.1	131.8	130.6	125.9
Enteric Fermentation	117.9	118.3	116.7	116.8	115.6	114.5	114.6	115.0
Coal Mining	81.9	62.6	62.8	58.9	56.2	55.6	52.4	53.8
Manure Management	31.2	36.4	38.8	38.8	38.1	38.9	39.3	39.1
Wastewater Treatment	24.8	31.7	32.6	33.6	34.3	34.7	35.8	36.8
Petroleum Systems	20.0	18.8	18.5	17.8	17.6	17.4	17.1	17.1
Rice Cultivation	7.1	7.5	7.9	8.3	7.5	7.6	6.8	6.9
Stationary Sources	7.8	7.4	6.9	7.1	7.3	6.7	6.4	6.7
Abandoned Coal Mines	6.1	8.1	7.2	7.3	7.7	6.9	6.4	6.4
Mobile Sources	4.8	4.0	3.9	3.6	3.4	3.1	2.9	2.7
Petrochemical Production	1.2	1.6	1.7	1.7	1.7	1.4	1.5	1.5
Iron and Steel	1.3	1.3	1.2	1.2	1.2	1.1	1.0	1.0
Agricultural Residue Burning	0.7	0.8	0.8	0.8	0.8	0.8	0.7	0.8
Total for U.S.	605.3	579.5	569.3	557.3	554.2	546.7	542.3	544.9

Source: US Emissions Inventory 2005: Inventory of U.S. Greenhouse Gas Emissions and Sinks: 1990-2003, http://www.epa.gov/methane/sources.html, accessed Feb. 14, 2007.

6 Ramanathan, V. & Carmichael, G. Global and regional climate changes due to black carbon. Geoscience March 23, 2008. TK TK

7 A very readable and accurate summary of methane sources and controls is "Methane May Pack Double the Climate Punch of Earlier Estimates," Environmental News Service, http://www.ens-newswire.com/ens/jul2005/2005-07-19-01.asp.

8 Peter Brimblecombe, "The Big Smoke: A History of Air Pollution in London since Medieval Times," Methuen, London (1987/88). One of the most entertaining and enlightening books ever written on the subject of air pollution. This is essential reading for a person in the field or aspiring to a career.

9 Mark Z. Jacobson, Atmospheric Pollution: history, science and regulation, Cambridge University Press, Cambridge, England (2002), p. 124.

10 Cooke, W.F.; Wilson, J.J.N. A global black carbon aerosol model. J of Geophys R. VOL. 101; ISSUE: D14 ; PBD: 27 Aug 1996.

A global inventory constructed for emissions of black carbon from fossil fuel combustion and biomass burning was implemented in a 3D global transport model and run for 31 model months, and results for January and July compared with measurements from the literature. The modeled values of black carbon mass concentration compared within a factor of 2 in continental regions and some remote regions but are higher than measured values in other remote marine regions and in the upper troposphere, explained by the coarse grid scale of the model, the simplicity of the current deposition scheme, and possibly too much black carbon being available for transport, which would also account for the disagreement in the upper troposphere. The disagreement may also be due to problems associated with the measurement of black carbon. Emissions from this database appear to provide a reasonable estimate of the annual emissions of black carbon to the atmosphere. Biomass burning emissions amount to 5.98 Tg and that from fossil fuel to 7.96 Tg. A local sensitivity analysis showed that black carbon has a lifetime between 6 and 10 days, depending on the transformation rate between hydrophobic and hydrophilic black carbon.

11 Forbes, M.S., Raison, R.J., Skjemstad, J.O. 2006. Formation, transformation and transport of black carbon (charcoal) in terrestrial and aquatic ecosystems. Science of the Total Environment 370, 190–206. Also, Preston, C.M., Schmidt, M.W.I. 2006. Black (pyrogenic) carbon: a synthesis of current knowledge and uncertainties with special consideration of boreal regions. Biogeoscience 3, 397–420.

12 Brodowski S., Amelung, W., Haumaier, L., Abetz, C., Zech, W. 2005. Morphological and chemical properties of black carbon in physical soil fractions as revealed by scanning electron microscopy and energy-dispersive X-ray spectroscopy. Geoderma 128, 116–129. Also, Forbes, M.S., Raison, R.J., Skjemstad, J.O. 2006. Formation, transformation and transport of black carbon (charcoal) in terrestrial and aquatic ecosystems. Science of the Total Environment 370, 190–206.

13 Bhugwant, C., et. al. Impact of traffic on black carbon aerosol concentration at la Réunion Island (Southern Indian Ocean). Atmospheric Environment Volume 34, Issue 20, 2000, Pages 3463–3473.

To gain information on particle pollution by mobile sources, 3 experiments were conducted during the 1996–1998 period at Saint-Denis, the biggest urban site of La Réunion island (21.5°S; 55.5°E), situated in the Indian Ocean. Black Carbon (BC) concentrations were recorded with an Aethalometer which show high levels whatever the season (daily average: 270–650 ng m-3). At this site, a marked diurnal BC concentration variation is also evidenced in accordance with the observed traffic pattern. Measured daytime BC concentrations are 2–4 times greater than nighttime values. Neither MBL height obtained by radio soundings nor wind speed or direction could explain satisfactorily the BC variations. A comparison with BC concentrations measured at other more remote sites of the island (Sainte-Rose and the altitude site Piton Textor) suggests that the background concentrations of the island are of the order 50 ngC m-3. These background values are almost never encountered in the main city (range: 80–2800 ngC m-3). We show that due to a singular convergence of parameters (topography of the island, road network, movement of population, quality of fuel), the city of Saint-Denis appears as polluted as continental European big cities.

14 Novakov T.; Bates T.S.; Quinn P.K. Shipboard measurements of concentrations and properties of carbonaceous aerosols during ACE-2. Tellus, Volume 52, Number 2, April 2000

Mass concentrations of total, organic and black carbon were derived by analyzing the supermicron and submicron aerosol fractions of shipboard collected samples in the eastern Atlantic Ocean as part of the second Aerosol Characterization Experiment (ACE-2). These analyses were complemented by experiments intended to estimate the water-soluble fraction of the submicron carbonaceous material. Results: Depending on the sample, between 35% and 80% of total aerosol carbon is associated with the submicron fraction. Total submicron carbon was well correlated with black carbon, a unique tracer for incomplete combustion. These correlations and the approximately constant total to black carbon ratios, suggest that the majority of submicron total carbon is of primary combustion derived origin. No systematic relationship between total submicron aerosol carbon and sulfate concentrations was found. Sulfate concentrations were, with a few exceptions, significantly higher than total carbon. Experiments demonstrated that water exposure removed between 36% and 72% of total carbon from the front filter, suggesting that a substantial fraction of the total submicron aerosol organic carbon is water-soluble. An unexpected result of this study is that water exposure of filter samples caused substantial removal of, nominally insoluble, submicron black carbon. Possible reasons for this observation are discussed.

15 [59]BERUBE, K.A., JONES, T.P., WILLIAMSON, B.J., WINTERS, C., MORGAN, A.J., & RICHARDS, R.J.Physicochemical characterisation of diesel exhaust particles: factors for assessing biological activityAtmospheric Environment 33 (1999) 1599-1614From Cardiff. Source was a 1985 Japanese ISEKI tractor burning Esso 2000 Diesel and a 20/30 mixture of Esso light engine oil. Operated at 2000 rpm. Details of methodology.Define four basic shapes:

1.Spherulites (individual particles); 2. Chains or clusters of spherulites; 3. Spherules (large bodies of spherulites; 4. Flake-like bodies. Equivalent spherical diameter of spherulites was 0.23 microns; Distributions of particle size by number showed 10% were ultrafines; 89.5% were fine (0.1-2.0 microns) and 0.4% coarse (greater than 2.5 microns). But distribution by mass showed 0.01% ultrafine, 52.6% fine; and 47.4% coarse. Electron probe X-ray microanalysis showed presence of C,O,Na,Mg,K,Al,Si,P,S,Cl,and Ca along with a range of metals (Ti,Mn,Fe,Zn,&Cr). By analysis before and after sonication of particles in water, the mobile sorbed metals were Mg,P ,Ca,Cr,Mn,Zn,Sr,Mo,Ba,Na,Fe,S, & Si. Stress differences between sonicated and impacted diesel particles–these differences are likely to affect toxicity. Excellent pictures. A definitive article.

16 Ch_lek, P. , et. al. Black carbon and absorption of solar radiation by clouds. Journal of Geophysical Research, Volume 101, Issue D18, p. 23365–23372

The exact solution of the scattered electromagnetic field from a water droplet containing an arbitrarily located spherical black carbon particle is used to investigate the effect of black carbon on the absorption of solar radiation by clouds. When droplet absorption is averaged over all possible locations of black carbon within a droplet, the averaged absorption is close to the value calculated using the effective medium approximation. The preferential black carbon location on the top or close to the bottom of the droplet leads to an

increased absorption. The estimated upper bound on the increased absorption of solar radiation (global and annual average) is 1-3 W/m^2 over the absorption of pure water clouds.

17 Jacobson, M.Z., Effects of absorption by soot inclusions within clouds and precipitation on global climate, J. Phys. Chem., 110, 6860–6873, 2006.

18 Hansen, A.D.A. Aerosol Black Carbon Measurements at the South Pole: Initial Results,

1986–1987. Geophysical Research Letters, VOL. 15, NO. 11, PAGES 1193–1196, 1988.

In December 1986 an aethalometer was installed at the NOAA/GMCC South Pole Observatory to measure concentrations of the combustion effluent tracer species aerosol black carbon (BC) with a time resolution of one hour. Hourly data covering a 1-year period from December 1986 through November 1987 showed infrequent events in which the concentrations increased greatly for periods of a few hours. These were attributed to local contamination. The remaining background data then yielded daily average BC concentrations generally ranging from 50 ng/m3 to 5 ng m/3, with a minimum in the early austral winter. The results imply long-range transport and suggest a minimum value of the order of 10 pg m/3 for its global background concentration.

19 McConnell, J.R., et. al. 20th-Century Industrial Black Carbon Emissions Altered Arctic Climate Forcing. 317 Science 5843, 7 Sep. 2007, pp. 1381–1384.

Black carbon (BC) from biomass and fossil fuel combustion alters chemical and physical properties of the atmosphere and snow albedo, yet little is known about its emission or deposition histories. Measurements of BC, vanillic acid, and non-sea-salt sulfur in ice cores indicate that sources and concentrations of BC in Greenland precipitation varied greatly since 1788 as a result of boreal forest fires and industrial activities. Beginning about 1850, industrial emissions resulted in a sevenfold increase in ice-core BC concentrations, with most change occurring in winter. BC concentrations after about 1951 were lower but increasing. At its maximum from 1906 to 1910, estimated surface climate forcing in early summer from BC in Arctic snow was about 3 watts per square meter, which is eight times the typical preindustrial forcing value.

20 Hansen, J. & Nazarenko, L. Soot Climate Forcing via Snow and Ice Albedos. PNAS.

Using the NASA GISS climate computer model to simulate effects of greenhouse gases and other factors on world climate and incorporating data from NASA spacecraft that monitor the Earth's surface, vegetation, oceans and atmospheric qualities, the calculated global warming from soot in snow and ice, by itself in an 1880–2000 simulation, accounted for 25 percent of observed global warming. NASA's Terra and Aqua satellites observe snow cover and reflectivity at multiple wavelengths, which allows quantitative monitoring of changing snow cover and effects of soot on snow. The researchers found that observed warming in the Northern Hemisphere was large in the winter and spring at middle and high latitudes. These observations were consistent with the researchers' climate model simulations, which showed some of the largest warming effects occurred when there was heavy snow cover and sufficient sunlight.

21 Ramanathan, V. et. al. Atmospheric brown clouds: Hemispherical and regional variations in long-range transport, absorption, and radiative forcing. J. Geophys. Res., 112, D22S21, doi:10.1029/2006JD008124.

The study uses satellite observations, global assimilated aerosol data sets, Atmospheric Brown Clouds (ABC) observatories, a Monte Carlo aerosol-cloud-radiation model and a regional chemical transport model (STEM-2K) to characterize the spatial extent of brown clouds, regional and megacity ABC hot spots, chemical composition and the direct radiative forcing. It presents the first annual cycle of aerosol observations and forcing from the ABC observatories in the Indo-Asia-Pacific regions. East Asia, Indo-Gangetic Plains, Indonesian region, southern Africa and the Amazon basin are the regional hot spots defined by the criteria that anthropogenic aerosol optical depths (AODs) should exceed 0.3 and absorbing AOD > 0.03. Over these hot spots, as well as in other polluted oceanic regions, the EC mass exceeds 0.5 ?g m-3, the OC mass exceeds 2 ?g m-3 and sulfate mass exceeds 10 ?g m-3 from the surface to 3 km. The brown clouds also have strong seasonal dependence. In the tropics the seasonal dependence is driven by pollution accumulating during the dry seasons, December to February in Northern Hemisphere tropics and June to August in Southern Hemisphere tropics. In the extratropics the pollution peaks during the summer. The brown cloud problem is not restricted to the tropical regions. Over the eastern half of US and western Europe the AODs exceeds 0.2 and absorption AODs exceed 0.02. Brown clouds also extend well into the western Pacific Ocean, the Indian Ocean reaching as far south as 60°S and the eastern Atlantic Ocean. The largest total SO_2 emission occurs over China and US, while SO_2 emission per unit surface area is maximum over Germany and England. The largest total EC and OC emissions occur over China, but the largest OC emission per unit surface area occur over India. As a result, the maximum negative annual mean TOA direct forcing is over India and Germany. The surface annual-diurnal mean dimming over the regional hot spots is of the order of-10 W m-2 and-20 W m-2 over megacity hotpots.

22 Menon, S., et. al. Climate Effects of Black Carbon Aerosols in China and India. 297 Science 5590, pp. 2250–2253, 27 September 2002, DOI: 10.1126/science.1075159.

In recent decades, there has been a tendency toward increased summer floods in south China, increased drought in north China, and moderate cooling in China and India while most of the world has been warming. Using a global climate model to investigate possible aerosol contributions to these trends, researchers found precipitation and temperature changes in the model that comparable to those observed if the aerosols included a large proportion of absorbing black carbon ("soot"), similar to observed amounts. Absorbing aerosols heat the air, alter regional atmospheric stability and vertical motions, and affect the large-scale circulation and hydrologic cycle with significant regional climate effects.

23 Andreae, M.O., GelencsÃ©r, A. 2006. Black carbon or brown carbon? The nature of light-absorbing carbonaceous aerosols. Atmospheric Chemistry and Physics 6, 3131–3148.

Although the definition and measurement techniques for atmospheric "black carbon" ("BC") or "elemental carbon" ("EC") have long been subjects of scientific controversy, the recent discovery of light-absorbing carbon that is not black ("brown carbon, or C brown") makes it imperative to reassess and redefine the components that make up light-absorbing carbonaceous matter (LAC) in the atmosphere. Evidence for the atmospheric presence of C brown comes from (1) spectral aerosol light absorption measurements near specific combustion sources, (2) observations of spectral properties of water extracts of continental aerosol, (3) laboratory studies indicating the formation of light-absorbing organic matter in the atmosphere, and (4) indirectly from the chemical analogy of aerosol species to colored natural humic substances. We show that brown carbon may severely bias measurements of "BC" and "EC" over vast parts of the troposphere, especially those strongly polluted by biomass burning, where the mass concentration of C brown is high relative to that of soot carbon. Chemical measurements to determine"EC" are biased by the refractory nature of C brown as well as by complex matrix interferences. Optical measurements of "BC" suffer from a number of problems: (1) many of the presently used instruments introduce a substantial bias into the determination of aerosol light absorption, (2) there is no unique conversion factor between light absorption and "EC"or "BC" concentration in ambient aerosols, and (3) the difference in spectral properties between the different types of LAC, as well as the chemical complexity of C brown, lead to several conceptual as well as practical complications. We also suggest that due to the sharply increasing absorption of C brown towards the UV, single-wavelength light absorption measurements may not be adequate for the assessment of absorption of solar radiation in the troposphere. We discuss the possible consequences of these effects for our understanding of tropospheric processes, including their influence on UV-irradiance, atmospheric photochemistry and radiative transfer in clouds.

24 Andreae, M.O., GelencsÃ©r, A. 2006. Black carbon or brown carbon? The nature of light-absorbing carbonaceous aerosols. Atmospheric Chemistry and Physics 6, 3131–3148.

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25 The Intergovernmental Panel on Climate Change (IPCC) was jointly established by the World Meteorological Organization (WMO) and the United Nations Environment Programme (UNEP) in 1988. Its terms of reference include (i) to assess available scientific and socio-economic information on climate change and its impacts and on the options for mitigating climate change and adapting to it and (ii) to provide, on request, scientific/technical/socio-economic advice to the Conference of the Parties (COP) to the United Nations Framework Convention on Climate Change (UNFCCC). From 1990, the IPCC has produced a series of Assessment Reports,

Special Reports, Technical Papers, methodologies and other products that have become standard works of reference, widely used by policymakers, scientists and other experts.

26 p. 2-5 and p. 2-33.

27 Sato M., Hansen J.,, et. al. Global atmospheric black carbon inferred from AERONET. Proceedings of the National Academy of Sciences Applied Biological Sciences, May 13, 2003.

AERONET, a network of well calibrated sunphotometers, provides data on aerosol optical depth and absorption optical depth at >250 sites around the world. The spectral range of AERONET allows discrimination between constituents that absorb most strongly in the UV region, such as soil dust and organic carbon, and the more ubiquitously absorbing black carbon (BC). AERONET locations, primarily continental, are not representative of the global mean, but they can be used to calibrate global aerosol climatologies produced by tracer transport models. We find that the amount of BC in current climatologies must be increased by a factor of 2–4 to yield best agreement with AERONET, in the approximation in which BC is externally mixed with other aerosols. The inferred climate forcing by BC, regardless of whether it is internally or externally mixed, is ~1 W/m^2 , most of which is probably anthropogenic. This positive forcing (warming) by BC must substantially counterbalance cooling by anthropogenic reflective aerosols. Thus, especially if reflective aerosols such as sulfates are reduced, it is important to reduce BC to minimize global warming.

28 Jacobson, M Z. Attribution of Regional and Global Climate Change: Relative Effects of Fossil-Fuel Soot, Methane, Other Greenhouse Gases and Particles, and Urbanization.

Black carbon, the main component of fossil-fuel soot (FFS), warms the air first by absorbing sunlight. Its absorption is enhanced by optical focusing when it becomes coated during vapor condensation or aerosol-aerosol coagulation, when it enters cloud drops or ice crystals during nucleation scavenging or aerosol-hydrometeor coagulation, and when it is surrounded by sea ice or snow following its precipitation or dry deposition. Its absorption over snow, sea ice, desert, fog, and cloud surfaces is further enhanced by the high reflectivity of these surfaces, which increases the number of photons hitting a soot particle. Although soot has a short lifetime, the air that it warms persists to larger scales. Soot's effective lifetime is also extended when it deposits to snow and sea ice. Since the organic material emitted with FFS is mostly hydrophobic, soot's effects on cloud activation are delayed thus weaker than sulfate's effects. Here new results for the climate response of fossil-fuel soot (black carbon, organic matter, sulfate), accounting for the factors listed above and for size resolution of aerosol particles and clouds and the aging of soot through the treatment of two size distributions, are presented. The results are compared with the climate responses of all anthropogenic aerosol particles, anthropogenic methane, all anthropogenic greenhouse gases, all anthropogenic greenhouse gases and aerosol particles, and urbanization. Fossil-fuel sources of black carbon treated include land-based, shipping, and aircraft. The study finds that fossil-fuel soot appears to have a stronger effect on global near-surface temperatures than either methane or urbanization, thus it may be the second-leading cause of historic near-surface global warming after carbon dioxide. Methane is found to have a stronger effect on near-surface temperatures than urbanization. FFS exacerbates warming due to greenhouse gases in Russia and over the Arctic sea ice. FFS causes little regional cooling in contrast to all aerosol particles, which, on their own, cause strong cooling in the southeast U.S., Europe, and China. The combination of all anthropogenic aerosol particles and greenhouse gases explains much of the difference between current and historic regional temperatures on a global scale. Whereas methane and other greenhouse gases cool the stratosphere, neither FFS nor

urbanization do so significantly. The results here apply only to fossil-fuel soot. Biomass-burning particles, which contain black carbon, have a different composition from FFS and a different climate effect.

Also, Amanda Leigh Haag, "The even darker side of brown clouds," Nature Reports Climate Change doi:10.1038/climate.2007.41.

29 Jacobson, M.Z. Strong radiative heating due to the mixing state of black carbon in

atmospheric aerosols. 409 Nature 6821, pp. 695–697 (2001).

Aerosols affect the Earth's temperature and climate by altering the radiative properties of the atmosphere. A large positive component of this radiative forcing from aerosols is due to black carbon-soot that is released from the burning of fossil fuel and biomass, and, to a lesser extent, natural fires, but the exact forcing is affected by how black carbon is mixed with other aerosol constituents. From studies of aerosol radiative forcing, it is known that black carbon can exist in one of several possible mixing states; distinct from other aerosol particles (externally mixed) or incorporated within them (internally mixed), or a black-carbon core could be surrounded by a well mixed shell. It had been previously assumed that aerosols existed predominantly as an external mixture. However, simulating the evolution of the chemical composition of aerosols shows that the mixing state and direct forcing of the black-carbon component approach those of an internal mixture, largely due to coagulation and growth of aerosol particles. This, in turn, implies a higher positive forcing from black carbon than previously thought, suggesting that the warming effect from black carbon may nearly balance the net cooling effect of other anthropogenic aerosol constituents. The magnitude of the direct radiative forcing from black carbon itself

exceeds that due to CH_4, suggesting that black carbon may be the second most important component of global warming after CO_2 in terms of direct forcing.

30 Jacobson, Mark Z. Strong radiative heating due to the mixing state of black carbon in atmospheric aerosols. Nature, v. 409, Issue 6821, pp. 695–697 (2001).

31 Andreae, M.O., GelencsÃ©r, A. 2006. Black carbon or brown carbon? The nature of light-absorbing carbonaceous aerosols. Atmospheric Chemistry and Physics 6, 3131–3148. Although the definition and measurement techniques for atmospheric "black carbon" ("BC") or "elemental carbon" ("EC") have long been subjects of scientific controversy, the recent discovery of light-absorbing carbon that is not black ("brown carbon, or C brown") makes it imperative to reassess and redefine the components that make up light-absorbing carbonaceous matter (LAC) in the atmosphere. Evidence for the atmospheric presence of C brown comes from (1) spectral aerosol light absorption measurements near specific combustion sources, (2) observations of spectral properties of water extracts of continental aerosol, (3) laboratory studies indicating the formation of light-absorbing organic matter in the atmosphere, and (4) indirectly from the chemical analogy of aerosol species to colored natural humic substances. We show that brown carbon may severely bias measurements of "BC" and "EC" over vast parts of the troposphere, especially those strongly polluted by biomass burning, where the mass concentration of C brown is high relative to that of soot carbon. Chemical measurements to determine"EC" are biased by the refractory nature of C brown as well as by complex matrix interferences. Optical measurements of "BC" suffer from a number of problems: (1) many of the presently used instruments introduce a substantial bias into the determination of aerosol light absorption, (2) there is no unique conversion factor between light absorption and "EC"or "BC" concentration in ambient aerosols, and (3) the difference in spectral properties between the different types of LAC, as well as the chemical complexity of C brown, lead to several conceptual as well as practical complications. We also suggest that due to the sharply increasing absorption of C brown towards the UV, single-wavelength light absorption measurements may not be adequate for the assessment of absorption of solar radiation in the troposphere. We discuss the possible consequences of these effects for our understanding of tropospheric processes, including their influence on UV-irradiance, atmospheric photochemistry and radiative transfer in clouds.

32 "Giant Atmospheric Brown Cloud Has Intercontinental Reach," ScienceDaily, Dec. 17, 2004. The south Asian brown haze covers most of the Arabian Sea, Bay of Bengal and the south Asian region. It occurs every year, and extends from about November to April and possibly longer. The black carbon and other species in the haze reduce the average radiative heating of the ocean by as much as 10 percent and enhance the atmospheric solar radiative heating by 50 to 100 percent. V. Ramanathan, V., Crutzen, P. J., Mitra, A. P. and Sikka, D. The Indian Ocean Experiment and the Asian Brown Cloud.

33 Veerabhadran Ramanathan, V., Ramana1, M.V., Roberts, G., et. al. Warming trends in Asia amplified by brown cloud solar absorption. Nature 448, 575–578 (2 August 2007).

Atmospheric brown clouds are mostly the result of biomass burning and fossil fuel consumption. They consist of a mixture of light-absorbing and light-scattering aerosols and therefore contribute to atmospheric solar heating and surface cooling. The sum of the two climate forcing terms—the net aerosol forcing effect—is thought to be negative and may have masked as much as half of the global warming attributed to the recent rapid rise in greenhouse gases. There is, however, at least a fourfold uncertainty in the aerosol forcing effect. Atmospheric solar heating is a significant source of the uncertainty, because current estimates are largely derived from model studies. Here we use three lightweight unmanned aerial vehicles that were vertically stacked between 0.5 and 3 km over the polluted Indian Ocean. These unmanned aerial vehicles deployed miniaturized instruments measuring aerosol concentrations, soot amount and solar fluxes. During 18 flight missions the three unmanned aerial vehicles were flown with a horizontal separation of tens of metres or less and a temporal separation of less than ten seconds, which made it possible to measure the atmospheric solar heating rates directly. We found that atmospheric brown clouds enhanced lower atmospheric solar heating by about 50 percent. Our general circulation model simulations, which take into account the recently observed widespread occurrence of vertically extended atmospheric brown clouds over the Indian Ocean and Asia, suggest that atmospheric brown clouds contribute as much as the recent increase in anthropogenic greenhouse gases to regional lower atmospheric warming trends. We propose that the combined warming trend of 0.25 K per decade may be sufficient to account for the observed retreat of the Himalayan glaciers.

34 Jacobsen, M.Z. The climate response of fossil-fuel and biofuel soot, accounting for soot's feedback to snow and sea ice albedo and emissivity, J. Geophys. Res. 109,D21201, doi:10.1029/2004JD004945, 2004.

35 Black Soot and Snow: A Warmer Combination

Hansen and Nazarenko used a leading worldwide-climate computer model to simulate effects of greenhouse gases and other factors on world climate. The model incorporated data from NASA spacecraft that monitor the Earth's surface, vegetation, oceans and atmospheric qualities. The calculated global warming from soot in snow and ice, by itself in an 1880–2000 simulation, accounted for 25 per-

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The researchers found that observed warming in the Northern Hemisphere was large in the winter and spring at middle and high latitudes. These observations were consistent with the researchers' climate model simulations, which showed some of the largest warming effects occurred when there was heavy snow cover and sufficient sunlight.

36 Flanner, M.G. et. Al. Present-day climate forcing and response from black carbon in snow. J. Geophys. Res., 112, D11202, doi:10.1029/2006JD008003.

To improve understanding of climate forcing and response from black carbon (BC) in snow, the Snow, Ice, and Aerosol Radiative (SNICAR) model was applied, coupled to a general circulation model with prognostic carbon aerosol transport. Interannual varying biomass burning BC emissions, snow aging, and aerosol scavenging by snow meltwater were accounted for. The rate of snow aging determines snowpack effective radius (r e), which directly controls snow reflectance and the magnitude of albedo change caused by BC. For a reasonable r e range, reflectance reduction from BC varies threefold. Inefficient meltwater scavenging keeps hydrophobic impurities near the surface during melt and enhances forcing. Applying biomass burning BC emission inventories for a strong (1998) and weak (2001) boreal fire year, global annual mean BC/snow surface radiative forcing from all sources (fossil fuel, biofuel, and biomass burning) were estimated at +0.054 (0.007–0.13) and +0.049 (0.007–0.12) W m-2, respectively. Snow forcing from only fossil fuel + biofuel sources is +0.043 W m-2 (forcing from only fossil fuels is +0.033 W m-2), suggesting that the anthropogenic contribution to total forcing is at least 80%. The 1998 global land and sea-ice snowpack absorbed 0.60 and 0.23 W m-2, respectively, because of direct BC/snow forcing. The forcing is maximum coincidentally with snowmelt onset, triggering strong snow-albedo feedback in local springtime. Consequently, the "efficacy" of BC/snow forcing is more than three times greater than forcing by CO_2. The 1998 and 2001 land snowmelt rates north of 50°N are 28% and 19% greater in the month preceding maximum melt of control simulations without BC in snow. With climate feedbacks, global annual mean 2-meter air temperature warms 0.15 and 0.10°C, when BC is included in snow, whereas annual arctic warming is 1.61 and 0.50°C. Stronger high-latitude climate response in 1998 than 2001 is at least partially caused by boreal fires, which account for nearly all of the 35% biomass burning contribution to 1998 arctic forcing. Efficacy was anomalously large in this experiment, however, and more research is required to elucidate the role of boreal fires, which we suggest have maximum arctic BC/snow forcing potential during April–June. Model BC concentrations in snow agree reasonably well (r = 0.78) with a set of 23 observations from various locations, spanning nearly 4 orders of magnitude. We predict concentrations in excess of 1000 ng g-1 for snow in northeast China, enough to lower snow albedo by more than 0.13. The greatest instantaneous forcing is over the Tibetan Plateau, exceeding 20 W m-2 in some places during spring. These results indicate that snow darkening is an important component of carbon aerosol climate forcing.

Research from ancient sediment cores indicates that a warming climate could make the world's arctic tundra far more susceptible to fires than previously thought. The findings are important given the potential for tundra fires to release organic carbon—which could add significantly to the amount of greenhouse gases already blamed for global warming.

http://www.sciencedaily.com/releases/2008/03/080304200902.htm

37 Bond, T. C. et. al. A technology-based global inventory of black and organic carbon

emissions from combustion, J. Geophys. Res., 109 (D14203),(2004). doi:10.1029/2003JD003,697.

38 Koch, D. & Hansen J. Distant origins of Arctic black carbon: A Goddard Institute for Space Studies Model E experiment, J. Geophys. Res.,110(D04204), (2005), doi:10.1029/2004JD005,296.

39 McConnell, J. R., et al. 20th-century industrial black carbon emissions altered arctic climate forcing, Science, 317(5843) (2007) 1381-1384, doi:10.1126/science.1144,856.

40 Quinn, P. K., et al. (2007), Short-lived pollutants in the Arctic: Their

climate impact and possible mitigation strategies, Submitted to Atmos. Chem. Phys.

41 Streets, D.G. et. al. Black carbon emissions in China. 35 Atmospheric Environment 25, Sep. 2001, pp. 4281–4296

Black carbon (BC) is an important aerosol species because of its global and regional influence on radiative forcing and its local effects on the environment and human health. We have estimated the emissions of BC in China, where roughly one-fourth of global anthropogenic emissions is believed to originate. China's high rates of usage of coal and biofuels are primarily responsible for high BC emissions. This paper pays particular attention to the application of appropriate emission factors for China and the attenuation of these emissions where control devices are used. Nevertheless, because of the high degree of uncertainty associated with BC emission factors, we provide ranges of uncertainty for our emission estimates, which are approximately a factor of eight. In our central case, we calculate that BC emissions in China in 1995 were 1342 Gg, about 83% being generated by the residential combustion of coal and biofuels. We estimate that BC emissions could fall to 1224 Gg by 2020. This 9% decrease in BC emissions can be contrasted with the expected

increase of 50% in energy use; the reduction will be obtained because of a transition to more advanced technology, including greater use of coal briquettes in place of raw coal in cities and towns. The increased use of diesel vehicles in the future will result in a greater share of the transport sector in total BC emissions. Spatially, BC emissions are predominantly distributed in an east–west swath across China's heartland, where the rural use of coal and biofuels for cooking and heating is widespread. This is in contrast to the emissions of most other anthropogenically derived air pollutants, which are closely tied to population and industrial centers.

42 [10] NEAS, L.M., SCHWARTZ, J., & DOCKERY, D.

A case-crossover analysis of air pollution and mortality in Philadelphia

Environmental Health Perspectives 107; 629–631; 1999

Reanalysis to counter criticism that previous data analysis by these authors did not sufficiently control for season and day of the week. Data from 1973–1980. Present finding with a case-crossover design is that 100 microgram/m3 increase in TSP is associated with increase in all cause mortality (OR of 1.056). For those over 65 years, OR was 1.074; and for cardiovascular disease was 1.063.

Data analysis confirms previous conclusions from time-series data.

[11]

SAMET, J.M., ZEGER, S.L., DOMINICI, F., CURRIERO, F., COURSAC, I., DOCKERY, D.W., SCHWARTZ, J., & ZANOBETTI, A.

The National morbidity, mortality, and air pollution study: Part II

Morbidity and mortality from air pollution in the United States

Health Effects Institute; Research Report: Number 94, Part II; June 2000; pp 82.

90 cities in different regions of the US, covering all areas. Daily PM_{10} values given for 1987 to 1994. Also O_3, SO_2, NO_2 and CO. Univariate analysis showed highest values for SO_2, with CO second, NO_2 third, and PM_{10} fourth. Distributed lag models give higher values, and authors note that the effects of pollution do not reach 0 until a lag of 5 days has occurred. Authors conclude: "Overall, this study provides strong evidence of association between PM_{10} levels and exacerbation of chronic heart and lung disease sufficiently severe to warrant hospitalization." Effect of PM_{10} on mortality generally higher in Northeast, industrial Midwest, and southern California than in other regions.

[1390] JERRETT, M., & FINKELSTEIN, M.

Geographies of risk in studies linking chronic air pollution exposure to health outcomes

J Toxicology & Environmental Health, Part A; 68; 1207–1242, 2005

A remarkable article that is difficult to summarize. It integrates new approaches to calculating individual and population exposures on the basis of using the nearest monitor coupled with the data on location from GPS information and time activity diaries. Extends this by also using individual data on occupational and socio-economic factors and comments on relevance of this information to longitudinal studies. "A key premise is that researchers should target studies with high degrees of overlap between geographies of exposure and susceptibility."

43 Glaser, B., et. al. Source Apportionment of Organic Pollutants of a Highway-Traffic-Influenced Urban Area in Bayreuth (Germany) Using Biomarker and Stable Carbon Isotope Signatures. Environ. Sci. Technol., 39 (11), 3911–3917, 2005. 10.1021/es050002p.

Traffic-and urban-influenced areas are prone to enhanced pollution with products of incomplete combustion of fossil fuels and biomass such as black carbon or polycyclic aromatic hydrocarbons (PAHs). Black carbon is composed of aromatic and graphitic structures and may act as a carrier for pollutants such as PAHs and heavy metals. However, little is known about possible contributions of traffic-derived black carbon to the black carbon inventory in soils. Similar uncertainties exist regarding the contribution of different pollutant sources to total PAH and black carbon contents. Therefore, the objective of this study was to quantify the importance of traffic pollution to black carbon and PAH inventories in soils. PAH contamination of soils adjacent to a major German highway in the urban area of Bayreuth with about 50,000 vehicles per day was in the same order of magnitude compared to highway-close soils reported in other studies. Using molecular (black carbon and PAHs) and compound-specific stable carbon isotope evidence (PAHs) it was demonstrated that this contamination originated not only from automobile exhausts, here primarily diesel, but also from tire abrasion and tailpipe soot which significantly contributed to the traffic-caused black carbon and PAH contamination. Low molecular weight PAHs were more widely transported than their heavy molecular counterparts (local distillation), whereas highway-traffic-caused black carbon contamination was distributed to at least 30 m from the highway.

44 In a carcinogenicity study, study groups of rats were treated with multiple dust instillations, i.e. 30 instillations of 0.5 mg amorphous SiO_2 at intervals of 2 weeks, 10 instillations of 0.5 mg of ultrafine carbon black or 1 mg coal at weekly intervals.

The analyses of the bronchoalveolar lavage fluid (BALF) 9 months after start of the life-time study found a 2.5-to 7.7-fold increase for lactate dehydrogenase (LDH), total protein, alkaline phosphatase and glutamyl transferase (GT) compared to the control. Cell

counts in the BALF were quartz without PVNO (leukocytes: 480.000, PMN: 190.000), quartz with PVNO (leukocytes: 300.000, PMN: 100.000), amorphous SiO_2 (leukocytes: 570.000, PMN: 315.000), carbon black (leukocytes: 390.000, PMN: 150.000) and coal (leukocytes: 200.000, PMN: 65.000).

45 Nemmar A, Hoet PH, Vanquickenborne B, Dinsdale D, Thomeer M, Hoylaerts MF, Vanbilloen H, Mortelmans L, Nemery B.

Five healthy volunteers, "Technegas," an aerosol consisting mainly of ultrafine (99m) Technetium-labeled carbon particles (<100 nm). The distribution of radioactivity after the inhalation of already after 1 minute radioactivity was detected in blood, reaching a maximum between 10 and 20 minutes, and remaining at this level up to 60 minutes. Thin layer chromatography of blood showed that in addition to a species corresponding to oxidized (99m)Tc, ie, pertechnetate, there was also a species corresponding to particle-bound (99m)Tc. Gamma camera images showed substantial radioactivity over the liver and other areas of the body. A similar study by others failed to replicate these results however. See Mills NL, Amin N, Robinson SD, Anand A, Davies J, Patel D, de la Fuente JM, Cassee FR, Boon NA, MacNee W, Millar AM, Donaldson K, Newby DE. Do inhaled carbon nanoparticles translocate directly into the circulation in humans? Am J Respir Crit Care Med. 173:426–431. doi: 10.1164/rccm.200506-865OC. 15-2-2006

46 GAUDERMAN, W.J., AVOL, E., GILLILAND, F., VORA, H., THOMAS, D., BERHANE, K., McCONNELL, R., KUENZLI, N., LURMANN, F., RAPPAPORT, E., MARGOLIS, H., BATES, D., & PETERS, J.The Effect of air pollution on lung development from 10 to 18 years of ageNew Engl. J. Med 351; 1057–1067, 20041759 children of average age 10 years followed for 8 years with annual review and PF testing. Rate of attrition was 10% per year. Recruited from 12 Southern California Communities. Community levels of pollutants show O_3 varying from 28 to 66 ppb from 10 am to 6 pm; PM_{10} from 15 to 69 micrograms/m^3; NO_2 from 4 to 40 ppb; $PM_{2.5}$ from 5 to 29 micrograms/m^3; Acid Vapor in ppb from 2 to 12 ppb; and elemental carbon from 0.1 to 1.3 micrograms/m^3.In both girls and boys, all pollutants except ozone were associated with slower rates of growth of FEV1 – for example for NO_2 over the range between communities, the growth of FEV_1 fell from about 1390 to 1290 in girls and from 2425 to 2330 in boys. Exclusion of highest and lowest points did not affect the regression relationship. Highest deficits recorded in relation to acid vapor exposure. Difference in MMEF generally larger than for other parameters, with the highest deficit of – 211 ml/sec recorded for NO_2. Table presents analysis of results from the main model, and for different models. These show same results for nonasthmatics; and no effects from gas stove use, maternal smoking in utero, pets at home, parental level of education, or short term effects of pollutants. A pioneer study.

47 S. Franco Suglia1, S.F. et. al. Association of Black Carbon with Cognition among Children in a Prospective Birth Cohort Study. Am J Epidemiol. 2008 Feb 1;167(3):280–6.

To assess relationship between black carbon and cognition, 202 Boston, Massachusetts, children (mean age = 9.7 years (standard deviation, 1.7) were enrolled in a prospective birth cohort study (1986–2001). Local black carbon levels were estimated using a validated spatiotemporal land-use regression model (mean predicted annual black carbon level, 0.56 mug/m(3) (standard deviation, 0.13). The Wide Range Assessment of Memory and Learning and the Kaufman Brief Intelligence Test were administered for assessment of cognitive constructs. In analysis adjusting for sociodemographic factors, birth weight, blood lead level, and tobacco smoke exposure, black carbon (per interquartile-range increase) was associated with decreases in the vocabulary (-2.2, 95% confidence interval (CI):-5.5, 1.1), matrices (-4.0, 95% CI:-7.6,-0.5), and composite intelligence quotient (-3.4, 95% CI:-6.6,-0.3) scores of the Kaufman Brief Intelligence Test and with decreases on the visual subscale (-5.4, 95% CI:-8.9,-1.9) and general index (-3.9, 95% CI:-7.5,-0.3) of the Wide Range Assessment of Memory and Learning. Higher levels of black carbon predicted decreased cognitive function across assessments of verbal and nonverbal intelligence and memory constructs.

48 KIM, J.J., SMORODINSKY, S., LIPSETT, M., SINGER, B.C., HODGSON, A.T., & OSTRO, B.Traffic-related air pollution near busy roads

Am J Respir Crit Care Med 170; 520–526; 2004

School-based cross sectional study conducted in Alameda County, in California which includes Oakland and about 20 kilometers south of it. Children in grades 3–5 enrolled, and 1,109 questionnaires were completed. 30% of households had incomes below the poverty line. Respiratory symptoms were associated with proximity to heavily traveled roads, and among those at their current residences for at least a year, the adjusted odds ratio for asthma in relationship to the interquartile difference in NO_2, was 1.07. The association with black carbon was also significant. Bronchitis prevalence rates were also associated with higher levels of both pollutants. Of the schools, lowest NO_2 was 19 ppb, and highest was 31 ppb.

49 [1340]MARSHALL, J.D., & BEHRENTZ, E.Vehicle self-pollution intake fraction: children's exposure to school bus emissionsEnviron Sci Technol 2005: 39; 2559-2563Data from South Coast Air Basin of California using tracer gas (SF_6) to estimate children's exposures. Six buses studied during nine runs with windows open and seven runs with closed windows. Results show high exposures of children to the school bus emissions, with exposures many times greater for the students on a particular bus than for the population at large.

50 Association of air pollution with increased incidence of ventricular tachyarrhythmias recorded by implanted cardioverter defibrillators

Environmental Health Perspectives, June, 2005 by Douglas W. Dockery, Heike Luttmann-Gibson, David Q. Rich, Mark S. Link, Murray A. Mittleman, Diane R. Gold, Petros Koutrakis, Joel D. Schwartz, Richard L. Verrier

Epidemiologic studies have demonstrated a consistent link between sudden cardiac deaths and particulate air pollution. We used implanted cardioverter defibrillator (ICD) records of ventricular tachyarrhythmias to assess the role of air pollution as a trigger of these potentially life-threatening events. The study cohort consisted of 203 cardiac patients with ICD devices in the Boston metropolitan area who were followed for an average of 3.1 years between 1995 and 2002. Fine particle mass and gaseous air pollution plus temperature and relative humidity were measured on almost all days, and black carbon, sulfate, and particle number on a subset of days. Date, time, and intracardiac electrograms of ICD-detected arrhythmias were downloaded at the patients' regular follow-up visits (about every 3 months). Ventricular tachyarrhythmias were identified by electrophysiologist review. Risk of ventricular arrhythmias associated with air pollution was estimated with logistic regression, adjusting for season, temperature, relative humidity, day of the week, patient, and a recent prior arrhythmia. We found increased risks of ventricular arrhythmias associated with 2-day mean exposure for all air pollutants considered, although these associations were not statistically significant. We found statistically significant associations between air pollution and ventricular arrhythmias for episodes within 3 days of a previous arrhythmia. The associations of ventricular tachyarrhythmias with fine particle mass, carbon monoxide, nitrogen dioxide, and black carbon suggest a link with motor vehicle pollutants. The associations with sulfate suggest a link with stationary fossil fuel combustion sources. Key words: air pollution, arrhythmias, epidemiology, fibrillation, heart arrest. Environ Health Perpect 113:670–674 (2005). doi:10.1289/ehp.7767 available via http://dx.doi.org/[Online 18 February 2005]

51 Peters, A., et. al. Air pollution and incidence of cardiac arrhythmia. Epidemiology. 2000 Jan;11 (1):11–7 10615837.

Air pollution episodes are associated with increased cardiovascular hospital admissions and mortality in time-series studies. Researchers tested the hypothesis that patients with implanted cardioverter defibrillators experience potentially life-threatening arrhythmias after such air pollution episodes. Comparing defibrillator discharge interventions among 100 patients with such devices in eastern Massachusetts, according to variations in concentrations of particulate matter, black carbon, and gaseous air pollutants that were measured daily for the years 1995 through 1997. A 26-ppb increase in nitrogen dioxide was associated with increased defibrillator interventions 2 days later (odds ratio = 1.8; 95% confidence interval = 1.1-2.9). Patients with ten or more interventions experienced increased arrhythmias in association with nitrogen dioxide, carbon monoxide, black carbon, and fine particle mass. These results suggest that elevated levels of air pollutants are associated with potentially life-threatening arrhythmia leading to therapeutic interventions by an implanted cardioverter defibrillator.

52 Gold, D.R., at. al. Air pollution and ST-segment depression in elderly subjects

Environmental Health Perspectives, July, 2005

Increased levels of daily ambient particle pollution have been associated with increased risk of cardiovascular morbidity. Black carbon (BC) is a measure of the traffic-related component of particles. Associations between ambient pollution and ST-segment levels in a repeated-measures study including 269 observations on 24 active Boston residents 61–88 years of age, each observed up to 12 times from June through September 1999. The protocol involved continuous Holter electrocardiogram monitoring including 5 minutes of rest, 5 minutes of standing, 5 minutes of exercise outdoors, 5 minutes of recovery, and 20 cycles of paced breathing. Pollution-associated ST-depression was estimated for a 10th-to 90th-percentile change in BC. The average ST-segment level, referenced to the P-R isoelectric values, for each portion of the protocol was calculated. The mean BC level in the previous 12 hours, and the BC level 5 hours before testing, predicted ST-segment depression in most portions of the protocol, but the effect was strongest in the postexercise periods. During postexercise rest, an elevated BC level was associated with-0.1 mm ST-segment depression ($p = 0.02$ for 12-hr mean BC; $p = 0.001$ for 5-hr BC) in continuous models. Elevated BC also predicted increased risk of ST-segment depression [greater than or equal to] 0.5 mm among those with at least one episode of that level of ST-segment depression. Carbon monoxide was not a confounder of this association. ST-segment depression, possibly representing myocardial ischemia or inflammation, is associated with increased exposure to particles, including black carbon, whose predominant source is traffic.

53 Jansen, K. L., et. al. Associations between health effects and particulate matter and black carbon in subjects with respiratory disease. Environ Health Perspect 113:1741–1746 (2005)

Measurements of fractional exhaled nitric oxide, spirometry, blood pressure, oxygen saturation of the blood, and pulse rate in 16 older subjects with asthma or chronic obstructive pulmonary disease (COPD) in Seattle, Washington. Data collected daily for 12 days. Simultaneously collected PM_{10} and $PM._{2.5}$ filter samples at a central outdoor site, as well as outside and inside the subjects' homes. Personal PM_{10} filter samples were also collected. All filters were analyzed for mass and light absorbance. Analyzed within-subject associa-

tions between health outcomes and air pollution metrics using a linear mixed-effects model with random intercept, controlling for age, ambient relative humidity, and ambient temperature. For the 7 subjects with asthma, a 10 microg/cubic meter increase in 24-hr average outdoor PM_{10} and $PM_{2.5}$ was associated with a 5.9 [95% confidence interval (CI), 2.9–8.9] and 4.2 ppb (95% CI, 1.3–7.1) increase in FE_{NO}, respectively. A 1 microg/cubic meter increase in outdoor, indoor, and personal black carbon (BC) was associated with increases in FE_{NO} of 2.3 ppb (95% CI, 1.1–3.6), 4.0 ppb (95% CI, 2.0–5.9), and 1.2 ppb (95% CI, 0.2–2.2), respectively. No significant association was found between PM or BC measures and changes in spirometry, blood pressure, pulse rate, or SaO2.

54 Raitakari1,O.T. and Celermajer, D.S. Flow-mediated dilatation. Br J Clin Pharmacol. 2000 November; 50(5): 397–404.

Arterial endothelial dysfunction is one of the key early events in atherogenesis, preceding structural atherosclerotic changes. It is also important in the late stages of obstructive atherosclerosis, predisposing to constriction and/or thrombosis. Endothelial function can be measured in coronary arteries and in the periphery by measuring vasomotor function after intra-arterial infusion of pharmacologic substances which enhance the release of endothelial nitric oxide. The disadvantage of these methods is their invasive nature, which generally makes them unsuitable for studies involving asymptomatic subjects. For this reason, noninvasive tests of endothelial function have been developed. In the most widely used of these, an ultrasound-based method, arterial diameter is measured in response to an increase in shear stress, which causes endothelium-dependent dilatation. Endothelial function assessed by this method correlates with invasive testing of coronary endothelial function, as well as with the severity and extent of coronary atherosclerosis. This noninvasive endothelial function testing has provided valuable insights into early atherogenesis, as well as into the potential reversibility of endothelial dysfunction by various strategies, including pharmacological agents (lipid lowering, ACE inhibition), l-arginine, antioxidants and hormones.

55 Adar,S.D., et. al. Ambient and Microenvironmental Particles and Exhaled Nitric Oxide Before and After a Group Bus Trip. Environ Health Perspect. 2007 April; 115(4): 507–512.

To examine associations between particle exposures and exhaled nitric oxide (FENO) 44 senior citizens, involving repeated trips aboard a diesel bus, samples of FENO collected before and after the trips were regressed against microenvironmental and ambient particle concentrations using mixed models controlling for subject, day, trip, vitamins, collection device, mold, pollen, room air nitric oxide, apparent temperature, and time to analysis. Although ambient concentrations were collected at a fixed location, continuous group-level personal samples characterized microenvironmental exposures throughout facility and trip periods. Two portable carts containing continuous air pollution monitors were used to measure group-level microenvironmental exposures to traffic-related pollutants, including fine particulate mass (< 2.5 microg/m aerodynamic diameter; $PM_{2.5}$), black carbon, and size-specific particle counts. Concentrations of $PM_{2.5}$, black carbon, fine particle counts, and coarse particle counts were systematically higher aboard the bus and during the trips than during periods spent at the living facilities. Black carbon, a common indicator for traffic, was most strongly enhanced by the bus trips, with a 9-fold increase in the mean concentration during bus periods. Concentrations of $PM_{2.5}$ and black carbon in ambient air were strongly correlated (r = 0.74). In pre-trip samples, both microenvironmental and ambient exposures to fine particles were positively associated with FENO. For example, an interquartile increase of 4 microg/m3 in the daily microenvironmental $PM_{2.5}$ concentration was associated with a 13% [95% confidence interval (CI), 2–24%) increase in FENO. After the trips, however, FENO concentrations were associated pre-dominantly with microenvironmental exposures, with significant associations for concentrations measured throughout the whole day. Associations with exposures during the trip also were strong and statistically significant with a 24% (95% CI, 15–34%) increase in FENO predicted per interquartile increase of 9 microg/m3 in $PM_{2.5}$.

56 Hoek G, Brunekreef B, Goldbohm S, Fischer P, van den Brandt PA. Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. Lancet 2002;360(9341):1203–9.

To assess the relation between traffic-related air pollution and mortality in participants of the Netherlands Cohort study on Diet and Cancer (NLCS), an ongoing study, a random sample of 5,000 was selected from the full cohort (age 55–69 years) from 1986 to 1994. Long-term exposure to traffic-related air pollutants (black smoke and nitrogen dioxide) was estimated for the 1986 home address. Exposure was characterized with the measured regional and urban background concentration and an indicator variable for living near major roads. The association between exposure to air pollution and (cause specific) mortality was assessed with Cox's proportional hazards models, with adjustment for potential confounders. Of 4,492 participants, 489 (11%) with data died during the follow-up period. Cardiopulmonary mortality was associated with living near a major road (relative risk 1.95, 95% CI 1.09–3.52) and, less consistently, with the estimated ambient background concentration (1.34, 0.68–2.64). The relative risk for living near a major road was 1.41 (0.94–2.12) for total deaths. Non-cardiopulmonary, non-lung cancer deaths were unrelated to air pollution (1.03, 0.54–1.96 for living near a major road).

57 Peters A, von Klot S, Heier M, Trentinaglia I, Hörmann A, Wichmann H-E et al. (2004)

Exposure to Traffic and the Onset of Myocardial Infarction.

N Engl J Med; 351(17):1721–1730.

To assess whether the relationship between exposure to traffic-related air pollutants and onset of myocardial infarction 691 cases of myocardial infarction were identified using data from the Cooperative Health Research in the Region of Augsburg Myocardial Infarction Registry in Augsburg, in southern Germany, for February 1999 to July 2001, who had survived for at least 24 hours after the event, completed the registry's standardized interview, and provided information on factors that may have triggered the myocardial infarction. Data on subjects' activities during the four days preceding the onset of symptoms were collected with the use of patient diaries. An association was found between exposure to traffic and the onset of a myocardial infarction within one hour afterward (odds ratio, 2.92; 95 percent confidence interval, 2.22 to 3.83; P<0.001). The time the subjects spent in cars, on public transportation, or on motorcycles or bicycles was consistently linked with an increase in the risk of myocardial infarction. Adjusting for the level of exercise on a bicycle or for getting up in the morning changed the estimated effect of exposure to traffic only slightly (odds ratio for myocardial infarction, 2.73; 95 percent confidence interval, 2.06 to 3.61; P<0.001). The subject's use of a car was the most common source of exposure to traffic; nevertheless, there was also an association between time spent on public transportation and the onset of a myocardial infarction one hour later, showing that transient exposure to traffic increases the risk of myocardial infarction in susceptible persons.

Peters A, Dockery DW, Muller JE, Mittleman MA (2001)

Increased particulate air pollution and the triggering of myocardial infarction.

Circulation. 2001 Jun 12;103(23):2810–5.

To assess whether increases in concentrations of ambient particles can trigger the onset of acute myocardial infarction (MI), 772 patients with MI in the greater Boston area between January 1995 and May 1996 were interviewed as part of the Determinants of Myocardial Infarction Onset Study. Hourly concentrations of particle mass <2.5 microm ($PM_{2.5}$), carbon black, and gaseous air pollutants were measured. A case-crossover approach was used to analyze the data for evidence of triggering. The risk of MI onset increased in association with elevated concentrations of fine particles in the previous 2-hour period. In addition, a delayed response associated with 24-hour average exposure 1 day before the onset of symptoms was observed. Multivariate analyses considering both time windows jointly revealed an estimated odds ratio of 1.48 associated with an increase of 25 microg/m(3) $PM_{2.5}$ during a 2-hour period before the onset and an odds ratio of 1.69 for an increase of 20 microg/m(3) $PM_{2.5}$ in the 24-hour period 1 day before the onset (95% CIs 1.09, 2.02 and 1.13, 2.34, respectively). The coarse fraction of PM_{10}, black carbon, and the gaseous air pollutants including carbon monoxide, NO_2, SO_2, and ozone showed positive associations, but none was statistically significant.

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71 Boy E., Bruce, N. & Delgado, H. Birth weight and exposure to kitchen wood smoke during pregnancy in rural Guatemala. Environ Health Perspect. 2002 Jan;110(1):109-14.

To assess whether domestic use of wood fuel is associated with reduced birth weight, independent of key maternal, social, and economic confounding factors, investigators studied 1,717 women and newborn children in rural and urban communities in rural Guatemala. They identified subjects through home births reported by traditional birth attendants in six rural districts (n = 572) and all public hospital births in Quetzaltenango city during the study period (n = 1,145). All were seen within 72 hr of delivery, and data were collected on the type of household fuel used, fire type, and socioeconomic and other confounding factors. Smoking among women in

the study community was negligible. Children born to mothers habitually cooking on open fires (n = 861) had the lowest mean birth weight of 2,819 g [95% confidence interval (CI), 2,790-2,848]; those using a chimney stove (n = 490) had an intermediate mean of 2,863 g (95% CI, 2,824-2,902); and those using the cleanest fuels (electricity or gas, n = 365) had the highest mean of 2,948 g (95% CI, 2,898-2,998) (p< 0.0001). The percentage of low birth weights (< 500 g) in these three groups was 19.9% (open fire), 16.8% (chimney stove), and 16.0% (electricity/gas), (trend (p = 0.08). Confounding factors were strongly associated with fuel type, but after adjustment wood users still had a birth weight 63 g lower (p = 0.05; 95% CI, 0.4-126). This is the first report of an association between biofuel use and reduced birth weight in a human population. Although there is potential for residual confounding despite adjustment, the better-documented evidence on passive smoking and a feasible mechanism through carbon monoxide exposure suggest this association may be real. Because two-thirds of households in developing countries still rely on biofuels and women of childbearing age perform most cooking tasks, the attributable risk arising from this association, if confirmed, would be substantial.

72 Rinne, S.T.. et. al. Use of Biomass Fuel Is Associated with Infant Mortality and Child Health in Trend Analysis Am. J. Trop. Med. Hyg., 76(3), 2007, pp. 585-59.

Biomass fuel used for cooking results in widespread exposure to indoor air pollution (IAP), affecting nearly 3 billion people throughout the world. Few studies, however, have tested for an exposure–response relationship between biomass fuel and health outcomes. To assess the relationship between biomass fuel, infant mortality, and children's respiratory symptoms. Eighty households in a rural community in Ecuador were selected based on their use of biomass fuel and questioned regarding a history of infant mortality and children's respiratory symptoms. Carbon monoxide (CO) and particulate matter (PM) were measured in a subset of these homes to confirm the relationship between biomass fuel use and IAP. Results showed a significant trend for higher infant mortality among households that cooked with a greater proportion of biomass fuel (P = 0.008). Similar trends were noted for history of cough (P = 0.02) and earache (P < 0.001) among children living in these households.

73 Kumar, S. & Mehra, S. ARI And Indoor Air Pollution: Its Burden And Correlation. The Internet Journal of Pulmonary Medicine. 2007. Volume 8 Number 2. http://www.ispub.com/ostia/index.php?xmlFilePath=journals/ijpm/vol8n2/ari.xml#r19

74 World Health Organization, Indoor air pollution in developing countries: a major environmental and public health challenge. Bulletin of the World Health Organization 2000.

75 Bruce N., Perez-Padilla R., & Albalak, R. Indoor air pollution in developing countries: a major environmental and public health challenge. Bull World Health Organ. 2000;78(9):1078-92.

Around 50% of people, almost all in developing countries, rely on coal and biomass in the form of wood, dung and crop residues for domestic energy. These materials are typically burnt in simple stoves with very incomplete combustion. Consequently, women and young children are exposed to high levels of indoor air pollution every day. There is consistent evidence that indoor air pollution increases the risk of chronic obstructive pulmonary disease and of acute respiratory infections in childhood, the most important cause of death among children under 5 years of age in developing countries. Evidence also exists of associations with low birth weight, increased infant and perinatal mortality, pulmonary tuberculosis, nasopharyngeal and laryngeal cancer, cataract, and, specifically in respect of the use of coal, with lung cancer. Conflicting evidence exists with regard to asthma. All studies are observational and very few have measured exposure directly, while a substantial proportion have not dealt with confounding. As a result, risk estimates are poorly quantified and may be biased. Exposure to indoor air pollution may be responsible for nearly 2 million excess deaths in developing countries and for some 4% of the global burden of disease. Indoor air pollution is a major global public health threat requiring greatly increased efforts in the areas of research and policy-making. Research on its health effects should be strengthened, particularly in relation to tuberculosis and acute lower respiratory infections. A more systematic approach to the development and evaluation of interventions is desirable, with clearer recognition of the interrelationships between poverty and dependence on polluting fuels.

76 U.S. Environmental Protection Agency (EPA) (2002) Health assessment document for diesel engine exhaust. Prepared by the National center for Environmental Assessment, Washington, D.C.

77 Mills, N.L. Ischemic and Thrombotic Effects of Dilute Diesel-Exhaust Inhalation in Men with Coronary Heart Disease. N Engl J Med 2007; 357:1075–1082.

Investigators recruited 20 men who had had a prior MI but were asymptomatic with no exertional angina and who were on optimal secondary-prevention medication. In the double-blind, randomized, crossover study—conducted at Umea University in Sweden—the men were exposed for one hour to either filtered air or dilute diesel-exhaust fumes (300 _g/m3) while intermittently riding a bicycle ergometer for two 15-minute periods, separated by 15-minute rest periods. Mills said the levels of diesel fumes in the study were chosen to mimic the sorts of air pollution that would be encountered in everyday life. During exposure, myocardial ischemia was quantified by ST-segment analysis using continuous 12-lead ECG. Six hours after exposure, vasomotor and fibrinolytic functions were assessed by means of intra-arterial agonist infusions. Heart rate increased similarly with exercise during both air and diesel exposures,

but there was as much as a threefold increase in myocardial ischemia during exposure to diesel-exhaust fumes compared with filtered air (-22.4 vs-8 mV-sec; p<0.001). Exposure to diesel fumes did not aggravate preexisting vasomotor dysfunction, but it did dampen the acute release of endothelial tissue plasminogen activator by 35%.

78 Stefan Speidl, W. S. et. al. An increase of C-reactive protein is associated with enhanced activation of endogenous fibrinolysis at baseline but an impaired endothelial fibrinolytic response after venous occlusion. J Am Coll Cardiol, 2005; 45:30–34, doi:10.1016/j.jacc.2004.09.052.

To determine whether chronic inflammation of the vascular wall might be associated with an impaired activation of the fibrinolytic system, 50 patients were enrolled six months after their first myocardial infarction. Plasma levels of the inflammatory marker C-reactive protein (CRP) were determined at basal conditions, and the fibrinolytic parameters tissue-type plasminogen activator (t-PA) and plasminogen activator inhibitor type-1 (PAI-1) were measured at basal conditions and after a standardized venous occlusion (VO) of the forearm. Patients with high CRP levels (Æ3 mg/l) showed a significantly higher t-PA activity at baseline compared with patients with medium (1 to 2.9 mg/l) and low (<1 mg/l) CRP levels ($p < 0.005$). In contrast, patients with low CRP levels showed a higher increase of t-PA activity ($p < 0.05$) and a higher reduction of PAI-1 activity during VO ($p < 0.05$) compared with patients with medium and high CRP levels. A multivariate analysis that included cardiovascular risk factors and medical treatment showed that CRP is an independent predictor of the t-PA response after a standardized VO. Chronic low-grade inflammation is associated with enhanced activation of endogenous fibrinolysis at baseline but a reduced fibrinolytic response to VO. This impaired endogenous fibrinolytic capacity might be an important contributor to the increased coronary event rate associated with elevated CRP levels.

79 The quote is found in Lisa Nainggolan, “First Evidence of Causal Link Between Diesel Fumes and Ischemia,” Sep. 17, 2007

September 17, 2007—A new study has shown that brief exposure to dilute diesel-exhaust fumes during exercise promotes myocardial ischemia and inhibits endogenous fibrinolytic capacity in men with stable coronary disease.[1] “Our findings point to ischemic and thrombotic mechanisms that may explain in part the observation that exposure to combustion-derived air pollution is associated with adverse cardiovascular events,” say Dr Nick Mills (Edinburgh University, Scotland) and colleagues in their paper in the September 13, 2007 issue of the New England Journal of Medicine.

Mills told heartwire that while a wealth of large-scale and robust studies have been conducted in the past five to 10 years looking at the association between air pollution and adverse cardiac outcomes, “these have been challenged because it’s been impossible to prove causality. What’s been missing in this field is an understanding of what the mechanism is that links exposure to adverse outcomes. We’re the first group to have conducted controlled exposures anywhere in the world, and our results are important because they provide strength to the observational studies, and they show that this is indeed a causal relationship we are talking about.”

The study is—Mills, N.L. Ischemic and Thrombotic Effects of Dilute Diesel-Exhaust Inhalation in Men with Coronary Heart Disease. N Engl J Med 2007; 357:1075–1082.

Although exposure to air pollution from traffic is associated with adverse cardiovascular events, the mechanisms for this association are unknown. To identify ischemic and thrombotic mechanisms that may explain in part the observation that exposure to combustion-derived air pollution is associated with adverse cardiovascular events, investigators conducted a controlled exposure to dilute diesel exhaust in patients with stable coronary heart disease to determine the direct effect of air pollution on myocardial, vascular, and fibrinolytic function.

In a double-blind, randomized, crossover study, 20 men with prior myocardial infarction were exposed, in two separate sessions, to dilute diesel exhaust (300 _g per cubic meter) or filtered air for 1 hour during periods of rest and moderate exercise in a controlled-exposure facility. During the exposure, myocardial ischemia was quantified by ST-segment analysis using continuous 12-lead electrocardiography. Six hours after exposure, vasomotor and fibrinolytic function were assessed by means of intraarterial agonist infusions.

During both exposure sessions, the heart rate increased with exercise (P<0.001); the increase was similar during exposure to diesel exhaust and exposure to filtered air (P=0.67). Exercise-induced ST-segment depression was present in all patients, but there was a greater increase in the ischemic burden during exposure to diesel exhaust (–22±4 vs. –8±6 millivolt seconds, P<0.001). Exposure to diesel exhaust did not aggravate preexisting vasomotor dysfunction, but it did reduce the acute release of endothelial tissue plasminogen activator (P=0.009; 35% decrease in the area under the curve).

The investigators concluded that brief exposure to dilute diesel exhaust promotes myocardial ischemia and inhibits endogenous fibrinolytic capacity in men with stable coronary heart disease. Our findings point to ischemic and thrombotic mechanisms that may explain in part the observation that exposure to combustion-derived air pollution is associated with adverse cardiovascular events. (ClinicalTrials.gov number, NCT00437138 [ClinicalTrials.gov].)

Source Information

80 McConnell, R., Berhane, K., Gilliand, F., London, S.J., Islam, T., Gauderman, W.J., Avol, E., Margolis, H.G., & Peters, J.M.

Asthma in exercising children exposed to ozone: a cohort study

Lancet 2002; 359; 386–391

From the Southern California Children's Study. Relevant numbers;

5762 children completed baseline questionnaires;

479 excluded because they were not at school when the questionnaire was administered;

883 excluded for a history of asthma;

312 excluded because of missing answers to "wheezing" questions;

26 excluded for chest illnesses such as cystic fibrosis:

527 excluded because they had less than one year of follow-up;

This left 3535 children with no initial history of asthma; 2752 of these had no history of wheezing; 1934 played sports; 273 played three or more team sports;

There were 46 low pollution communities (O_3 daytime mean 40.0 ppb); and 46 high pollution communities (O3 mean 59.6 ppb). PM_{10} twice as high in high ozone communities (43.3 vs 21.6) and $PM_{2.5}$ three times higher (21.4 vs 7.6). NO_2 three times higher in high ozone communities (29.2 vs 10.8 ppb).

It was shown that development of asthma prospectively was three times higher in children participating in more than 3 sports in high ozone communities, compared to children who did no sports in both communities or did fewer than 3 sports in high ozone communities. No differences in development of asthma if other pollutants were studied. Excellent discussion; 32 references. Convincing argument as to why standard cross-sectional comparisons might show no differences in prevalence of asthma.

81 See, e.g., Agricultural Research Services, U.S. Department of Agriculture, "Effects of Ozone Air Pollution on Plants," http://www.ars.usda.gov/Main/docs.htm?docid=8453. Ozone penetrates stomata and destroys organic molecules in the plant tissue.

82 See H Sandermann, A. R. Wellburn & R.L. Heath (Eds), Forest Decline and Ozone: A Comparison of Controlled Chamber and Field Experiments, Springer Verlag, Berlin, 1997, explores the relationship between forest decline and ozone. It comprises a broad range of methods concerning field ecology, model ecosystem research, and basic physiological and biochemical research.

83 See e.g. Bell, M.L. et. Al. The Exposure-Response Curve for Ozone and Risk of Mortality and the Adequacy of Current Ozone Regulations. Environmental Health Perspectives Volume 114, Number 4, April 2006.

84 Shindell, D. (2007), Local and remote contributions to Arctic warming, Geophys. Res. Lett., 34, L14704, doi:10.1029/2007GL030221.

Investigating the relative impact of local and remote radiative forcing by tropospheric aerosols and ozone on Arctic climate using GISS climate model simulations, Shindell found that during boreal summer, Arctic climate is well-correlated with either the global or Arctic forcing. During other seasons, however, large-scale dynamics strongly influence the Arctic, so that the surface temperature response follows the global or Northern Hemisphere extratropical forcing much more closely. The decoupling is so strong that Arctic surface temperature trends often show the opposite sign to the local forcing. The analysis also demonstrates that ozone and aerosols affect Arctic climate more strongly per unit global forcing than well-mixed greenhouse gases, typically 2.5–5 times in non-summer seasons, making them powerful levers for influencing Arctic climate. However, controlling atmospheric burdens of climate-altering pollutants outside the polar region appears to be at least as important as controlling them within for mitigation of Arctic warming.

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89 Bascom R, Naclerio RM, Fitzgerald TK, Kagey-Sobotka A, Proud D. Effect of ozone inhalation on the response to nasal challenge with antigen of allergic subjects. Am Rev Respir Dis 1990;142:594–601.

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93 Gardner DE. Use of experimental airborne infections for monitoring altered host defenses. Environ Health Perspect 1982; 43:99–107.

94 Gilmour MI, Park P, Selgrade MK. Ozone-enhanced pulmonary infection with Streptococcus Zooepidemicus in mice: The role of alveolar macrophage function and capsular virulence factors. Am Rev Respir Dis 1993;147:753–60.

95 Gilmour MI, Selgrade MK. A comparison of the pulmonary defenses against Streptococcal infection in rats and mice following O_3 exposure: A possible mechanisms of disease resistance in rats. Toxicol Appl Pharmacol 1993.

96 Harkema JR, Plopper CG, Hyde DM, George JAS, Wilson DW, Dungworth DL. Response of the macaque nasal epithelium to ambient levels of ozone: a morphologic and morphometric study of the transitional and respiratory epithelium. Am J Pathol 1987;128:129–144.

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100 Gardner DE. Use of experimental airborne infections for monitoring altered host defenses. Environ Health Perspect 1982;43:99–107.

101 “Executive Summary,” Air Quality Criteria for Ozone and Related Photochemical Oxidants, United States Environmental Protection Agency, (Washington, DC: Office of Research and Development), February 1994.

102 McConnell, R., Berhane, K., Gilliand, F., London, S.J., Islam, T., Gauderman, W.J., Avol, E., Margolis, H.G., & Peters, J.M.

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103 Ito, K., De Leon, S.F., Lippmann, M. Associations Between Ozone and Daily Mortality: Analysis and Meta-Analysis. Epidemiology. 16(4):446–457, July 2005.

There is ample evidence that short-term ozone exposure is associated with transient decrements in lung functions and increased respiratory symptoms, but the short-term mortality effect of such exposures has not been established.

A review and meta-analysis of short-term ozone mortality studies found a combined estimate of 0.39% (95% confidence interval = 0.26-0.51%) per 10-ppb increase in 1-hour daily maximum ozone for the all-age nonaccidental cause/single pollutant model (43 studies). Adjusting for the funnel plot asymmetry resulted in a slightly reduced estimate (0.35%; 0.23-0.47%). In a subset for which particulate matter (PM) data were available (15 studies), the corresponding estimates were 0.40% (0.27-0.53%) for ozone alone and 0.37% (0.20-0.54%) with PM in model. The estimates for warm seasons were generally larger than those for cold seasons. An additional time-series analysis for 7 U.S. cities (Chicago, Detroit, Houston, Minneapolis-St. Paul, New York City, Philadelphia, and St. Louis) found that including PM in the model did not substantially reduce the ozone risk estimates. However, the difference in the weather adjust-

ment model could result in a 2-fold difference in risk estimates (eg, 0.24% to 0.49% in multicity combined estimates across alternative weather models for the ozone-only all-year case).

104 Hoek G, Schwartz JD, Groot B, Eilers P. Effects of ambient particulate matter and ozone on daily mortality in Rotterdam, The Netherlands. Arch Environ Health. 1997 Nov–Dec; 52(6):455–63.

The association between daily variations in all-cause mortality from 1983–1991 in Rotterdam, the Netherlands, and ambient air pollution was investigated. Twenty-four-hour average concentrations of total suspended particulates, Black Smoke, ozone, sulfur dioxide, and carbon monoxide were available on a daily basis. Every other day, total iron content in total suspended particulates samples was available. Poisson regression analysis was used to study associations between air pollution and mortality; generalized additive models were used to adjust for confounders (e.g., seasonal trends, weather). Daily mortality was associated most consistently with previous-day concentrations of total suspended particulates (relative risk = 1.05 for a change of 91 microg/m3) and ozone (relative risk = 1.06 for a change of 67 microg/m3). Total iron was associated less consistently with mortality than total suspended particulate mass was. The associations of mortality with ozone and total suspended particulates were independent of sulfur dioxide and carbon monoxide. The relative risks of total suspended particulates and particularly ozone were higher for subjects older than 78 y. The relationship between mortality and ozone did not deviate significantly from linear. The relationship between mortality and total suspended particulates was linear below 100 microg/m3 and leveled off at higher concentrations. If a threshold exists for the effects on mortality of these components, it exists at very low levels.

105 Stieb, D.M. et. Al. Association between ozone and asthma emergency department visits in Saint John, New Brunswick, Canada. Environ Health Perspect. 1996 December; 104(12): 1354–1360.

To assess the relationship of asthma emergency department (ED) visits to daily concentrations of ozone and other air pollutants in Saint John, New Brunswick, Canada, data on ED visits with a presenting complaint of asthma (n = 1987) were abstracted for the period 1984–1992 (May–September). Air pollution variables included ozone, sulfur dioxide, nitrogen dioxide, sulfate, and total suspended particulate (TSP); weather variables included temperature, humidex, dewpoint, and relative humidity. Daily ED visit frequencies were filtered to remove day of the week and long wave trends, and filtered values were regressed on air pollution and weather variables for the same day and the 3 previous days. The mean daily 1-hr maximum ozone concentration during the study period was 41.6 ppb. A positive, statistically significant ($p < 0.05$) association was observed between ozone and asthma ED visits 2 days later, and the strength of the association was greater in nonlinear models. The frequency of asthma ED visits was 33% higher (95% CI, 10-56%) when the daily 1-hr maximum ozone concentration exceeded 75 ppb (the 95th percentile). The ozone effect was not significantly influenced by the addition of weather or other pollutant variables into the model or by the exclusion of repeat ED visits. However, given the limited number of sampling days for sulfate and TSP, a particulate effect could not be ruled out. There was a significant association between ozone and asthma ED visits, despite the vast majority of sampling days being below then-current U.S. and Canadian standards.

106 Bell, M.L., McDermott, A., Zeger, S.L. Samet, J.M., and Dominici, F. Ozone and Short-term Mortality in 95 US Urban Communities, 1987–2000. JAMA. 2004;292:2372–2378.

Using analytical methods and databases developed for the National Morbidity, Mortality, and Air Pollution Study, a national average relative rate of mortality associated with short-term exposure to ambient ozone for 95 large US urban communities representing about 40% of the total US population from 1987–2000 was estimated. Distributed-lag models were used to estimate community-specific relative rates of mortality adjusted for time-varying confounders (particulate matter, weather, seasonality, and long-term trends) and hierarchical models for combining relative rates across communities to estimate a national average relative rate, taking into account spatial heterogeneity. A 10-ppb increase in the previous week's ozone was associated with a 0.52% increase in daily mortality (95% posterior interval [PI], 0.27%–0.77%) and a 0.64% increase in cardiovascular and respiratory mortality (95% PI, 0.31%–0.98%). Effect estimates for aggregate ozone during the previous week were larger than for models considering only a single day's exposure. Results were robust to adjustment for particulate matter, weather, seasonality, and long-term trends.

107 Alexandros Gryparis, A., et. al. Acute Effects of Ozone on Mortality from the "Air Pollution and Health A European Approach" Project. American Journal of Respiratory and Critical Care Medicine Vol 170. pp. 1080–1087, (2004).

In the Air Pollution and Health: A European Approach (APHEA2) project, the effects of ambient ozone concentrations on mortality were investigated. Data were collected on daily ozone concentrations, the daily number of deaths, confounders, and potential effect modifiers from 23 cities/areas for at least 3 years since 1990. Effect estimates were obtained for each city with city-specific models and were combined using second-stage regression models. No significant effects were observed during the cold half of the year. For the warm season, an increase in the 1-hour ozone concentration by 10 _g/m3 was associated with a 0.33% (95% confidence interval [CI], 0.17–0.52) increase in the total daily number of deaths, 0.45% (95% CI, 0.22–0.69) in the number of cardiovascular deaths, and 1.13% (95% CI, 0.62–1.48) in the number of respiratory deaths. The corresponding figures for the 8-hour ozone were similar. The associa-

tions with total mortality were independent of SO_2 and particulate matter with aerodynamic diameter less than 10 _m (PM_{10}) but were somewhat confounded by NO_2 and CO. Individual city estimates were heterogeneous for total (a higher standardized mortality rate was associated with larger effects) and cardiovascular mortality (larger effects were observed in southern cities). The dose-response curve of ozone effects on total mortality during the summer did not deviate significantly from linearity.

108 Agriculture and Agri-food Canada, Measuring plant response to ozone, http://www.agr.gc.ca/nlwis-snite/index_e.cfm?s1=pub&s2=ha_sa&page=73.

109 Reilly, S. et. al. Global economic effects of changes in crops, pasture, and forests due to changing climate, carbon dioxide, and ozone. Energy Policy 35 (11) 5370–5383 doi:10.1016/j.enpol.2006.01.040 (November 2007).

110 Sitch, S. Et. Al. "Indirect radiative forcing of climate change through ozone effects on the land-carbon sink. Nature 448, 791–794 (16 August 2007) | doi:10.1038/nature06059.

Tropospheric ozone is known to damage plants, reducing plant primary productivity and crop yields, yet increasing atmospheric carbon dioxide concentrations are thought to stimulate plant primary productivity. Increased carbon dioxide and ozone levels can both lead to stomatal closure, reducing the uptake of either gas, and in turn limiting the damaging effect of ozone and the carbon dioxide fertilization of photosynthesis. Researchers estimated the impact of projected changes in ozone levels on the land-carbon sink using a global land carbon cycle model modified to include the effect of ozone deposition on photosynthesis and to account for interactions between ozone and carbon dioxide through stomatal closure. They found a "significant suppression" of the global land-carbon sink as increases in ozone concentrations affect plant productivity. In consequence, more carbon dioxide accumulates in the atmosphere. They suggest that the resulting indirect radiative forcing by ozone effects on plants could contribute more to global warming than the direct radiative forcing due to tropospheric ozone increases.

111 Fuglestvedt, J.S. Climatic forcing of nitrogen oxides through changes in tropospheric ozone and methane; global 3D model studies. Atmospheric Environment,Volume 33, Issue 6, March 1999, Pages 961–977.

A three-dimensional global chemical tracer model and a radiation transfer model were used to study the role of NO_X emissions in global warming. Through production of tropospheric ozone, NO_X emissions lead to positive radiative forcing and warming. But by affecting the concentration of OH radicals, NO_X also reduces the levels of CH_4, thereby giving negative forcing and cooling. The lifetime of NO_X varies from hours to days, giving large spatial variations in the levels of NO_X. Geographical regions representing different chemical and physical conditions were selected to project chemical and radiative effects of reducing NO_X emissions by 20% in each region. Due to nonlinearities in the O_3 chemistry as well as differences in convective activity, there are large geographical differences in the effect of NO_X on O_3 as well as variations in the annual profile of the changes. The effect of NO_X emissions on methane is also found to depend on the localization of the emissions. The calculated ozone and methane forcing are of similar magnitude but of opposite sign. The methane effect acts on a global scale with a delay of approximately a decade, while the ozone effect is of regional character and occurs during weeks.

112 Fuglestvedt, J.S. Climatic forcing of nitrogen oxides through changes in tropospheric ozone and methane; global 3D model studies. Atmospheric Environment,Volume 33, Issue 6, March 1999, Pages 961–977.

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113 Houghton, J. T. et al. (eds) Climate Change 2007: The Science of Climate Change (Cambridge Univ. Press, 2007).

114 Shindell, D., et. Al. Role of tropospheric ozone increases in 20th-century climate change. J. Geophys. Res., 111, D08302, doi:10.1029/2005JD006348.

To simulate the warming effect of ozone, researchers employed the NASA Goddard Institute for Space Studies (GISS) chemistry model, using the spatial and temporal distribution of precursor emissions of tropospheric ozone from 1890 to 1990, finding that tropospheric ozone has contributed to the greater 20th-century warming in the Northern Hemisphere extratropics compared with the tropics and in the tropics compared with the Southern Hemisphere extratropics. Additionally, ozone increased more rapidly during the latter

half of the century than the former, causing more rapid warming during that time. Other climate forcings do not substantially accelerate warming rates in the tropics relative to other regions, suggesting that tropospheric ozone increases related to industrialization in the developing world have contributed to the accelerated tropical warming. During boreal, or northern, summer, tropospheric ozone causes enhanced warming (>0.5°C) over polluted northern continental regions. Finally, the Arctic climate response to tropospheric ozone increases is large during fall, winter, and spring when ozone's lifetime is comparatively long and pollution transported from mid-latitudes is abundant. The model indicates that tropospheric ozone could have contributed about 0.3° C annual average and about 0.4° C–0.5° C during winter and spring to the 20th-century Arctic warming. According to the authors, "pollution controls could thus substantially reduce the rapid rate of Arctic warming."

115 Matthes, S. et. al. Global impact of road traffic emissions on tropospheric ozone. Atmos. Chem. Phys., 7, 1707–1718, 2007.

Road traffic is one of the major anthropogenic emission sectors for NO_X , CO and NMHCs (non-methane hydrocarbons). To assess the global impact of 1990 road traffic emissions on the atmosphere, investigators applied ECHAM4/CBM, a general circulation model coupled to a chemistry module, which includes higher hydrocarbons. This improved on previous global modeling studies, which concentrated on road traffic NO_X and CO emissions only. Including NMHC emissions from road traffic that NMHC emissions from road traffic play a key role for the impact on ozone. They are responsible for (indirect) long-range transport of NO_X from road traffic via the formation of PAN, which is not found in a simulation without NMHC emissions from road traffic. Long-range transport of NMHC-induced PAN impacts on the ozone distribution in Northern Hemisphere regions far away from the sources, especially in arctic and remote maritime regions. In July total road traffic emissions (NO_X , CO and NMHCs) contribute to the zonally averaged ozone distribution by more than 12% near the surface in the Northern Hemisphere midlatitudes and arctic latitudes. In January, road traffic emissions contribute near the surface in northern and southern extratropics more than 8%. Sensitivity studies for regional emission show that effective transport of road traffic emissions occurs mainly in the free troposphere. In tropical latitudes of America up to an altitude of 200 hPa, global road traffic emissions contribute about 8% to the ozone concentration. In arctic latitudes NMHC emissions from road transport are responsible for about 90% of PAN increase from road transport, leading to a contribution to ozone concentrations of up to 15%.

116 Niemeir, U. et. al. Global impact of road traffic on atmospheric chemical composition and on ozone climate forcing. Journal of Geophysical Research, Vol. 111, D09301,doi:10.1029/2005JD006407, 2006.

Automobile emissions are known to contribute to local air pollution and to photochemical smog in urban areas. The impact of road traffic on the chemical composition of the troposphere at the global scale and on climate forcing is less well quantified. Calculations performed with the chemical transport MOZART-2 model show that the concentrations of ozone and its precursors (NO_X, CO, and hydrocarbons) are considerably enhanced in most regions of the Northern Hemisphere in response to current surface traffic. During summertime in the Northern Hemisphere, road traffic has increased the zonally averaged ozone concentration by more than 10% in the boundary layer and in the extratropics by approximately 6% at 500 hPa and 2.5% at 300 hPa. The summertime surface ozone concentrations have increased by typically 1–5 ppbv in the remote regions and by 5–20 ppbv in industrialized regions of the Northern Hemisphere. The corresponding ozone-related radiative forcing is 0.05 Wm-2. In order to assess the sensitivity of potential changes in road traffic intensity, two additional model cases were considered, in which traffic-related emissions in all regions of the world were assumed to be on a per capita basis the same as in Europe and in the United States, respectively. In the second and most dramatic case, the surface ozone concentration increases by 30–50 ppbv (50–100%) in south Asia as compared to the present situation. Under this assumption, the global radiative forcing due to traffic-generated ozone reaches 0.27 Wm-2.

117 Houghton, J. T. et al. (eds) Climate Change 2007: The Science of Climate Change (Cambridge Univ. Press, 2007).

118 de F. Forster, P.M. et al. Further Estimates of Radiative Forcing Due to Tropospheric Ozone Changes. Geophys. Res. Lett., 23(23), 3321–3324, Nov. 15, 1996.

Estimates made by two 2-D (latitude-height) chemical transport models show large uncertainty, but continue to support the case that tropospheric ozone changes make a substantial contribution (about 15%) to the total greenhouse gas radiative forcing.

119 Volz, A. & Kley, D. Evaluation of the Montsouris series of ozone measurements made in the nineteenth century. Nature 332, 240–242 (17 March 1988); doi:10.1038/332240a0

Questions regarding pre-industrial or 'background' ozone concentrations have led to the search for data from the early days of ozone monitoring, during the second half of the last century. Unfortunately, most measurements were then made using Schönbein test paper, giving only semi-quantitative information due to poor standardization and the influence of humidity and wind speed on its sensitivity. Volz and Kley reinvestigated a set of ozone measurements gathered at the Observatoire de Montsouris, located on the outskirts of Paris, where a quantitative method was established in 1876 and used continuously for 34 years. The evaluation of the technique, together with the analysis of nearly 3,000 of the original daily measurements that previously remained unnoticed in a statistical bulletin of the City

of Paris, provides conclusive evidence that ozone levels in central Europe 100 years ago averaged 10 p.p.b. and exhibited a seasonal variation, with a maximum during the spring months. Comparisons with modern data show that ozone levels in rural areas have more than doubled over the past century and that the tropospheric ozone budget is now strongly influenced by photochemical production due to increased levels of NO_X.

120 Volz, A. & Kley, D. Evaluation of the Montsouris series of ozone measurements made in the nineteenth century. Nature 332, 240–242 (17 March 1988); doi:10.1038/332240a0

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121 Nolle, M. Et. Al. A study of historical surface ozone measurements (1884–1900) on the island of Gozo in the central Mediterranean. Atmospheric Environment Volume 39, Issue 30, September 2005, Pages 5608–5618.

Surface ozone measurements using the Schönbein method were made from 1884–1900 on the rural island of Gozo (Malta). To assess the relative seasonal changes of the ozone concentration researchers, in combination with historical meteorological measurements (temperature, relative humidity, wind speed and direction), employed a new approach to humidity correction of the historical Schönbein measurements using boundary-layer considerations of the old and a nearby modern measuring site. The humidity-corrected Schönbein measurements from Gozo indicate—contrary to current ozone concentrations on Gozo—a clear annual ozone minimum in the summer. Average ozone-mixing ratios in the central Mediterranean could have increased by a factor of five since that time. However, due to the shortcomings of the Schönbein method, quantitative conclusions must be interpreted with care.

122 Schmidt, M. Evidence of a 50-year increase in tropospheric ozone in Upper Bavaria. Ann. Geophys., 12, 1197–1206, 1994

In a series of ozone-sonde soundings at the Hohenpeißenberg observatory, starting in 1967, the most striking features are increases of \sim2.2% per year in all tropospheric heights up to 8 km during the past 24 years. These facts have recently been published and discussed by several authors. In this paper, we present some evidence for the increase of tropospheric ozone concentrations during the past 50 years 1940–1990 in the territory of the northern edge of the Bavarian Alps, including the Hohenpeißenberg data. In December 1940 and August 1942, probably the first exact wet-chemical vertical soundings of ozone up to 9 km height were made by an aircraft in the region mentioned. These results were published in the earlier literature. We have converted the results of the flights on 4 days in December 1940 and on 6 days in August 1942 to modern units and have compared them with the Hohenpeißenberg ozone-sonde data of the December and August months. We also compared the data at the ground with the August results of Paris-Montsouris 1886–1898. Our results show an increase of ozone concentration at all tropospheric heights in Upper Bavaria during the past 50 years, compared with the Montsouris data in August during the past 105 years. In the recently published papers, the increases since 1967 were approximated linearly. Our results, extended to the past, show non-linear trends, with steeper increases since 1975–1979. Possible reasons for these findings are discussed. Quite recently (in case of the December months since 1986/87, the August months since 1990), the ozone mixing ratios at and above Hohenpeißenberg seem to have decreased.

123 Naja, M. Changes in Surface Ozone Amount and Its Diurnal and Seasonal Patterns, from 1954–55 to 1991–93, Measured at Ahmedabad, India. S. Lal, Geophys. Res. Lett., 23(1), 81–84, Jan. 1, 1996.

Despite the crucial role of ozone as a greenhouse gas and in the production of OH radicals, there are few systematic, long-term measurements in the tropics. The measurements presented here show a linear increase of 1.45% per year in average ozone between the two periods analyzed; background concentrations increased by 0.49% per year.

124 Jiang, Y. & Yung, Y.L. Concentrations of Tropospheric Ozone from 1979 to 1992 over Tropical Pacific South America from TOMS Data. Science, 272(5262), 714–716, May 3, 1996.

Satellite measurements indicate that tropospheric ozone increased by 1.48 ± 0.40 percent per year or 0.21 ± 0.06 Dobson unit over South America and the surrounding oceans. An increase in biomass burning in the Southern Hemisphere can account for this trend.

125 Hough, A.M & Derwent, R.G. Changes in the global concentration of tropospheric ozone due to human activities. Nature 344, 645–648 (12 April 1990); doi:10.1038/344645a0.

Evidence from records of ground-level measurements demonstrate that the average tropospheric concentration of ozone in the Northern Hemisphere has increased. In particular, the comparison of recent observations with those made at the Montsouris laboratory in Paris between 1876 and 1910, suggests that the surface concentration of ozone at mid to high latitudes has more than doubled in the past 100 years. This has potential implications for a wide range of environmental issues both because of the direct effects of elevated concentrations of ozone on man and ecosystems and because ozone is a radiatively active gas which could contribute significantly to global warming if its concentration were to increase. Used a global tropospheric model to simulate the chemistry of the pre-industrial atmosphere and that of the present day. The model results for surface ozone concentrations in the pre-industrial atmosphere agree well with the Montsouris data, and the calculated concentrations for the present day agree with recent observations of a wide range of chemical species. Estimates of the future growth in emissions of nitrogen oxides (NO_X) were used to make similar calculations for the year 2020. On the basis of these estimates, the global tropospheric concentration of ozone will continue to increase at a rate faster than during the past 100 years. The potential for further increases in tropospheric ozone needs to be taken into account when assessing the impact of air pollution emissions and the adequacy of measures to control them.

126 Peter Brimblecombe, Air, Composition and Chemistry, 2d Ed., Press Synidate of the University of Cambridge, Cambridge, England (1996) pp. 47–54.

127 The principal oxidants in the lower atmosphere are ozone (O_3) and two by-products of O_3 photodissociation, the hydroxyl radical (OH) and hydrogen peroxide (H_2O_2). A number of critical atmospheric chemical problems depend on the earth's "oxidizing capacity," which is essentially the global burden of these oxidants. Thompson, A.M. The Oxidizing Capacity of the Earth's Atmosphere: Probable Past and Future Changes. Science 22 May 1992: Vol. 256. no. 5060, pp. 1157–1165 DOI: 10.1126/science.256.5060.1157.

128 Guy P. Brasseur, G.P., Muller, J-F. Tie, X.X. and Horowitz, L. Tropospheric Ozone and Climate: Past, Present and Future, in Present and Future of Modeling Global Environmental Change: Toward Integrated Modeling, Eds., T. Matsuno and H. Kida, pp. 63–75 TERRAPUB, 2001.

Relying on the IMAGES model to back-calculate pre-industrial average OH concentration, researchers concluded that it has decreased in the free troposphere, primarily as a result of the increase in carbon monoxide concentrations. In the boundary layer of the northern hemisphere, the concentration of OH increases due primarily to enhanced conversion of HO 2 to OH by elevated concentrations of NO_X. Nitrogen oxides have a considerably shorter lifetime than carbon monoxide. Therefore, the NO_X effect (leading to OH increase) dominates near the emissions sources while that of CO (leading to OH decrease) provides the largest influence in the free troposphere. The net effect is a reduction in the globally averaged OH density. Based on the IMAGES calculations, the mean lifetimes of methane and methylchloroform (respectively 8.9 and 4.8 years for present-day conditions, have increased since the pre-industrial era by approximately 1.3 year and 7 months, respectively.

129 Miguel, A.H. et. al. On-Road Emissions of Particulate Polycyclic Aromatic Hydrocarbons and Black Carbon from Gasoline and Diesel Vehicles. Environ. Sci. Technol.,/ *32* (4), 450–455, 1998.

Motor vehicles are a significant source of fine carbonaceous particle emissions. Fuels have been reformulated and vehicle technologies have advanced, so an updated assessment of vehicular emissions is needed. Gas-and particle-phase pollutant concentrations were measured in the Caldecott Tunnel in the San Francisco Bay Area during the summer of 1996. Separate samples were collected for uphill traffic in two tunnel bores: one bore was influenced by heavy-duty diesel truck emissions; a second bore was reserved for light-duty vehicles. Fine particle black carbon and PAH concentrations were normalized to fuel consumption to compute emission factors. Light-duty vehicles and heavy-duty diesel trucks emitted, respectively, 30 Â± 2 and 1440 Â± 160 mg of fine black carbon particles per kg of fuel burned. Diesel trucks were the major source of lighter PAH, whereas light-duty gasoline vehicles were the dominant source of higher molecular weight PAH such as benzo[/a/]pyrene and dibenz[/a/,/h/]anthracene. Size-resolved measurements of particulate PAH showed significant fractions of diesel-derived PAH to be present in both the ultrafine size mode (<0.12 m) and the ac cumulation mode (0.12-2 m). In contrast, gasoline engine-derived PAH emissions were found almost entirely in the ultrafine mode.

130 Novakov, T. Black carbon emissions in the United Kingdom during the past four decades: an empirical analysis. Atmospheric Environment V. 38, Issue 25, Aug. 2004, p. 4155–4163, doi:10.1016/j.atmosenv.2004.04.031.

We use data from a unique 40-year record of 150 urban and rural stations in the "Black Smoke and SO_2 Network" in Great Britain to infer information about sources of atmospheric black carbon (BC). The data show a rapid decline of ambient atmospheric BC between 1962 and the early 1990s that exceeds the decline in official estimates of BC emissions based only on amount of fuel use and mostly fixed emission factors. This provides empirical confirmation of the existence and large impact of a time-dependent "technology factor" that must multiply the rate of fossil fuel use. Current ambient BC amounts in Great Britain comparable to those in western and central Europe, with diesel engines being the principal present source. From comparison of BC and SO_2 data we infer that current BC emission

inventories understate true emissions in the UK by about a factor of two. The results imply that there is the potential for improved technology to achieve large reduction of global ambient BC. There is a need for comparable monitoring of BC in other countries.

131 Novakov, T. Black carbon emissions in the United Kingdom during the past four decades: an empirical analysis. Atmospheric Environment V. 38, Issue 25, Aug. 2004, p. 4155–4163, doi:10.1016/j.atmosenv.2004.04.031.

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132 John Roach, "Arctic Melt Opens Northwest Passage," National Geographic News, Sep.er 17, 2007, http://news.nationalgeographic.com/news/2007/09/070917-northwest-passage.html.

133 Granier, C. Ozone pollution from future ship traffic in the Arctic northern passages. Geophysical Research Letters, Vol. 33, L13807, doi:10.1029/2006GL026180, 2006

With sea ice expected to recede in the Arctic during the 21st century as a result of projected climate warming, global shipping patterns will change considerably in the decades ahead. The opening of viable shipping routes through the Northern passages will generate new environmental problems including the degradation of air quality in the Arctic. The release of considerable amounts of carbon monoxide, nitric oxide and other chemical substances by the ship's combustion engines will enhance the level of atmospheric photooxidants and other secondary pollutants in this region. Here we show that, during the summer months, surface ozone concentrations in the Arctic could be enhanced by a factor of 2–3 in the decades ahead as a consequence of ship operations through the northern passages. Projected ozone concentrations of 40–60 ppbv from July to September are comparable to summertime values currently observed in many industrialized regions in the Northern Hemisphere.

134 Andreae, M.O. The dark side of aerosols. 409 Nature 671, Feb. 8, 2001.

135 Goddard Institute for Space Studies, National Aeronautics and Space Administration, "Methane's Impacts on Climate Change May Be Twice Previous Estimates" July 18, 2005, http://www.giss.nasa.gov/research/news/20050718/, Comments on Shindell, D.T., G. Faluvegi, N. Bell, and G.A. Schmidt 2005. An emissions-based view of climate forcing by methane and tropospheric ozone. Geophys. Res. Lett. 32, L04803, doi:10.1029/2004GL021900.

136 Fiore, A.M., et. Al. Linking ozone pollution and climate change: The case for controlling methane. Geophys. Res. Lett., 29(19), 1919, doi:10.1029/2002GL015601.

A 2030 simulation based on IPCC A1 emissions projections shows a longer and more intense U.S. O_3 pollution season despite domestic emission reductions, indicating that intercontinental transport and a rising O_3 background. Methane (CH_4) emission controls were found to be a powerful lever for reducing both global warming and air pollution via decreases in background tropospheric ozone (O_3). Reducing anthropogenic CH_4 emissions by 50% nearly halves the incidence of U.S. high-O_3 events and lowers global radiative forcing by 0.37 W m-2 (0.30 W m-2 from CH_4, 0.07 W m-2 from O_3) in a 3-D model of tropospheric chemistry.

137 Atherton, C.S. et al. The Role of Anthropogenic Emissions of NO_X on Tropospheric Ozone over the North Atlantic Ocean: A Three-Dimensional, Global Model Study. Atmospheric Environment, Volume 30, Number 10, May 1996 , pp. 1739–1749(11), 1739–1749. The model is run with a baseline scenario and one in which North American fossil fuel NO_X emissions are reduced 50%. The NO_X reduction produces a 30% reduction in the total mass of tropospheric ozone exported from North America to the North Atlantic Ocean.

138 Easter, R.C. et. al. Analysis of Mid-tropospheric Carbon Monoxide Data Using a Tiiree-dimensional Global Atmospheric Chemistry Numerical Model. Presented at the 20th International Technical Meeting on Air Pollution Modelling and its Application, Nov. 29–Dec. 3, 1993 Valencia, Spain.

Two simulations were performed where total CO emissions were increased and decreased by 50 percent. As seen in Table 2, increasing total CO emissions increased the global average CO mixing ratio 27 percent, while halving total emissions decreased the average mixing ratio by 25 percent. In the base simulation, CO production from CH_4 oxidation was equal to 56 percent of the total CO emissions. Thus, increasing (decreasing) the CO emissions by 50 percent changes the overall CO source strength by +32 percent (or-32 percent). Due to the nonlinear effects of chemical feedbacks, the changes in global average CO mixing ratio do not respond linearly to changes in CO emissions. Further, three simulations were performed where each of the major CO emissions categories were omitted.

The response of the global average CO mixing ratio resulting from these simulations follows that expected from the relative magnitude of emissions from each category. The largest source category is CO emissions from nonmethane hydrocarbon oxidation; omitting this source reduced the global average mixing ratio by 20 percent. Omitting anthropogenic and biomass burning CO emissions resulted in a global average mixing ratio reduction of 14 percent and 15 percent, respectively.

139 Dentener, F. The impact of air pollutant and methane emission controls on tropospheric ozone and radiative forcing: CTM calculations for the period 1990–2030. Atmos. Chem. Phys., 5, 1731–1755, 2005. The radiative forcing of ozone and methane would be reduced to approximately-0.1 Wm-2. This can be compared to the 0.14–0.47 Wm-2 increase of methane and ozone radiative forcings associated with the SRES scenarios of the IPCC.

140 Penner, J.E. Towards the development of a global inventory for black carbon emissions. International conference on carbonaceous particles in the atmosphere; 3-5 Apr 1991, Vienna, Austria.

The authors developed a global inventory for black carbon (BC) emi measured ambient concentration ratios of black carbon and SO_2 at locations throughout the world. They extended the data base for black carbon by using "smoke" measurements at a variety of monitoring sites and a calibration factor for black carbon derived herein from ambient smoke and BC measurements. They demonstrate that BC to SO_2 ratios are well correlated at most sites and that distinct ratios of BC to SO_2 apply to source areas from economically distinct regions. However, within any one economic region, the ratio of BC to SO_2 appears to be relatively constant. These facts are used to construct a global inventory of black carbon emissions by using previously published inventories for the emissions of sulfur from fossil fuel use. The derived inventory totals nearly 24 Tg C/yr. This inventory is compared to a crude inventory based on emission factors and published fuel use statistics for wood and bagasse burning, diesel fuel, and domestic and commercial coal use. The combined emissions from wood, diesel, and coal can explain more than 75% of the total global emissions and usually are within a factor of two of the derived regional emissions from the BC/S ratio method. The black carbon inventory, totaling nearly 24 Tg C/yr, is used in the Lawrence Livermore National Laboratory global chemistry/climate model to simulate the world-wide distribution of black carbon. The predicted concentrations are compared with available measurements from throughout the world. This comparison supports the magnitude of the inventory which the authors have derived to within a factor of two, although significant uncertainties with respect to the treatment of scavenging and deposition in the model remain.

141 A. M. Stamatelos A review of the effect of particulate traps on the efficiency of vehicle diesel engines. Energy Conversion and Management, V. 38, Issue 1, Jan. 1997, Pages 83-99.

Particulate traps are becoming more widely used on city buses, some delivery trucks and fork lift trucks. The possible use of diesel particulate traps will lead to a fuel consumption penalty imposed on the baseline engine that is due to the trap back pressure as well as to the energy requirements of the regeneration technique adopted to incinerate the collected soot at will. The combined effect of trap back pressure imposed on the engine and additional energy required for trap regeneration on the overall efficiency of the diesel power plant is examined in this paper. This effect varies according to engine type, trap type and size, regeneration system used, and the vehicle driving mode. Because of the strong interaction among the above parameters, optimization of trap systems on efficiency grounds is complicated. This complexity is even more pronounced in the case of diesel-powered passenger cars, where the full exploitation of their efficiency advantage over gasoline-powered cars is constrained by the necessity of an optimized solution of the particulate emission problem. The main diesel particulate trap regeneration philosophies existing today are reviewed in terms of their effect on the total efficiency of the diesel power plant. This is done by means of representative examples, concerning systems which may be suitable for large-scale application. The conclusions indicate that the price that must be paid for environmental protection, in the case of diesel particulate control systems, may be substantially reduced by system design optimization.

142 Cherng-Yuan Lin. Reduction of particulate matter and gaseous emission from marine diesel engines using a catalyzed particulate filter. Ocean Engineering, V. 29, Issue 11, Sep. 2002, Pages 1327–1341

Diesel engines are used widely as the power sources of coastal ships and international vessels primarily due to their high thermal efficiency, high fuel economy and durable performance. However, the gaseous and solid substances exhausted from diesel engines during the combustion process cause air pollution, in particular around harbor regions. In order to effectively reduce particulate matter and gaseous pollution emissions, a catalyzed particulate filter was equipped in the tail pipe of a marine diesel engine. The engine's performance and emission characteristics under various engine speeds and torques were measured using a computerized engine data control and acquisition system accompanied with an engine dynamometer. The effectiveness of installing a catalyzed particulate filter on the reduction of pollutant emissions was examined. The experimental results show that the exhaust gas temperature, carbon monoxide and smoke opacity were reduced significantly upon installation of the particulate filter. In particular, larger conversion of carbon monoxide to carbon dioxide—and thus larger CO_2 and lower CO emissions—were observed for the marine diesel engine equipped with a catalyzed particulate filter and operated at higher engine speeds. This is presumably due to enhancement of the catalytic oxidation reaction

that results from an exhaust gas with stronger stirring motion passing through the filter. The absorption of partial heating energy from the exhaust gas by the physical structure of the particulate filter resulted in a reduction in the exhaust gas temperature. The particulate matter could be burnt to a greater extent due to the effect of the catalyst coated on the surface of the particulate filter. Moreover, the fuel consumption rate was increased slightly while the excess oxygen emission was somewhat decreased with the particulate filter.

143 Petzold, A. et. al.In situ observations and model calculations of black carbon emission by

aircraft at cruise altitude. Journal of Geophysical Research, Volume 104, Issue D18, p. 22171–22182. http://www.agu.org/journals/jgr. *Publication Date:* 00/1999

The exhaust aerosol of two aircraft at cruise was extensively characterized in the size range from 0.003 to 2 _m for plume ages <=2 s. The black carbon (BC) exhaust aerosol of an older technology engine (Rolls-Royce/Snecma M45H Mk501) consisted of a primary BC mode with a modal diameter of 0.035 _m and a mode of coagulated BC particles with a peak near 0.15-0.16 _m in diameter. The total number density at the nozzle exit plane was 3(10^7 cm^-3. In contrast, a modern technology engine (CFM International CFM56-3B1) emitted far smaller BC particles with a primary mode at 0.025 _m and a coagulated mode at 0.15 _m, as well as fewer particles by number with a concentration of 9(10^6 cm^-3. The single-scattering albedo of the jet exhaust aerosol was 0.035+/-0.02 inside the plume, indicating a dominant contribution of ultrafine (D<0.1_m) BC particles to light extinction. Black carbon number emission indices EI(N) varied from 3.5(10^14 (CFM56-3B1) to 1.7(10^15 kg^-1 (M45H Mk501) with corresponding mass emission indices EI(BC) of 0.011 and 0.1 g kg^-1. Previously reported corresponding values for a CF6-80C2A2 engine were 6(10^14 kg^-1 and 0.023 g kg^-1 , respectively. A comparison between EI(BC) values calculated by a new correlation method and measured data shows an excellent agreement, with deviations <10% at cruise conditions. By extending the EI(BC) calculation method to a globally operating aircraft fleet, a fleet-averaged emission index EI(BC)=0.038gkg^-1 is calculated.

144 Streets D.G. et. al. Black carbon emissions in China. Atmospheric Environment, Volume 35, Number 25, September 2001 , pp. 4281–4296(16). Emissions of BC in China are roughly one-fourth of global anthropogenic emissions. China's high rates of usage of coal and biofuels are primarily responsible for high BC emissions. Investigators calculate that BC emissions in China in 1995 were 1342 Gg, about 83% being generated by the residential combustion of coal and biofuels, and estimate that BC emissions could fall to 1224 Gg by 2020. This 9% decrease in BC emissions is contrasted with the expected increase of 50% in energy use; the reduction will be obtained because of a transition to more advanced technology, including greater use of coal briquettes in place of raw coal in cities and towns.

145 Timm, B. Air Quality Modeling and Health Benefits of a Woodstove Change-out Program, May 18, 2006, U.S. Environmental Protection Agency.

146 Timm, B. Air Quality Modeling and Health Benefits of a Woodstove Change-out Program, May 18, 2006, U.S. Environmental Protection Agency.

(Worth Noting Endnotes)

1 Technically he was in the employ of General Motors, but the auto company was controlled by the chemical giant. DuPont's link with General Motors began with Pierre S. du Pont, who bought GM stock in 1914. In 1915 Pierre was elected a GM director, then board chairman, to help strengthen GM's management. After World War I, GM executive and former DuPont treasurer John J. Raskob persuaded DuPont's directors to invest $25 million in GM. Pierre became GM's president in 1920. By then DuPont's GM holdings provided half of DuPont's total earnings. DuPont disposed of all its GM stock in 1961. E.I. du Pont de Nemours, "DuPont, GM & Cars," http://heritage.dupont.com/touchpoints/tp_1918/overview.shtml.

2 Clair Patterson, "An Alternative Perspective—Lead Pollution in the Human Environment: Origin, Extent, and Significance," in Lead in the Human Environment, National Academy of Sciences (Washington, D.C., 1980).

3 Herbert L. Needleman, Human Lead Exposure, CRC Press, Inc., Boca Raton, Fla., 1991.

4 Agency for Toxic Substances and Disease Registry, The Nature and Extent of Lead Poisoning in Children in the United States: A Report to Congress, US Department of Health and Human Services, Public Health Service, 1988.

5 Elizabeth O'Brien, The Lead Group, "Countries where Leaded Petrol is Possibly Still Sold for Road Use As at 22nd February 2007," http://www.lead.org.au/fs/fst27.html

6 Magda Lovei, Phasing out lead from gasoline: worldwide experience and policy implications, World Bank, Washington, D.C.

7 Sarah-Leigh Paul, "Chemicals firm calls for a rethink on possible MMT ban," Creamer Media's Engineering News, Sep. 9, 2005, http://www.engineeringnews.co.za/article.phpa_id=72850.

8 From the Afton website, http://www.aftonchemical.com/Products/mmt/index.htm:

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mmt® (Methylcyclopentadienyl Manganese Tricarbonyl) Fuel Additive is an organic manganese compound that is easy and safe to handle, and compatible with all fuels. mmt® is used at very low treat rates (ppm level); just a few drops added per gallon of gasoline can increase octane by 1 or 2 octane numbers. It has been utilized for over thirty years as an efficient octane improver in unleaded gasoline and in every application has a well-proven record of acceptable performance in consumer use.

mmt® increases octane levels and helps refiners to beneficially alter fuel composition to meet the stringent environmental and fuel quality specifications that are so crucial to reducing emissions and energy consumption. Refining and blending economics are greatly improved by allowing more efficient unit operation and blending of lower cost components. mmt® also helps vehicles maintain their emission performance over their useful life by protecting catalysts and oxygen sensors from degradation.

The main component of mmt® is manganese, an element that occurs naturally in our environment. Much is known about manganese and its potential impact on public health, whether due to use of mmt® or from other natural or industrial sources. mmt® is one of the most comprehensively tested fuel additives in history. Through repeated evaluation, mmt® has demonstrated no identifiable risk to public health or welfare. The use of mmt® has been reviewed by government agencies and approved for use around the world. Over 150 refiners in 45 countries in Europe, Africa, Asia, Central and South America, as well as the United States and Canada, currently use mmt® to produce high quality gasoline, providing fuel for millions of cars with over a trillion miles of trouble free operation.

9 Ethyl Corporation, Securities and Exchange Commission, Form 10-K, 2004-02-27, http://www.sec.gov/Archives/edgar/data/33656/000119312504030731/d10k.htm

10 Rosner and Markowitz at pp. 99-101.

11 Rosner and Markowitz at pp. 99–101.

12 "Odd Gas Kills One, Makes Four Insane; Stricken at Work in Standard's Experiment Laboratory in Elizabeth, The New York Times, Oct. 27, 1924.

13 "ANOTHER MAN DIES FROM INSANITY GAS; Might Other Standard Oil Workers Suffering From Poison Said to be Tetra-Ethyl Lead," The New York Times, Oct. 28, 1924.

14 Rosner and Markowitz, pp. 121–25.

15 Clarkson, T.W. Metal Toxicity in the Central Nervous System. Environmental Health Perspectives, Vol. 75, Nov., 1987 (Nov., 1987), pp. 59–64 doi:10.2307/3430577

16 Rice, D.C. Anatomical Substrates of Behavioral Impairment Induced by Developmental Lead Exposure in Monkeys: Inferences from Brain Lesions. Integrative and Comparative Biology, Volume 37, Number 4, Pp. 409–425.

There is a substantial literature exploring the behavioral consequences of developmental lead exposure in the monkey; deficits have been observed on a number of tasks assessing learning and memory including spatial delayed alternation, discrimination reversal, matching to sample, and concurrent discrimination. Differences in performance between control and lead-exposed monkeys have also been observed on intermittent schedules of reinforcement. Comparison of the effects of lead with the extensive literature on the consequences of lesions in discrete areas of brain on the same tasks may provide insight into the possible sites of brain damage responsible for lead-induced behavioral impairment. Available data strongly suggest that prefrontal cortical areas are damaged by lead, based on the pattern of performance deficits across specific tasks. In addition, a constellation of global deficits including perseveration, increased distractibility, inability to change response strategy, and inability to inhibit inappropriate responding are hallmarks of both prefrontal damage and developmental lead exposure. Evidence also implicates basal forebrain structures in behavior impairment produced by lead based on the pattern of deficits across numerous tasks, although the evidence is much weaker than for prefrontal cortex. In contrast, the pattern of behavioral impairment produced by limbic system lesions is different in many respects from that produced by lead; in addition, the scant neuropathological data available suggest that limbic structures are not a target of lead even at high blood lead levels in the monkey. Comparison of the pattern of damage following lead exposure with the effects of lesions, presented here, provides direction for further morphological or neurochemical exploration of lead-induced brain damage in the monkey.

17 Weber, G.F. Final common pathways in neurodegenerative diseases: regulatory role of the glutathione cycle. Neuroscience & Biobehavioral Reviews Volume 23, Issue 8, December 1999, Pages 1079–1086.

Attempts to unify diverse mechanisms of neurotoxicity have led to the concept of final common pathways which characterize frequently occurring cellular responses to disruption of homeostasis. The clinical presentation and common patho-biochemistry of reactive oxygen intermediates of Guam's disease have suggested that such pathways may be operative in three major neurodegenerative disorders: Alzheimer's dementia, amyotrophic lateral sclerosis and Parkinson's disease. A candidate-signaling pathway in this regard is characterized by the cascade arachidonic acid/HPETE/!OH/cGMP followed by activation of cGMP-dependent kinase and phosphorylation of NF-kB proteins and possibly CREB. This sequence may lead to apoptosis as well as long-term potentiation and memory and constitutes a biochemical correlate to excitotoxicity. The predominant control of !OH release from HPETE, a checkpoint in this pathway, is exerted by the glutathione cycle, a central biochemical process that is also intimately associated with the synthesis of the neurotransmitters glutamate and GABA and is connected to energy metabolism. Modifications in the activity of the glutathione cycle may provide treatment options.

18 Siegel, G. et. al. Basic Neurochemistry: Molecular, Cellular and Medical Aspects Sixth Edition, pp. Lippincott–Raven Publishers, Philadelphia, Penn. 1999.

19 Casdorph, H.R. & Walker, M., Toxic Metal Syndrome: How Metal Poisonings Can Affect Your Brian, pp. 211–15, Avery, 1994.

20 Casdorph, H.R. & Walker, M., Toxic Metal Syndrome: How Metal Poisonings Can Affect Your Brian, pp. 211–15, Avery, 1994.

21 Kitazawa, M. et. al. Oxidative Stress and Mitochondrial-Mediated Apoptosis in Dopaminergic Cells Exposed to Methylcyclopentadienyl Manganese Tricarbonyl. J Pharmacol Exp Ther. 2002 Jul;302(1):26–35.

Methylcyclopentadienyl manganese tricarbonyl (MMT), an organic manganese-containing gasoline additive, was investigated to determine whether MMT potentially causes dopaminergic neurotoxic effects. MMT is acutely cytotoxic and dopamine-producing cells (PC-12) seemed to be more susceptible to cytotoxic effects than nondopaminergic cells (striatal gamma-aminobutyric acidergic and cerebellar granule cells). MMT also potently depleted dopamine apparently by cytoplasmic vesicular release to the cytosol, a neurochemical change resembling other dopaminergic neurotoxicants. Generation of reactive oxygen species (ROS), an early effect in toxicant-induced apoptosis, occurred within 15 min of MMT exposure. MMT caused a loss of mitochondrial transmembrane potential (Delta Psi m), a likely source of ROS generation. The ROS signal further activated caspase-3, an important effector caspase, which could be inhibited by antioxidants (Trolox or N-acetyl cysteine). Predepletion of dopamine by using alpha-methyl-p-tyrosine (tyrosine hydroxylase inhibitor) treatment partially prevented caspase-3 activation, denoting a significant dopamine and/or dopamine by-product contribution to initiation of apoptosis. Genomic DNA fragmentation, a terminal hallmark of apoptosis, was induced concentration dependently by MMT but completely prevented by pretreatment with Trolox, deprenyl (monoamine oxidase-B inhibitor), and alpha-methyl-p-tyrosine. A final set of critical experiments was performed to verify the pharmacological studies using a stable Bcl-2-overexpressing PC-12 cell line. Bcl-2-overexpressing cells were significantly refractory to MMT-induced ROS generation, caspase-3 activation, and loss of Delta Psi m and were completely resistant to MMT-induced DNA fragmentation. Taken together, the results presented herein demonstrate that oxidative stress plays an important role in mitochondrial-mediated apoptotic cell death in cultured dopamine-producing cells after exposure to MMT.

22 Massaro, E.J. Handbook of Neurotoxicology, p. 196, Humana Press, Totowa, N.J. (2002).

23 Ardeleanu, A. et. al. Emission rates and physico-chemical characteristics of Mn particles emitted by vehicles using Methylcyclopentadienyl Manganese Tricarbonyl (MMT) as an octane improver. Water, Air, & Soil Pollution Volume 115, Numbers 1-4 / October, 1999.

Since 1990, methylcyclopentadienyl manganese tricarbonyl (MMT) has been added to all gasoline in Canada as an antiknock agent. The objective of this study is to determine the percentage of manganese emitted by different types of automobiles and to evaluate the size and chemical characteristics of the Mn-containing particles. Nine vehicles with different mileage and engine capacity were tested using standard procedures for urban and highway driving cycles. One ran on gasoline without MMT and served as a control. The particles were collected using two separate systems: a trapping device consisting of a water tank connected to the tailpipe and a pumping device linked to a cassette containing Teflon filters. Water samples were analyzed by neutron activation to determine the amount of Mn emitted at the tailpipe for each test. Teflon filters were analyzed by electron microscopy to determine the size and the chemical characteristics of the particles. The amount of manganese emitted from the tailpipe varied from 4 to 41% of the manganese consumed, depending on the driving cycle and the vehicle. For the urban cycle, the emission rate was positively correlated with previous mileage. Almost all particles found on teflon filters had a size less than 5 mgrm. They appeared to be mainly Mn oxides but other elements could be masked by the gold and paladium peaks.

24 Zayed, J., Hong, B. and L'espérance, G. Characterization of Manganese-Containing Particles Collected from the Exhaust Emissions of Automobiles Running with MMT Additive. Environ. Sci. Technol., 33 (19), 3341–3346, 1999. 10.1021/es990709.

Methylcyclopentadienyl manganese tricarbonyl (MMT) is an organometallic compound used as an octane improver in unleaded gasoline. The objective of this study was to determine the physical and the chemical characteristics of the manganese (Mn) compounds emitted from vehicles using MMT. Particles emitted from the tailpipe were trapped and characterized by scanning electron microscopy (SEM) and X-ray energy dispersive spectrometry (EDS) and by analytical transmission electron microscopy (ATEM). Results support the conclusion that Mn is emitted from the tailpipe primarily as a mixture of Mn-phosphate and Mn-sulfate with a size ranging between 0.2 and 10 m. ATEM characterization shows that the isolated particles consist of manganese-oxygen-phosphorus-sulfur (Mn-O-P-S) (in order of a descending peak intensity), indicating that Mn-phosphate is the main constituent of the residual particles. Moreover, all the Mn-containing particles investigated were amorphous. Further toxicological studies with a mixture of Mn-phosphate and Mn-sulfate are needed to provide successful implementation of evidence-based risk assessment approaches.

25 Normandin, L. et. al. Manganese Distribution in the Brain and Neurobehavioral Changes Following Inhalation Exposure of Rats to Three Chemical Forms of Manganese. NeuroToxicology Volume 25, Issue 3, March 2004, Pages 433–441.

The central nervous system is an important target for manganese (Mn) intoxication in humans; it may cause neurological symptoms similar to Parkinson's disease. Manganese compounds emitted from the tailpipe of vehicles using methylcyclopentadienyl manganese tricarbonyl (MMT) are primarily Mn phosphate, Mn sulfate, and Mn phosphate/sulfate mixture. The purpose of this study is to compare the patterns of Mn distribution in various brain regions (olfactory bulb, frontal parietal cortex, globus pallidus, striatum and cerebellum) and other tissues (lung, liver, kidney, testis) and the neurobehavioral damage following inhalation exposure of rats to three Mn species. Rats (n=15 rats per Mn species) were exposed 6 h per day, 5 days per week for 13 consecutive weeks to metallic Mn, Mn phosphate or Mn phosphate/sulfate mixture at about 3000 ug m-3 and compared to controls. At the end of the exposure period, spontaneous motor activity was measured for 36 h using a computerized autotrack system. Mn in tissues was determined by instrumental neutron activation analysis (INAA). The Mn concentrations in the brain were significantly higher in rats exposed to Mn phosphate and Mn phosphate/sulfate mixture than in control rats or rats exposed to metallic Mn. Exposure to Mn phosphate/sulfate mixture caused a decrease in the total ambulatory count related to locomotor activity. Our results confirm that Mn species and solubility have an influence on the brain distribution of Mn in rats.

See also Leavens, T.L. Evaluating Transport of Manganese from Olfactory Mucosa to Striatum by Pharmacokinetic Modeling. Tox-Sci Advance Access published online on March 19, 2007

Toxicological Sciences, doi:10.1093/toxsci/kfm061.

26 Dorman, D.C. et. al. Influence of Particle Solubility on the Delivery of Inhaled Manganese to the Rat Brain: Manganese Sulfate and Manganese Tetroxide Pharmacokinetics Following Repeated (14-Day) Exposure. Toxicology and Applied Pharmacology, Volume 170, Issue 2, 15 January 2001, Pages 79–87.

Dissolution rate can influence the pulmonary clearance of a metal and thus affect its delivery to the brain and other organs. The goal of this study was to determine the exposure-response relationship for the relatively soluble sulfate ($MnSO_4$) and insoluble tetroxide (Mn_3O_4) forms of inhaled manganese in adult male CD rats. Rats were exposed 6 h/day for 7 days/week (14 exposures) to either $MnSO_4$ or Mn_3O_4 at 0, 0.03, 0.3, or 3 mg Mn/m3. End-of-exposure olfactory bulb, striatum, cerebellum, bile, lung, liver, femur,

serum, and testes (n = 6 rats/concentration/chemical) manganese concentrations and whole-body 54Mn elimination were then determined. Increased whole-body 54Mn clearance rates were observed in animals from the high-dose (3 mg Mn/m3) MnSO4 and Mn3O4 exposure groups. Elevated manganese concentrations in the lung were observed following MnSO4 and Mn3O4 exposure to u0.3 mg Mn/m3. Increased olfactory bulb and femur manganese concentrations were also observed following MnSO4 exposure at u0.3 mg Mn/m3. Elevated striatal, testes, liver, and bile manganese concentrations were observed following exposure to MnSO4 at 3 mg Mn/m3. Elevated olfactory bulb, striatal, femur, and bile manganese concentrations were observed following exposure to Mn3O4 at 3 mg Mn/m3. Animals exposed to MnSO4 (3 mg Mn/m3) had lower lung and higher olfactory bulb and striatal manganese concentrations compared with levels achieved following similar Mn3O4 exposures. Our results suggest that inhalation exposure to soluble forms of manganese results in higher brain manganese concentrations than those achieved following exposure to an insoluble form of manganese.

27 Adkins, B. et. al. Acute exposure of laboratory mice to manganese oxide. American Industrial Hygiene Association Journal, Volume 41, Issue 7 July 1980 , pages 494–500.

An acute inhalation exposure of laboratory mice to respirable Mn3O4 aerosols is described. The generation system consisted of a Wright dust generator which produced 1.40 _m aerosols. A non-linear loss of deposited manganese from mouse lungs over the initial 24-hour post-exposure period was observed. Systemic distribution of the manganese was observed in various tissues following exposure.

28 Oberdörster, G. Nanoparticles (NP) and the Brain: Pathways of Translocation and Effects. International Conference on Nanotechnology, Occupational and Environmental Health and Safety.

29 Oberdoerster, G et. al. Translocation of Inhaled Ultrafine Particles to the Brain Inhalation Toxicology [Inhalation Toxicol.]. Vol. 16, no. 6-7, pp. 437–445. Jun 2004.

Ultrafine particles (UFP, particles <100 nm) are ubiquitous in ambient urban and indoor air from multiple sources and may contribute to adverse respiratory and cardiovascular effects of particulate matter (PM). Depending on their particle size, inhaled UFP are efficiently deposited in nasal, tracheobronchial, and alveolar regions due to diffusion. Our previous rat studies have shown that UFP can translocate to interstitial sites in the respiratory tract as well as to extrapulmonary organs such as liver within 4 to 24 h postexposure. There were also indications that the olfactory bulb of the brain was targeted. Our objective in this follow-up study, therefore, was to determine whether translocation of inhaled ultrafine solid particles to regions of the brain takes place, hypothesizing that UFP depositing on the olfactory mucosa of the nasal region will translocate along the olfactory nerve into the olfactory bulb. This should result in significant increases in that region on the days following the exposure as opposed to other areas of the central nervous system (CNS). We generated ultrafine elemental super(13)C particles (CMD = 36 nm; GSD = 1.66) from [super(13)C] graphite rods by electric spark discharge in an argon atmosphere at a concentration of 160 mu g/m super(3). Rats were exposed for 6 h, and lungs, cerebrum, cerebellum and olfactory bulbs were removed 1, 3, 5, and 7 days after exposure. Super(13)C concentrations were determined by isotope ratio mass spectroscopy and compared to background super(13)C levels of sham-exposed controls (day 0). The background corrected pulmonary super(13)C added as ultrafine super(13)C particles on day 1 postexposure was 1.34 mu g/lung. Lung super(13)C concentration decreased from 1.39 mu g/g (day 1) to 0.59 mu g/g by 7 days postexposure. There was a significant and persistent increase in added super(13)C in the olfactory bulb of 0.35 mu g/g on day 1, which increased to 0.43 mu g/g by day 7. Day 1 super(13)C concentrations of cerebrum and cerebellum were also significantly increased but the increase was inconsistent, significant only on one additional day of the postexposure period, possibly reflecting translocation across the blood-brain barrier in certain brain regions. The increases in olfactory bulbs are consistent with earlier studies in nonhuman primates and rodents that demonstrated that intranasally instilled solid UFP translocate along axons of the olfactory nerve into the CNS. We conclude from our study that the CNS can be targeted by airborne solid ultrafine particles and that the most likely mechanism is from deposits on the olfactory mucosa of the nasopharyngeal region of the respiratory tract and subsequent translocation via the olfactory nerve. Depending on particle size, >50% of inhaled UFP can be depositing in the nasopharyngeal region during nasal breathing. Preliminary estimates from the present results show that similar to 20% of the UFP deposited on the olfactory mucosa of the rat can be translocated to the olfactory bulb. Such neuronal translocation constitutes an additional not generally recognized clearance pathway for inhaled solid UFP, whose significance for humans, however, still needs to be established. It could provide a portal of entry into the CNS for solid UFP, circumventing the tight blood-brain barrier. Whether this translocation of inhaled UFP can cause CNS effects needs to be determined in future studies.

30 Massaro, E.J. Handbook of Neurotoxicology, p. 197, Humana Press, Totowa, N.J. (2002).

These are the the striatum, globus pallidus and substantia nigra, which are part of the basal ganglia. See also Shinotoh, H. et. al. MRI and PET studies of manganese-intoxicated monkeys. Neurology, Vol 45, Issue 6 1199–120.

Using MRI and PET, we investigated the consequences of manganese intoxication in a primate model of parkinsonism and dystonia. Three rhesus monkeys were injected intravenously with doses of 10 to 14 mg/kg of MnCl2 on seven occasions, each a week

apart. Two animals became hypoactive with abnormal extended posturing in the hind limbs. These motor disturbances did not improve with administration of levodopa. In all three monkeys, T1-weighted MRI demonstrated high signal intensities in the regions of the striatum, globus pallidus, and substantia nigra. No significant changes were found on [18F]6-fluoro-L-dopa, [11C]raclopride, or [18F]fluorodeoxyglucose PET. These results are consistent with the pathologic findings, which were primarily confined to the globus pallidus, and indicate that manganese intoxication is associated with preservation of the nigrostriatal dopaminergic pathway, despite clinical evidence of parkinsonian deficits. Chronic manganese intoxication may cause parkinsonism by damaging output pathways downstream to the nigrostriatal dopaminergic pathway. This is consistent with the demonstrated lack of therapeutic response to levodopa.

31 Moore, S.P. & Psarros, T.G., The Definitive Neurological Surgery Board Review, pp. 41–4, Wolters Kluwer.

32 Chan, C.S., Surmeiera, D.J. & Yung, W-H. Striatal Information Signaling and Integration in Globus Pallidus: Timing Matters. Neurosignals, Vol. 14, No. 6, 2005.

Advances in research on globus pallidus (GP) suggest that this 'long thought to be' relay in the 'indirect pathway' plays a unique and critical role in basal ganglia function. The traditional idea of parallel processing within the basal ganglia is also challenged by recent findings. It is now clear that axons of GP neurons form large, perisomatic baskets around target neurons in all major basal ganglia nuclei, thereby exerting a profound influence on the output of the entire basal ganglia. GP neurons are autonomously active both in vivo and in vitro. It is believed that temporal information carried along the corticostriatopallidal pathway is critical for proper motor execution. The importance of appropriately controlled discharge of GP neurons is highlighted by psychomotor disorders such as Parkinson's disease, in which alterations in the pattern and synchrony of discharge in GP neurons are thought to contribute to motor symptoms. Several lines of evidence suggest that the aberrant activity of GP neurons following dopamine depletion is caused by alteration in the synaptic input from both striatum and subthalamic nucleus. In normal subjects, the capability of striatal input in translating cortical input into precisely timed responses in GP neurons is mediated by (1) the expression of postsynaptic GABAA receptor composed of subunits with fast kinetic properties; (2) an effective GABA reuptake system in terminating the action of synaptically released GABA, and (3) the existence of dendritic HCN channels that actively abbreviate the time course of the inhibitory postsynaptic potentials and reset rhythmic discharge. Despite the rapid pace in uncovering the elements that shape the activity along the striatopallidosubthalamic pathway, the origin of rhythmic, synchronized bursting of GP neurons seen in parkinsonism has not been fully established experimentally. Further elucidation of the factors that control the information transfer in the striatopallidal synapses is thus critical to our understanding of basal ganglia function and establishing treatment for Parkinson's disease and other basal ganglia disorders.

33 Chan, C.S., Surmeiera, D.J. & Yung, W-H. Striatal Information Signaling and Integration in Globus Pallidus: Timing Matters. Neurosignals, Vol. 14, No. 6, 2005.

34 Gorrell, J.M. et. al.Occupational exposure to manganese, copper, lead, iron, mercury and zinc and the risk of Parkinson's disease. Neurotoxicology. 1999 Apr-Jun;20(2-3):239–47.

A population-based case-control study was conducted in the Henry Ford Health System (HFHS) in metropolitan Detroit to assess occupational exposures to manganese, copper, lead, iron, mercury and zinc as risk factors for Parkinson's disease (PD). Non-demented men and women 50 years of age who were receiving primary medical care at HFHS were recruited, and concurrently enrolled cases (n = 144) and controls (n = 464) were frequency-matched for sex, race and age (+/-5 years). A risk factor questionnaire, administered by trained interviewers, inquired about every job held by each subject for 6 months from age 18 onward, including a detailed assessment of actual job tasks, tools and environment. An experienced industrial hygienist, blinded to subjects' case-control status, used these data to rate every job as exposed or not exposed to one or more of the metals of interest. Adjusting for sex, race, age and smoking status, 20 years of occupational exposure to any metal was not associated with PD. However, more than 20 years exposure to manganese (Odds Ratio [OR] = 10.61, 95% Confidence Interval [CI] = 1.06, 105.83) or copper (OR = 2.49, 95% CI = 1.06,5.89) was associated with PD. Occupational exposure for > 20 years to combinations of lead-copper (OR = 5.24, 95% CI = 1.59, 17.21), lead-iron (OR = 2.83, 95% CI = 1.07,7.50), and iron-copper (OR = 3.69, 95% CI = 1.40,9.71) was also associated with the disease. No association of occupational exposure to iron, mercury or zinc with PD was found. A lack of statistical power precluded analyses of metal combinations for those with a low prevalence of exposure (i.e., manganese, mercury and zinc). Our findings suggest that chronic occupational exposure to manganese or copper, individually, or to dual combinations of lead, iron and copper, is associated with PD.

35 Lee, L.A. & Slater, P. Role of globus pallidus and substantia nigra efferent pathways in striatally evoked head turning in the rat. Journal Experimental Brain Research. Volume 44, Number 2 / October, 1981.

36 Rhoades, R.A. & Tanner, G.A., Medical Physiology 2d Edition, pp. 103–4, Lippincott, Williams & Wilkins, Baltimore, Md., 2003.

37 Kuhn, W. High prevalence of parkinsonism after occupational exposure to lead-sulfate batteries. Neurology. 1998 Jun;50(6):1885–6.

Seven of nine postal workers exposed to lead-sulfate batteries over a period of up to 30 years developed parkinsonian symptoms. One of the remaining two showed left-hand bradykinesia and one was not available for examination. The high prevalence and cause of parkinsonism in these patients remains unexplained. Lead intoxication may play a role in the occurrence of parkinsonian symptoms, but involvement of sulfate and other sulfur compounds must also be considered.

38 Kamel, F. et. al. Lead Exposure and Amyotrophic Lateral Sclerosis. Epidemiology. 13(3):311–319, May 2002.

Investigators evaluated the relation of lead exposure to ALS, using both biological measures and interviews, in a case-control study conducted in New England from 1993 to 1996. Cases (N = 109) were recruited at two hospitals in Boston, Massachusetts. Population controls (N = 256) identified by random-digit dialing were frequency-matched to cases by age, sex, and region of residence within New England. Risk of ALS was associated with self-reported occupational exposure to lead (odds ratio [OR] = 1.9; 95% confidence interval [CI] = 1.1-3.3), with a dose response for lifetime days of lead exposure. Blood and bone lead levels were measured in most cases (N = 107) and in a subset of controls (N = 41). Risk of ALS was associated with elevations in both blood and bone lead levels. ORs were 1.9 (95% CI = 1.4-2.6) for each [mu]g/dl increase in blood lead, 3.6 (95% CI = 0.6-20.6) for each unit increase in log-transformed patella lead, and 2.3 (95% CI = 0.4-14.5) for each unit increase in log-transformed tibia lead.

39 Gray, F. et. Al. Luyso-pallido-nigral atrophy and amyotrophic lateral sclerosis. Acta Neuropathologica. Volume 66, Number 1 / March, 1985.

The clinical and pathologic findings in a 34-year-old woman with basal ganglia degeneration and amyotrophic lateral sclerosis are reported. The duration of symptoms was 2 years. A maternal uncle had a parkinsonian syndrome with onset at 45 years of age. Neuropathologic examination revealed extensive neuronal loss and gliosis in the corpus Luysii. Nerve cell loss and gliosis also involved both parts of the globus pallidus, and the substantia nigra. The corticospinal tracts were demyelinated in the spinal cord, and neuronal loss was observed in the anterior horns. Only one similar case of pallido-luyso-nigral atrophy associated with amyotrophic lateral sclerosis has, to our knowledge, been reported previously.

40 Vinken, P.J. et. al., Eds. Diseases of the Motor System, pp. 232–33, Elsevier Health Science, Amsterdam, 1991. By P. J. Vinken

41 Mergler, D. et. al. Nervous system dysfunction among workers with long-term exposure to manganese. Environ Res. 1994 Feb;64(2):151–80.

Neurological disorders, bearing many similarities to Parkinson's disease, have been associated with environmental and occupational exposure to manganese (Mn). To document early nervous system dysfunction associated with long-term exposure to Mn, a battery of neurofunctional tests was administered to workers employed in Mn alloy production. Study participation was 95% (n = 115). A matched pair design was used; actively working men, with no history of workplace exposure to neurotoxins, were recruited from the region as referents. Matching was done on the variables: age (+/-3 years), educational level (+/-2 years), smoking status, and number of children. Stationary environmental sampling indicated that Mn levels varied widely (geometric means: Mn dust, 0.89 mg/m3; respirable Mn, 0.04 mg/m3). The alloy workers had significantly higher levels of whole blood Mn (geometric mean: 1.03 microgram/100 ml vs 0.68 microgram/100 ml); no differences were observed for urinary Mn. Univariate analysis (paired t test, Signed Rank and McNemar) and multivariate analysis of variance (Hotelling-Lawley statistic) revealed that the pairs differed on symptom reporting, emotional state, motor functions, cognitive flexibility, and olfactory perception threshold; verbal fluency, basic mathematics, reading capability, and attentional capacity were similar. These findings are consistent with current knowledge on brain Mn activity and suggest that manifestations of early manganism can be observed in well designed population studies, using sensitive testing methods.

42 Bowler, R.M. et. al. Dose-effect relationships between manganese exposure and neurological, neuropsychological and pulmonary function in confined space bridge welders.Occupational and Environmental Medicine 2007;64:167–177.

Confined space welding in construction of a new span of the San Francisco-Oakland Bay Bridge without adequate protection was studied using a multidisciplinary method to identify the dose-effect relationship between adverse health effects and Mn in air or whole blood. Bridge welders (n = 43) with little or no personal protection equipment and exposed to a welding fume containing Mn, were administered neurological, neuropsychological, neurophysiological and pulmonary tests. Outcome variables were analysed in relation to whole blood Mn (MnB) and a Cumulative Exposure Index (CEI) based on Mn-air, duration and type of welding. Welders performed a mean of 16.5 months of welding on the bridge, were on average 43.8 years of age and had on average 12.6 years of education.

The mean time weighted average of Mn-air ranged from 0.11–0.46 mg/m3 (55% >0.20 mg/m3). MnB >10 _g/l was found in 43% of the workers, but the concentrations of Mn in urine, lead in blood and copper and iron in plasma were normal. Forced expiratory volume at 1s: forced vital capacity ratios (FEV1/FVC) were found to be abnormal in 33.3% of the welders after about 1.5 years of welding at the bridge. Mean scores of bradykinesia and Unified Parkinson Disease Rating Scale exceeded 4 and 6, respectively. Computer assisted

tremor analysis system hand tremor and body sway tests, and University of Pennsylvania Smell Identification Test showed impairment in 38.5/61.5, 51.4 and 88% of the welders, respectively. Significant inverse dose-effect relationships with CEI and/or MnB were found for IQ (p<=0.05), executive function (p<=0.03), sustaining concentration and sequencing (p<=0.04), verbal learning (p<=0.01), working (p<=0.04) and immediate memory (p<=0.02), even when adjusted for demographics and years of welding before Bay Bridge. Symptoms reported by the welders while working were: tremors (41.9%); numbness (60.5%); excessive fatigue (65.1%); sleep disturbance (79.1%); sexual dysfunction (58.1%); toxic hallucinations (18.6%); depression (53.5%); and anxiety (39.5%). Dose-effect associations between CEI and sexual function (p<0.05), fatigue (p<0.05), depression (p<0.01) and headache (p<0.05) were statistically significant.

43 Witholt, R. Gwiazda, R. H.& Smith, D. R. The neurobehavioral effects of subchronic manganese exposure in the presence and absence of pre-parkinsonism. Neurotoxicology and Teratology, Volume 22, Issue 6, November-December 2000, Pages 851–861.

Recent studies have implicated chronic elevated exposures to environmental agents, such as metals (e.g., manganese, Mn) and pesticides, as contributors to neurological disease. In particular, there is a concern that sensitive subpopulations such as the aged may be at increased risk for the onset of neurologic disorders because elevated exposures to Mn is associated with increased incidence of parkinsonism. Here, we utilized a rat model of pre-parkinsonism to investigate the effects of Mn exposure on neurotoxicity and the exacerbation of parkinsonism. A pre-parkinsonism state was induced using a unilateral intrastriatal injection of 6-hydroxydopamine (6-OHDA), followed 4 weeks later by Mn exposure (4.8 mg Mn/kg(3 intraperitoneal injections/week) for 5 weeks. Female Sprague–Dawley rats (n=44) were divided among the following treatments: (A) control, saline/vehicle; (B) Mn only; (C) 6-OHDA only; and (D) 6-OHDA+Mn. Brain Mn levels were measured by ICP–MS. Neurobehavioral function was assessed following Mn exposure using a functional observational battery (FOB) consisting of 10 neurobehavioral tests. Unilateral 6-OHDA lesions produced significant ipsilateral vs. contralateral striatal dopamine depletions (60–70%), but no measurable impairment of neurobehavioral function, thereby substantiating this pre-parkinsonism (i.e., subthreshold) model. In contrast, Mn exposure resulted in significant impairment of neurobehavioral function for eight of the 10 FOB tests. No effects of Mn exposure on striatal dopamine depletion were detected, despite the 3.4-fold increase in brain Mn levels over controls. Notably, Mn exposure in the presence of a pre-parkinsonism state significantly exacerbated the neurobehavioral impairment in the reactivity to handling (P<.049) and hopping contralateral rear limb (P<.033) FOB tests. While the persistence and Mn dose-response relationship of these neurobehavioral effects were not evaluated here, these results nonetheless suggest that chronic Mn exposure may increase the risk of neurobehavioral impairment in subpopulations that are in a pre-parkinsonism state.

44 Huang, C.C. et. al. Progression after chronic manganese exposure. NEUROLOGY 1993;43:1479.

We report a longitudinal follow-up study on six patients with chronic manganese-induced parkinsonism following cessation of manganese exposure. Compared with the 1987 study, their parkinsonian symptoms showed a slow progression, particularly in gait disturbances such as freezing during turning and walking backward with retropulsion. The mean disability scores on the King's College Hospital Rating Scale were 15.0 Å 4.2 in 1987 and 28.3 Å 6.7 in 1991 (p = 0.003, paired t test). Review of the video records also confirmed a worsening of parkinsonism, especially in difficulty turning. Three of six patients receiving levodopa treatment had an initial improvement. The response decreased after 2 to 3 years. During the therapy, they did not develop on-off fluctuation or dyskinesia. We conclude that patients with manganese-induced parkinsonism may develop increasing neurologic dysfunction long after cessation of exposure and that their responses to levodopa are different from those of patients with Parkinson's disease.

45 Lucchini R. et. al. Long-term exposure to "low levels" of manganese oxides and neurofunctional changes in ferroalloy workers. Neurotoxicology. 1999 Apr–Jun;20(2-3):287–97.

Occupational exposure to manganese can cause early neurobehavioral effects in low-or a-symptomatic workers. A battery of neuropsychological tests was administered to a group of 61 ferroalloy male workers and 87 controls. The average (geometric mean) manganese concentrations in total dust at the plant have changed from 1981 to 1997 respectively from 1597.03 micrograms/m3 to 239 micrograms/m3 at the furnace area; from 151.53 to 255.76 micrograms/m3 at the casting area; from 167 to 54.7 micrograms/m3 at the maintenance (welding operations), yielding a current overall value of 54.25 micrograms/m3. A cumulative exposure index was calculated for each alloy worker and the average value (geometric mean) resulted to be 1204.87 micrograms/m3 x years, which divided by the average length of exposure (15.17 years), showed the concentration of 70.83 micrograms/m3 of manganese in total dust. Blood and urinary manganese geometric means resulted significantly higher in the exposed workers (9.18 micrograms/l and 1.53 micrograms/g creatinine, respectively) than in controls (5.74 micrograms/l and 0.40 microgram/g creatinine, respectively). A positive correlation was observed between the airborne manganese concentrations in total dust and blood manganese (n = 55; R = 0.36; R2 = 0.13; p = 0.0068), whereas no association resulted between cumulative exposure index and both blood manganese and urinary manganese. Higher

prevalence of symptoms reporting was observed in the alloy workers concerning irritability, loss of equilibrium and rigidity. Tremor parameters including the central frequency and its dispersion, resulted to be statistically different in the exposed workers compared to the controls. Motor functions exploring the coordination of rapid and alternating movements and memory functions resulted to be impaired in the manganese workers. Dose-effect relationships were observed between the cumulative exposure index and some of the test results, whereas no relationship was found with the airborne manganese concentrations and the biological indicators of exposure. These findings are consistent with the existing knowledge of a cumulative mechanism of action of manganese, which must be carefully considered when setting safe exposure levels. In order to be protective for the entire working life, the average annual exposure level should be lower than 100 micrograms/m3.

46 R. H. Gwiazda, R.H. et. al. Low Cumulative Manganese Exposure Affects Striatal GABA but not Dopamine. NeuroToxicology Volume 23, Issue 1, May 2002, Pages 69–76.

The introduction of the anti-knock methylcyclopentadienyl manganese (Mn) tricarbonyl (MMT) in gasoline has raised concerns about the potential for manganese neurotoxicity. Because subpopulations such as the elderly in the early stages of neurodegenerative disease may be at increased risk for manganese toxicity, a pre-Parkinsonism rat model was used to evaluate whether sub-chronic manganese exposure can aggravate the neurochemical and behavioral dysfunctions characteristic of Parkinsonism. Sub-threshold levels of dopamine depletion of 3.5, 53 and 68% were generated via intrastriatal unilateral 6-hydroxydopamine (6-OHDA) doses. A sub-chronic dosing regimen of low cumulative manganese exposure (4.8 mg Mn/kg body weight, 3 i.p. injections per week(5 weeks) was started 4 weeks after 6-OHDA treatments. Neurochemical and neuromotor (functional observational battery (FOB)) measures were evaluated. Manganese produced significant ($P<0.05$) reductions of 30–60% in motor function. This effect was exacerbated in the presence of a pre-Parkinsonism condition [Neurotox. Teratol. 22 (2000) 851]. Manganese did not affect striatal dopamine, but resulted in significant increases in striatal-aminobutyric acid (GABA) of 16 and 22% ($P<0.01$) in both striati and a borderline non-significant 4% increase in frontal cortex ($P=0.076$). Manganese treatment produced increased aspartate ($P<0.01$) in the manganese and 6-OHDA treated striatum. In light of previous studies predominantly showing dopamine depletion with elevated manganese exposures, the significant effects of manganese on striatal GABA but not on striatal dopamine at the low cumulative exposure administered here suggest a progression in manganese toxicity with increasing cumulative dose, whereby GABA levels are adversely affected before striatal dopamine levels. Because these neurochemical disruptions were accompanied by motor dysfunction that was exacerbated in the presence of a pre-Parkinsonism condition, an increased environmental burden of manganese may have deleterious effects on populations with sub-threshold neurodegeneration in the basal ganglia (e.g. pre-Parkinsonism).

47 Rybicki B.A. et. al. Parkinson's disease mortality and the industrial use of heavy metals in Michigan. Mov Disord. 1993;8(1):87–92.

Parkinson's disease (PD) mortality rates in Michigan counties for 1986–1988 were calculated with respect to potential heavy metal exposure (iron, zinc, copper, mercury, magnesium, and manganese) from industry based on recent census data. Individuals were counted as a PD death if the diagnosis was listed as an "underlying" or "related" cause of death on the death certificate. Counties with an industry in the paper, chemical, iron, or copper related-industrial categories (ICs) had statistically significantly ($p < 0.05$) higher PD death rates than counties without these industries. Significant correlations of chemical ($rs = 0.22$; $p = 0.05$), paper ($rs = 0.22$; $p = 0.05$) and iron ($rs = 0.29$; $p = 0.008$) industry densities with PD death rates were also present. Counties were divided into high (> 15/100,000 individuals 45 years old and over) and low (< = 15/100,000) PD death rate counties by cluster analysis. Geographically, counties with high PD mortality were located mainly in the southern half of the lower peninsula and eastern half of the upper peninsula; low PD death rate counties formed two distinct clusters in the western edge of the upper peninsula and the north-central portion of the lower peninsula. Other possible risk factors that may explain the varied distribution of PD death rates in Michigan were examined. Those significantly correlated with PD mortality included population density ($rs = 0.31$; $p = 0.005$), farming density ($rs = 0.25$; $p = 0.02$), and well water use ($rs = -0.24$; $p = 0.03$). These ecologic findings suggest a geographic association between PD mortality and the industrial use of heavy metals.

48 Ferraz, H.B. et. al. Chronic exposure to the fungicide maneb may produce symptoms and signs of CNS manganese intoxication. NEUROLOGY 1988; 38:550.

Manganese (Mn) poisoning, a well-known hazard in miners and industrial workers, shares many features with Parkinson's disease. Two young agricultural workers with a parkinsonian syndrome, who mentioned exposure to the fungicide maneb (manganese ethylene-bis-dithiocarbamate), led us to investigate a new possible source of Mn intoxication. Fifty male rural workers with occupational exposure to maneb were compared with 19 rural workers without fungicide exposure. We noted significantly higher prevalence of plastic rigidity with cogwheel phenomenon, headache, fatigue, nervousness, memory complaints, and sleepiness in the exposed group. In

addition, we saw other neurologic signs, such as postural tremor, cerebellar signs, and bradykinesia, although without statistical significance. The data suggest that occupational exposure to pesticides containing Mn is a possible source of Mn intoxication of the CNS.

49 Rosner and Markowitz, 347.

50 Jack Lewis, "Lead Poisoning: A Historical Perspective," U.S. Environmental Protection Agency, http://www.epa.gov/history/topics/perspect/lead.htm.

51 David Rosner and Gerald Markowitz, "A 'Gift of God'?: The Public Health Controversy over Leaded Gasoline during the 1920s," American Journal of Public Health Vol. 75, No. 4 (April 1985), pgs. 344–352.

52 Gilbert, S.G. & Weiss, B. A rationale for lowering the blood lead action level from 10 to 2 ug/dL. Neurotoxicology. 2006 September; 27(5): 693–701.

Fifteen years ago, in 1991, the U.S. Centers for Disease Control and Prevention (CDC) established 10 ug/dL as the lowest level of concern for children's blood lead levels. This value is extremely important because, historically, policy makers and public health officials generally have acted to remove sources of lead exposure only after the CDC's level of concern had been exceeded. A growing body of evidence, however, reveals that blood lead levels below 10 ug/dL may impair neurobehavioral development. There is now sufficient and compelling scientific evidence for the CDC to lower the blood lead action level in children. This review argues that a level of 2 ug/dL is a useful and feasible replacement. Although it can be argued, in turn, that no threshold for the health effects of lead is demonstrable, analytically a blood level of 2 ug/dL is readily and accurately measured and provides a benchmark for successful prevention. Lowering the level of concern would encourage and accelerate the investments needed to ensure that children are protected from lead exposure in their homes, schools, and play settings. Such a program would also offer economic advantages because of the coupling between lead, educational attainment, earnings and anti-social conduct. By lowering the blood action level, CDC will promote policies and initiatives designed to further reduce children's exposure to this potent developmental neurotoxicant.

53 Gilbert, S.G. & Weiss, B. A rationale for lowering the blood lead action level from 10 to 2 ug/dL. Neurotoxicology. 2006 September; 27(5): 693–701.

54 Magda Lovei, Phasing out lead from gasoline: worldwide experience and policy implications, World Bank, Washington, D.C.

55 Agency for Toxic Substances and Disease Registry, The Nature and Extent of Lead Poisoning in Children in the United States: A Report to Congress, US Department of Health and Human Services, Public Health Service, 1988.

56 Gilbert, S.G. &Weiss, B. A rationale for lowering the blood lead action level from 10 to 2 ug/dL. Neurotoxicology. 2006 September; 27(5): 693–701. doi: 10.1016/j.neuro.2006.06.008.

57 Nevin, R. How Lead Exposure Relates to Temporal Changes in IQ, Violent Crime, and Unwed Pregnancy. Environmental Research Volume 83, Issue 1, May 2000, Pages 1–22.

His study compares changes in children's blood lead levels in the United States with subsequent changes in IQ, based on norm comparisons for the Cognitive Abilities Test (CogAT) given to representative national samples of children in 1984 and 1992. The CogAT norm comparisons indicate shifts in IQ levels consistent with the blood lead to IQ relationship reported by an earlier study and population shifts in average blood lead for children under age 6 between 1976 and 1991. The CogAT norm comparisons also support studies indicating that the IQ to blood lead slope may increase at lower blood lead levels. Furthermore, long-term trends in population exposure to gasoline lead were found to be remarkably consistent with subsequent changes in violent crime and unwed pregnancy. Long-term trends in paint and gasoline lead exposure are also strongly associated with subsequent trends in murder rates going back to 1900. The findings on violent crime and unwed pregnancy are consistent with published data describing the relationship between IQ and social behavior. The findings with respect to violent crime are also consistent with studies indicating that children with higher bone lead tend to display more aggressive and delinquent behavior. This analysis demonstrates that widespread exposure to lead is likely to have profound implications for a wide array of socially undesirable outcomes.

58 Needleman, H.L. Bone lead levels and delinquent behavior. J. of the Am Med Assn. Vol. 275 No. 5, February 7, 1996.

OBJECTIVE. To evaluate the association between body lead burden and social adjustment. DESIGN. Retrospective cohort study.

SETTING. Public school community.

PARTICIPANTS. From a population of 850 boys in the first grade at public schools, 503 were selected on the basis of a risk scale for antisocial behavior. All of the 850 boys who scored in the upper 30th percentile of the distribution on a self-reported antisocial behavior scale were matched with an equal number drawn by lot from the lower 70% of the distribution. From this sample, 301 students accepted the invitation to participate.

EXPOSURE MEASURE. K x-ray fluorescence spectroscopy of tibia at subjects' age of 12 years.

MAIN OUTCOME MEASURES. Child Behavior Checklist (CBCL), teachers' and parents' reports, and subjects' self-report of antisocial behavior and delinquency at 7 and 11 years of age. RESULTS. Subjects, teachers, and parents were blind to the bone lead

measurements. At 7 years of age, borderline associations between teachers' aggression, delinquency, and externalizing scores and lead levels were observed after adjustment for covariates. At 11 years of age, parents reported a significant lead-related association with the following CBCL cluster scores: somatic complaints and delinquent, aggressive, internalizing, and externalizing behavior. Teachers reported significant associations of lead with somatic complaints, anxious/depressed behavior, social problems, attention problems, and delinquent, aggressive, internalizing, and externalizing behavior. High-lead subjects reported higher scores in subjects' self-reports of delinquency at 11 years. High-lead subjects were more likely to obtain worse scores on all items of the CBCL during the 4-year period of observation. High bone lead levels were associated with an increased risk of exceeding the clinical score (T > 70) for attention, aggression, and delinquency.

CONCLUSION. Lead exposure is associated with increased risk for antisocial and delinquent behavior, and the effect follows a developmental course.

59 Chen, A. et. al. Lead Exposure, IQ, and Behavior in Urban 5-to 7-Year-Olds: Does Lead Affect Behavior Only by Lowering IQ PEDIATRICS Vol. 119 No. 3 March 2007, pp. e650-e658 (doi:10.1542/peds.2006-1973).

BACKGROUND. Lead exposure in childhood lowers IQ scores, but its effect on children's behavior is less clear. Because IQ, per se, affects behavior, measuring the direct effect of lead requires measuring and then adjusting for IQ. In addition, either peak blood lead concentration, usually at 2 years old, or the lower blood lead level measured at school age may be the most relevant. Few studies have all of this information.

OBJECTIVES. The purpose of this work was to differentiate the direct effect of lead on behavior and the indirect effect through IQ and to examine the strength of the association for peak and concurrent blood lead concentration.

METHODS. Data come from a clinical trial of the chelating drug succimer to prevent cognitive impairment in 780 urban 12-to 33-month-olds with blood lead concentrations of 20 to 44 _g/dL. The children were followed from ages 2 to 7 years. The trial data were analyzed as a prospective observational study.

RESULTS. Blood lead concentration at 2 years old was not associated with Conners' Parent Rating Scale-Revised scores at 5 years of age or Behavioral Assessment Systems for Children scores at 7 years of age. Blood lead level at 7 years of age had direct effects on the Behavioral Assessment Systems for Children behavioral symptoms index, externalizing, and school problems at age 7.

60 Mendelsohn, A.L. Low-Level Lead Exposure and Behavior in Early Childhood. PEDIATRICS Vol. 101 No. 3 March 1998, p. e10.

OBJECTIVE. To assess whether small elevations in blood lead level were associated with measurable behavioral changes in a group of poor children between 1 and 3 years old.

METHODS. The study population consisted of children presenting for routine well-child care to the pediatric clinic at Bellevue Hospital Center, a large urban public hospital. The following inclusion criteria were used for entry into the study: age 12 to 36 months; capillary lead screening result <1.21 _mol/L (25 _g/dL); no known prior history either of blood lead level >1.21 _mol/L (25 _g/dL) or lead exposure requiring chelation therapy; Latino or African-American; English or Spanish spoken in the home; biological mother as primary caretaker; child not presently attending day care; full-term, singleton gestation; birth weight at least 2500 g; no known neurologic or developmental disorder; and no severe chronic disease, including human immunodeficiency virus infection. Study enrollment was simultaneously stratified by capillary lead level and age.

All children between 12 and 36 months attending the pediatric clinic during the study period received screening capillary blood measures of lead level following the recommendations of the Centers for Disease Control and Prevention and the American Academy of Pediatrics as part of routine primary care. During periods of enrollment, consecutive lead measurements performed in the pediatric clinic were reviewed by one of the researchers. For those children meeting entry criteria based on lead level and age, further eligibility based on the remainder of the inclusion criteria was determined through parental interview and review of the medical record.

Lead exposure was assessed with a single capillary blood specimen, using atomic absorption spectrophotometry. Subjects were considered to be lead-exposed if their lead level was between 0.48 and 1.20 _mol/L (10 and 24.9 _g/dL) and nonexposed if their lead level was between 0 and 0.48 _mol/L (0 and 9.9 _g/dL).

Behavior was assessed using the Behavior Rating Scale (BRS) of the Bayley Scales of Infant Development, second edition. The BRS in this age group consists of three components: an Emotional Regulation Factor that measures hyperactive/distractible/easy-frustration behaviors; an Orientation-Engagement Factor that measures fear/withdrawal/disinterest behaviors; and a Motor Quality Factor that assesses the appropriateness of movement and tone. The BRS is scored as a percentile; lower scores reflect more problematic behaviors. Researchers performing the BRS were blinded to capillary lead results.

Information was collected concerning factors that might confound the relationship between lead and behavior. Demographic factors were collected, including: child's age, gender, and country of origin; mother's age, marital status, parity, country of origin, and

primary language spoken; parental education, and occupation and receipt of public assistance. Socioeconomic status was determined using the Hollingshead Two-Factor Index of Social Position. Maternal verbal IQ was assessed using the Peabody Picture Vocabulary Test-Revised. Maternal depression was assessed using the Center for Epidemiologic Studies-Depression Scale. Cognitive stimulation provided in the home was assessed using a new office-based instrument, the StimQ, which measures the quantity and quality of play materials and parent-toddler activities in the child's home. To assess the child for iron deficiency, we performed a hematocrit and mean corpuscular volume at the time of the capillary lead evaluation. A presumptive diagnosis of iron deficiency was made if the child was either anemic (defined as a hematocrit <32) or had a mean corpuscular volume <72.

RESULTS. The study sample consisted of 72 children. Children in the lead-exposed group (n = 41) had a mean BRS behavior score that was 15.8 points lower than that of children in the nonexposed group (n = 31), which was significant by the Student's t test. For the emotional regulation factor measuring hyperactive/impulsive/easy-frustration behaviors, children in the exposed group had a mean score that was 14.6 points lower than that of the nonexposed group, which was significant by the Student's t test. For the orientation-engagement factor measuring fear/withdrawal/disinterest behaviors, children in the exposed group had a mean score that was 14.1 points lower, significant by the Student's t test.

Multiple linear regression analyses were used to examine the independent relationship between BRS (total and factor scores) and lead group, after adjusting for potential confounders. Six variables were related to either lead group or BRS behavior score in unadjusted analysis and were, therefore, included as potential confounders in each of the multiple regressions: child's age and gender, and mother's age, verbal IQ, depression score, and provision of cognitive stimulation.

In the analysis of the relationship between the BRS total score and lead group, the adjusted mean BRS behavior score in the exposed group was 17.3 points (95% confidence [CI]: 3.3, 31.3) lower than that of children in the nonexposed group (sr =-0.27). In the analysis of the relationship between the emotional regulation factor and lead group, the adjusted mean factor score in the exposed group was 16.6 points (95% CI: 2.1, 31.2) lower than that for the nonexposed group (sr =-0.25). In the analysis of the relationship between the orientation-engagement factor and lead group, the exposed group had an adjusted mean score that was 14.2 points (95% CI:-2.1, 30.5) lower than that for the nonexposed group (sr =-0.20).

In these multiple regression analyses, mother's depression score was significantly associated with a lower total BRS score (sr =-0.25) and with lower emotional regulation factor (sr =-0.23). Older children had higher BRS scores (sr = 0.20), and had significantly higher emotional regulation factor scores (sr = 0.22). A relationship was observed between male gender and lower emotional regulation scores that did not reach significance (sr =-0.21). Iron deficiency, cognitive stimulation provided in the home and mother's verbal IQ were not related to any measures of behavior.

CONCLUSTIONS. Low-level lead exposure is associated with adverse behavioral changes in very young preschool children. This association may be particularly important for poor children, who are also at risk for behavior problems on the basis of other environmental factors such as maternal depression. Clinicians should consider screening for behavioral problems in very young children with low-level lead exposure.

61 Paul B. Stretesky, P.B. & Lynch, M.J. The Relationship Between Lead Exposure and Homicide. Arch Pediatr Adolesc Med. 2001;155:579–582.

Context Previous studies have suggested that excessive lead exposure is related to aggressive and violent behavior.

OBJECTIVE. To evaluate the association between estimated air lead concentrations and homicide rates.

DESIGN. Cross-sectional ecological study.

SETTING. All counties in the contiguous 48 states of the United States.

EXPOSURE MEASURE. Estimated air lead concentrations and blood lead levels.

MAIN OUTCOME MEASURE. The homicide rate in each county.

RESULTS. Negative binomial regression was used to examine the relationship between air lead concentrations and the incidence of homicide across counties in the United States (N = 3111). After adjusting for sociologic confounding factors and 9 measures of air pollution, the only indicator of air pollution found to be associated with homicide rates was air lead concentration. Across all counties, estimated air lead concentrations ranged from 0 to 0.17 _g/m3. The adjusted results suggest that the difference between the highest and lowest level of estimated air lead is associated with a homicide incidence rate ratio of 4.12 (95% confidence interval, 1.02-16.61).

CONCLUSION. The results of this study support recent findings that there is an association between lead exposure and violent behavior.

62 Hafeman, D. et. al. Association between Manganese Exposure through Drinking Water and Infant Mortality in Bangladesh. Environmental Health Perspectives Volume 115, Number 7, July 2007.

Manganese is a common natural contaminant of groundwater in Bangladesh. In this cross-sectional study investigators assessed the association between water manganese and all-cause infant mortality in the offspring of female participants in the Health Effects of Arsenic Longitudinal Study Cohort. In 2001, drinking water samples were collected, a history of well use was obtained, and a history of birth outcomes was ascertained. To avoid misclassification of exposure, women were included only if they had been drinking from the same well for most of their childbearing years (marriage years – well years Æ 2). Of a total of 26,002 births among 6,537 mothers, 3,837 children were born to women with this profile. The current analysis was based on the portion of these infants (n = 3,824) with recorded exposure and outcome status, 335 of whom died before reaching 1 year of age. Infants exposed to water manganese greater than or equal to the 2003 World Health Organization standard of 0.4 mg/L had an elevated mortality risk during the first year of life compared with unexposed infants [odds ratio (OR) = 1.8 ; 95% confidence interval (CI) , 1.2–2.6]. Adjustment for water arsenic, indicators of social class, and other variables did not appreciably alter these results. When the population was restricted to infants born to recently married parents (marriage year1991 or after) , this elevation was more pronounced (OR = 3.4 ; 95% CI, 1.5–7.9).

63 Dörner, K. et. al. Longitudinal manganese and copper balances in young infants and preterm infants fed on breast-milk and adapted cow's milk formulas. 1989 May;61(3):559-72.

Mn and Cu intake and retention in twenty full-term infants and six preterm infants were studied on the basis of 72 h balances. The age of the infants was 2-16 weeks and the gestational age of the preterm infants (triplets) 34 and 36 weeks. Three nutrition schemes were pursued: breast-fed, formula-fed with unsupplemented adapted formula and formula-fed with trace element supplementation. 2. The mean Mn concentration of all breast-milk samples (n 2339) was 6.2 micrograms/l. The two formulas had similar Mn concentrations (77 and 99 micrograms/l) but had different Fe, Cu (121 and 619 micrograms/l), Zn and I contents. The mean Cu concentration in mother's milk was 833 micrograms/l. 3. The following mean daily Mn intakes and retentions (micrograms/kg) respectively were measured: breast-fed full-term 1.06 (SD 0.43) and 0.43 (SD 0.65), formula-fed full-term 14.2 (SD 3.1) and 2.8 (SD 4.8), formula-fed preterm 15.0 (SD 2.2) and 0.06 (SD 5.87). The results for Cu were 114.5 (SD 22.3) and 88.0 (SD 46.5) micrograms/kg in breast-fed, 19.8 (SD 4.2) and 4.6 (-11.5-9.6) in the unsupplemented formula-fed and 106.4 (SD 18.9) and 55.5 (SD 20.3) in the supplemented formula full-term infant group. No significant influence of the trace element contents of the formulas on the relative retention of Mn or Cu was found. 4. Young preterm infants, and to some degree young full-term infants, often had negative Mn balances caused by a high faecal excretion. The formulas with a Mn concentration below 100 micrograms/l gave a sufficient supply of Mn. Preterm infants fed on the unsupplemented formula had a marginal Cu supply and their first balances were negative (-3.8 (SD 1.8) micrograms/kg). 5. In accordance with the estimated safe and adequate daily dietary intakes (recommended dietary allowances), formula-fed infants receive much more Mn than breast-fed infants and their absolute retention is higher. 6. Cu from breast-milk had a significantly better biological availability than that from cow's milk formula. If retentions similar to those in breast-fed infants are intended, we conclude, therefore, that cow's milk formula should be fortified with Cu up to a level of at least 600 micrograms/l.

64 Roels H et. al. Influence of the route of administration and the chemical form (MnCl2, MnO2) on the absorption and cerebral distribution of manganese in rats. Arch Toxicol 71(4): 223-30 (1997).

The absorption and cerebral distribution of manganese (Mn) were studied with respect to the route of administration and the chemical form of the Mn compound. Different groups of adult male rats received either MnCl2, 4H2O or MnO2 once a week for 4 weeks at a dose of 24.3 mg Mn/kg body wt. (b.w.) by oral gavage (g.) or 1.22 mg Mn/kg b.w. by intraperitoneal injection (i.p.) or intratracheal instillation (i.t.). Control rats were treated with 0.9% saline. Four days after the last administration the rats were killed and the concentration of Mn measured in blood, hepatic and cerebral tissues (cortex, cerebellum, and striatum). The liver Mn concentration was not affected by the treatments whatever the chemical form or the route of administration of the Mn compound. Administration of MnCl2 by g., i.p., and i.t. routes produced equivalent steady-state blood Mn concentrations (about 1000 ng Mn/100 ml), representing increases of 68, 59, and 68% compared with controls, respectively. Mn concentrations were significantly increased in the cortex but to a lesser extent (g., 22%; i.p., 36%; i.t., 48%) and were higher in the cerebellum after i.p. and i.t. administrations than after oral gavage. Rats treated i.t. with MnCl2 showed an elective increase of the striatal Mn concentration (205%). In contrast, MnO2 given orally did not significantly increase blood and cerebral tissue Mn concentrations; the low bioavailability is most likely due to the lack of intestinal resorption. Administration of MnO2 i.p. and i.t., however, led to significant increases of Mn concentrations in blood and cerebral tissues. These increments were not significantly different from those measured after MnCl2 administration, except for striatal Mn after i.t. which was markedly less (48%) after MnO2 administration. A comparison of the blood Mn kinetics immediately after g. and i.t. treatment with MnCl2 or MnO2 indicated that the higher elevation of blood Mn concentration (> 2000 ng Mn/100 ml) after i.t. administration of MnCl2 could account for the elective uptake of Mn in the striatum observed in repeated dosing experiments. It is concluded that the modulation of Mn distribution in brain regions according to the route of administration and the chemical form of the Mn compound may be explained on the basis of different blood Mn kinetics and regional anatomic specificities of the striatal region.

65 Elder A. et. al. Translocation of inhaled ultrafine manganese oxide particles to the central nervous system. Environ Health Perspect 114(8): 1172-8 (2006).

Studies in monkeys with intranasally instilled gold ultrafine particles (UFPs ; < 100 nm) and in rats with inhaled carbon UFPs suggested that solid UFPs deposited in the nose travel along the olfactory nerve to the olfactory bulb. To determine if olfactory translocation occurs for other solid metal UFPs and assess potential health effects, investigators exposed groups of rats to manganese (Mn) oxide UFPs (30 nm ; ~ 500 _g/m3) with either both nostrils patent or the right nostril occluded. They analyzed Mn in lung, liver, olfactory bulb, and other brain regions, and we performed gene and protein analyses. After 12 days of exposure with both nostrils patent, Mn concentrations in the olfactory bulb increased 3.5-fold, whereas lung Mn concentrations doubled ; there were also increases in striatum, frontal cortex, and cerebellum. Lung lavage analysis showed no indications of lung inflammation, whereas increases in olfactory bulb tumor necrosis factor-alpha mRNA (~ 8-fold) and protein (~ 30-fold) were found after 11 days of exposure and, to a lesser degree, in other brain regions with increased Mn levels. Macrophage inflammatory protein-2, glial fibrillary acidic protein, and neuronal cell adhesion molecule mRNA were also increased in olfactory bulb. With the right nostril occluded for a 2-day exposure, Mn accumulated only in the left olfactory bulb. Solubilization of the Mn oxide UFPs was < 1.5% per day. This demonstrates that the olfactory neuronal pathway is efficient for translocating inhaled Mn oxide as solid UFPs to the central nervous system and that this can result in inflammatory changes and suggests that despite differences between human and rodent olfactory systems, this pathway is relevant in humans.

66 Wasserman, G.A. et. al. Water Manganese Exposure and Children's Intellectual Function in Araihazar, Bangladesh. Environ Health Perspect 114: 124-129 (2006)

T assess the neurotoxicity of exposure to manganese via drinking water investigators conducted a cross-sectional investigation of intellectual function in 142 10-year-old children in Araihazar, Bangladesh, who had been consuming tube-well water with an average concentration of 793 _g Mn/L and 3 _g arsenic/L. Children and mothers came to a field clinic, where children received a medical examination in which weight, height, and head circumference were measured. Children's intellectual function was assessed on tests drawn from the Wechsler Intelligence Scale for Children, version III, by summing weighted items across domains to create Verbal, Performance, and Full-Scale raw scores. Children provided urine specimens for measuring urinary As and creatinine and were asked to provide blood samples for measuring blood lead, As, Mn, and hemoglobin concentrations. After adjustment for sociodemographic covariates, water Mn was associated with reduced Full-Scale, Performance, and Verbal raw scores, in a dose-response fashion ; the low level of As in water had no effect. In the United States, roughly 6% of domestic household wells have Mn concentrations that exceed 300 _g Mn/L, the current U.S. Environmental Protection Agency lifetime health advisory level. The results demonstrate that in both Bangladesh and the United States, some children are at risk for Mn-induced neurotoxicity.

67 Takser, et. al. Manganese, Monoamine Metabolite Levels at Birth, and Child Psychomotor Development. NeuroToxicology

Volume 24, Issues 4-5, August 2003, Pages 667-674, Eighth International Symposium on Neurobehavioral Methods and Effects in Occupational and Environmental Health, Brescia, Italy, June 23-26, 2002.

Studies have demonstrated neurobehavioral impairment related to manganese (Mn) exposure in the workplace and association with irreversible neurodegenerative disorders resembling idiopathic Parkinson disease. To assess the a relationship between Mn accumulation in the foetus during pregnancy and obtain information on developmental effects of environmental low-level exposure in human, investigators conducted a prospective epidemiological study in 247 healthy pregnant women and their babies to determine the long-term effect of in utero Mn levels on child's psychomotor development. Concurrently, they examined the relationship between Mn tissue levels at delivery and foetal plasma monoamine metabolites. Of the newborns, 195 were examined at 9 months, 126 at 3 years and 100 at 6 years. At 9 months, the Brunet–Lézine scales were administered. The McCarthy scales of children's abilities were used at 3 and 6 years. After adjustment for potential confounding co-factors (child's gender, mother's educational level), negative relationships were observed between cord blood Mn levels and several psychomotor sub-scales at age of 3 years: "attention" (partial r=-0.33, P<0.001), "non-verbal memory" (partial r=-0.28, P<0.01), and "hand skills" (partial r=-0.22, P<0.05). No significant relationships were observed between Mn measures at birth and the general psychomotor indices, Brunet–Lézine developmental quotient (DQ) at 9 months or McCarthy general cognitive index (GCI) at 3 and 6 years. Maternal blood Mn levels were negatively associated with foetal plasma HVA and 5-HIAA concentrations (adjusted for labour duration, child's gender, and smoking during pregnancy), but the adjustment for monoamine levels at birth did not change the association between the Mn levels and the psychomotor scores. These results suggest that environmental Mn exposure in utero affects early psychomotor development.

68 Ericson, J.E. et. al. Prenatal manganese levels linked to childhood behavioral disinhibition. Neurotoxicology and Teratology,Volume 29, Issue 2, March-April 2007, Pages 181-187.

Although manganese (Mn) is an essential mineral, high concentrations of the metal can result in a neurotoxic syndrome affecting dopamine balance and behavior control. Investigators conducted an exploratory study showing an association between Mn deposits in

tooth enamel, dating to the 20th and 62–64th gestational weeks, and childhood behavioral outcomes. In a sample of 27 children, 20th week Mn level was significantly and positively correlated with measures of behavioral disinhibition, specifically, play with a forbidden toy (36 months), impulsive errors on a continuous performance and a children's Stroop test (54 months), parents' and teachers' ratings of externalizing and attention problems on the Child Behavior Checklist (1st and 3rd grades), and teacher ratings on the Disruptive Behavior Disorders Scale (3rd grade). By way of contrast, Mn level in tooth enamel formed at the 62–64th gestational week was correlated only with teachers' reports of externalizing behavior in 1st and 3rd grades. The source(s) of Mn exposure in the sample were unknown.

69 Collipp PJ, Chen SY and Maitinsky S (1983). Manganese in infant formulas and learning disability. Ann Nutr Metab 27(6): 488-94.

The concentration of manganese in the hair of normal newborn infants was found to increase significantly from 0.19 micrograms/g at birth to 0.965 micrograms/g at 6 weeks of age and 0.685 micrograms/g at 4 months when they were fed infant formula. There was an insignificant increase to 0.330 micrograms/g at age 4 months in breast-fed infants. After this age there was a slow decline in hair manganese to 0.268 micrograms/g in normal children at age 8 years and 0.434 in learning disabled (hyperactive) children. This is the third study reporting elevated hair manganese in learning disabled children.

70 Zhang et. Al. 1995.

71 Ethyl Corp. v. Browner, 51 F.3d 1053 (D.C. Cir. 1995); Ethyl Corp. v. Browner, 67 F.3d 941 (D.C. Cir. 1995) and Ethyl Corp. v. Browner, 306 F.3d 1144 (D.C. Cir. 2002).

72 Ethyl Corp. v. Browner, 51 F.3d 1053 (D.C. Cir. 1995), which limited EPA's authority under § 211(f) to consider potential public health concerns as a basis for denying permission to introduce new fuels or fuel additives into commerce.

73 Ethyl Canada Inc. v. The Attorney General of Canada and the Minister of the Environment, No. 97-CV-126708 (Ontario Court General Division) and the associated Ethyl Corp. v. Government of Canada proceeding arising under the Chapter 11 investment provisions of the North American Free Trade Agreement ("NAFTA"), which collectively resulted in a settlement awarding the plaintiff monetary compensation as a result of a Canadian government ban on the importation or inter-provincial trade of the fuel additive, MMT.

74 Sanford Gaines, "Environmental Policy Implications of Investor-State Arbitration Under NAFTA Chapter 11," Commission of Environmental Cooperation, Third North American Symposium on Assessing the Environmental Effects of Trade, Nov. 30-Dec.1, 2005, Montreral, Canada.

75 George Monbiot, " Running on MMT," The London Guardian, Aug., 1998.

76 Kevin L. Fast, "TITLE II OF THE CLEAN AIR ACT: MOBILE SOURCES AND FUELS AND FUEL ADDITIVES EXPERIENCE," http://kevinfastlaw.com/title2.html.

77 Michael P. Walsh, "Car Lines," http://www.walshcarlines.com/

78 Michael P. Walsh, "Car Lines," http://www.walshcarlines.com/

79 The John D. and Catherine T. MacArthur Foundation, "MacArthur Fellows Program," http://www.macfound.org/site/c.lkLXJ8MQKrH/b.1139453/k.F627/Search_for_a_Fellow.htm.

80 Kevin L. Fast, "A Cautionary Tale: How Even Knowledgeable Experts Can Be Misled by the Precautionary Principle," http://kevinfastlaw.com/Response%20to%20Lead%20Lessons%20Article.pdf.

81 Cite TK TK

82 Afton Chemical, "History of mmt®," http://www.aftonchemical.com/Products/mmt/History+of+mmt%C2%AE.htm