SINGLETON SHIRE HEALTHY ENVIRONMENT GROUP

"The impact on Health of Air Quality in Australia"

A community-based group looking to address environmental issues affecting Singleton Shire residents
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SSHEG is Not Anti Mining or Anti Power Stations, we seek identification of What is making our Children and Community Sick so they can be mitigated by OH&S Compliance Orders.

SSHEG Focus On Health

Senate Committee Submission March 2013

Supplementary Submission Summary covering letter

"The Impact on Health of Air Quality in Australia"

A Review of the current understanding of the known Air Quality Pollutants by SSHEG has exposed the recently Internationally Medically recognised Health dangers of Diesel Exhaust Pollutants.

Specifically, the 24 year investigation into the Toxicity of Diesel Exhaust Pollution from 1988 resulted in June 2012 after a one week Expert Review of Medical Research that identified environmental factors that can increase the risk of human cancer; with the *Group1* *"-Carcinogenic to humans"* is a cause of lung Cancer and also noted a positive association with an increased risk of Bladder Cancer.(Attachment S25) Ten nitroarenes found in diesel engine exhaust were also evaluated.

There are a range of Diesel Exhaust Particulate Matter (Attachment S26) and Attachment S27 shows the expected Human Health Risks from this List of Toxic Pollutants found in Diesel Exhaust.

It is the Occupational Safety of Diesel Machinery in Underground Mining that initially focused attention on the Dangers of Carbon Monoxide in Exhaust Fumes, however the complex nature of the Diesel Exhaust Fine Particulate Matter even at low concentrations emerged as the real Danger to Miners Health and particularly Lung Cancer.

"Kurt Straif, the director of the International Agency for Research on Cancer IARC, said Diesel fumes are now "*on the same order of magnitude as Passive Smoking*". This now suggests that where initial studies show a risk in heavily exposed occupational groups that this is soon after followed with positive findings for the general population".

Similarly, World Health Organisation(WHO) experts *said "Diesel Engine Fumes can cause Lung Cancer and belong in the same potentially deadly category as asbestos, arsenic and mustard gas".*

"Most recently, the U.S. National Cancer Institute and CDC's National Institute for Occupational Safety and Health (NIOSH) published two long-anticipated mortality analyses of more than 12,000 underground mine workers. Both the cohort mortality analysis and the case-control study reported an increased risk of death from lung cancer with exposure to diesel exhaust".

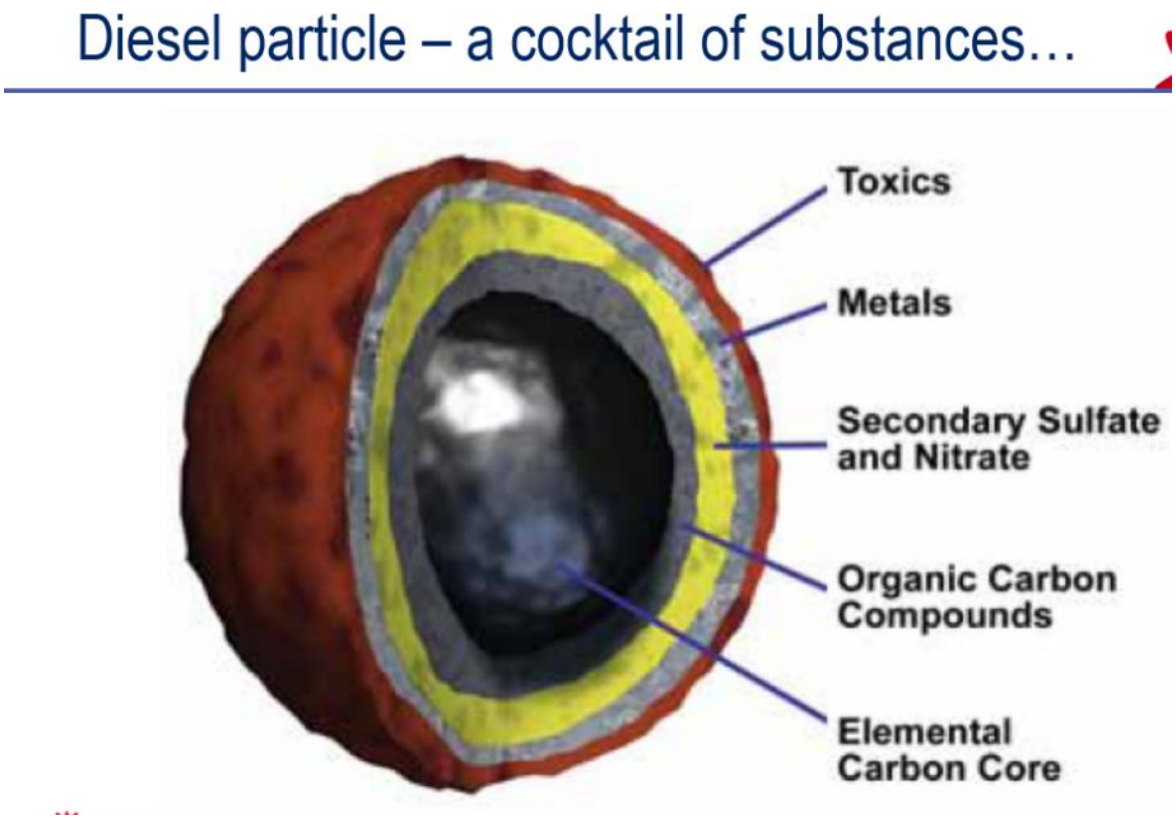


Figure S1 Illustration of Diesel Particle PM 1-2.5 which is dramatically different from the common perception of black diesel Exhaust fumes being like charcoal or soot.

The ramifications of this Diesel Engine Pollution Classification leads directly to the Hunter Valley Independent Health Study sought by the Singleton Community warranting a detailed research focus:-

Firstly, for the direct Air Quality and Health Risk Impact of Diesel Equipment usage in the Hunter Valley, particularly off-road Diesel usage. (Attachment S28),

and **Secondly, investigating Hunter Valley Pollutants by applying the Particulate Matter Synergy Mechanisms that have been uncovered that transport Diesel Exhaust Pollutants via pathways that result in recognised Human Disease outcomes. (Attachment S29 & S32)**

To date SSHEG has focused on Pollution Source Emissions into the Environment to understand the Toxicity of individual Particulate Matter, Gaseous Pollutants and Aerosol concentrations drifting from these Pollution Sources to expose Residents of Hunter Valley Communities.

Much is known of the Aerosol Particulate Matter that forms as "Brown Haze or Smog" from the Gaseous Pollutants (SOx & NOx ; the largest Mass and Volume Emissions), the Earths Solar influences, and the expected chemical interchange with fine and ultrafine Particulate Matter; however the extent of the adhering of Aerosol pollutants onto Particulates, such as outlined in Attachment S32 needs further investigation.

The Human Disease Risk of these small and numerous "Aerosol Particulate Matter" has been lost in the search for more Toxic Pollutants. The same cocktail of chemicals and others, for instance are present in Power Station Stack Plumes as in Diesel Exhausts; in modern times with less "Carbon"; however the Fly Ash Particulate Matter would be expected to act similarly to the elementary carbon core of Diesel Exhaust Fumes. These concepts need to be now investigated.

SSHEG Historians have raised in the past the Health concerns of the "Hunter Valley Cocktail of Pollutants", but the 2012 classification of Diesel Exhaust fumes as carcinogenic now provides a detailed relationship approach to quantify these Cocktail of Pollutants in a different way.

That is, the Diesel Synergy now exists to evaluate the various forms of "Combustion Processes and Fuel Quality" that produce the Pollutants; for example, Diesel Internal Combustion Engines in Mine Equipment and Vehicles, Coal and Co fired Combustion Boilers in Power Stations, Mine Blasting Explosions, and Coal and Wood Combustion Heaters, Forest Fires; and through to Cigarette Smoking.

Clearly, the National Pollution Inventory NPI needs to be altered to identify the Diesel Exhaust Pollutants released, especially into the Hunter Valley; that is the Diesel quantities used, and sepatate listed Diesel quantities of the Gas-Phase Emission Components as listed in Table 2 in Attachment S27. This should also include a NPI listing for the Co Fuels fired in the Power Stations.

‘‘The vast bulk of particulate matter derives from mining (96.8%), and of sulphur dioxide from power generation (92.3%). Mining and power generation combined account for nearly 100% of the particulate matter and sulphur dioxide in the air. The combined total for oxides of nitrogen also accounts for around 90% of the airshed total. Carbon monoxide from these sources, on the other hand, constitutes about 40% of the airshed total: being mainly emitted from internal combustion engines, it is derived from diffuse sources such as commercial and private motor vehicles, as much as those used in the process of mining, and those emanating from trains and trucks transporting coal.

The Question SSHEG Submission Nov 2009 Asked the NSW Government is:-

“What in the Environment is making our Children Sick???”

“We took the kids out of the coal mines, but now we’ve brought the coal mines to the kids!” (A resident)

“Very strong diesel-type odour – was obvious during the night as well. Caller has had a bad headache from the odour and feels nauseous. Also is quite wheezy – caller suffers from asthma and odour has exacerbated it today. Also sore throat, sneezing and coughing. Family has also been suffering with asthma”. (Complaint to NSW Environmental Protection Authority Hotline, reported by Connor et al 2008)

After six years of investigations, it may be that Disease could be the culprit involved and is appears to be amongst the following ;

1. Power Station Plume Fly Ash Particulates , both as emitted and after Aerosol interaction in Hunter Valley Smog.
2. Diesel Exhaust Fumes from Fuel of unknown Quality.
3. Mine Blast Plumes.
4. Aerosol Smog particulates as PM4, PM2.5 PM1 and PM0.1

All of the above relate to Products of Combustion, with Diesel Internal Combustion Engines Exhaust Pollution characterized by “Black Puffs” of “Soot” every time these engines on Trucks, Trains and Equipment suddenly accelerate; a legacy of Diesel Injection Control Systems.

Dr Neville Hodkinson

Singleton Shire Healthy Environment Group

26th March 2013.

Attachment S25 International Agency for Research on Cancer IARC

IARC verdicts on diesel and gasoline engine exhausts, and ten nitroarenes

A Lancet Oncology report summarises the conclusions from IARC's June 2012 meeting on diesel and gasoline engine exhausts and some nitroarenes. The full meeting report will ultimately be issued as volume 105 of IARC's prestigious series of Monographs on the Evaluation of Carcinogenic Risks to Humans.

Epidemiological studies linking exposure to lung, and possibly bladder, cancer provided "sufficient" evidence for the carcinogenicity of diesel engine exhaust in humans. Animal evidence associating lung cancer with exposure was also judged to be "sufficient", and "strong evidence" was seen for a genotoxic mode of action. As a result, diesel engine exhaust was classified as "carcinogenic to humans" (Group 1).

Human data on the carcinogenicity of gasoline engine exhaust were "inadequate", but animal studies provided "sufficient evidence" for the carcinogenicity of its condensates (increased lung and skin tumours were observed). "Strong evidence" was seen for a genotoxic mode of action. Overall, gasoline engine exhaust was considered to be "possibly carcinogenic to humans" (Group 2B).

Ten nitroarenes found in diesel engine exhaust were also evaluated, with conclusions based on laboratory animal and mechanistic evidence. All were seen to be genotoxic to various extents in different assays, and the following were classified as "probably carcinogenic to humans" (Group 2A):

- 6-nitrochrysene
- 1-nitropyrene

Those below were considered to be "possibly carcinogenic to humans" (Group 2B):

- 3,7-dinitrofluoranthene
- 3,9-dinitrofluoranthene
- 1,3-dinitropyrene
- 1,6-dinitropyrene
- 1,8-dinitropyrene
- 3-nitrobenzanthrone
- 2-nitrofluorene
- 4-nitropyrene

Benbrahim-Tallaa L *et al.* (2012). Carcinogenicity of diesel-engine and gasoline-engine exhausts and some nitroarenes. *Lancet Oncology* **13**, 663-4.

"As a result of the combustion process, diesel engines emit diesel particulate matter (DPM), exhaust gases, including a wide range of organic vapours, and a small amount of metallic compounds. For the purposes of this guideline, these components are collectively referred to as diesel emissions.

Diesel emissions are a particular problem in enclosed environments such as underground mines and workshops, where exhaust particulates and gases can accumulate if ventilation is inadequate. Diesel emissions pose both short and long-term risks to health, ranging from mild effects, such as headaches, irritation and nausea, to respiratory disease and cancer. There is also the issue of chemical asphyxiation from carbon monoxide.

The IARC was careful to state that the classification of diesel emissions as a carcinogen was independent of determining the duration, frequency and concentration of exposure required to produce an actual risk. As with many exposures, the probability of harm increases with the level of exposure, and this was an important aspect of the IARC's findings. The IARC working group pointed out that the main studies that led to this conclusion were in highly exposed workers"

Morphology and structure of DPM

The high surface area to volume ratios of the core particles of DPM mean they absorb significant quantities of hydrocarbons originating from the unburnt fuel, lubricating oils and compounds formed during the combustion cycle (Figure 1). More than 1,800 compounds have been identified, including polycyclic aromatic hydrocarbons, condensed liquid hydrocarbons, metals and sulphate compounds.

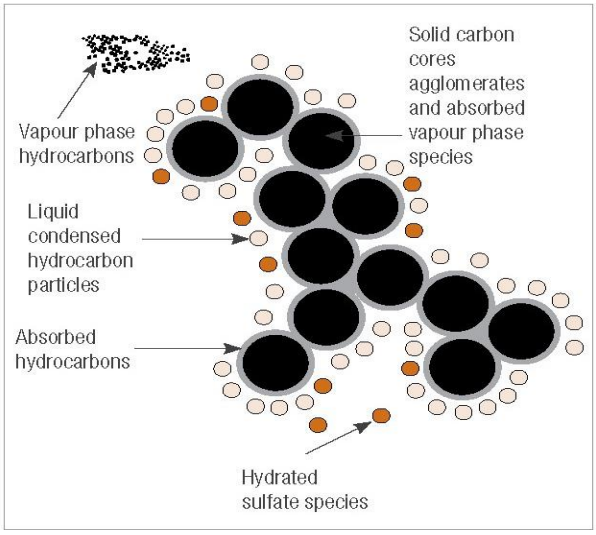


Figure 1 Schematic representation of DPM (after Twiggs and Phillips, 2009)

Size and weight distribution of Diesel Particulate Matter - DPM

The size and weight distribution of DPM depends on the fuel, engine, machinery, maintenance, work practices and environment. Typically:

- about 90 per cent of DPM is less than 0.03 µm (30 nm) in diameter, but comprises only 10 per cent of the mass (Kittelson et al., 2002)
- most of the mass of DPM is composed of carbonaceous agglomerates and adsorbed materials, ranging in size from about 0.03 to 0.5 µm (Kittelson et al., 2002)
- the remaining 5 to 20 per cent of the DPM mass consists of particulates larger than 1 µm, which are generally deposited on cylinder and exhaust system surfaces (Kittelson et al., 2002; Watts et al., 2009).
- While there are no national regulations or standards in place that limit emissions from non-road diesel engines, Australia has benefited from the importation of engines compliant with United States (EPA Tier 1 to 4), European Union (Stage I to IV) and other emission standards, which has contributed to reduced emissions. Industry data submitted to Resources Safety over the past few years indicate that it is reasonably practicable for underground mines to achieve compliance with the AIOH recommendation of 0.1 mg/m^3 for

DPM. However, some sites have not effectively controlled emissions to maintain employee DPM exposure levels below 0.1 mg/m^3.

- **Gaseous emissions in DPM**

- ***Carbon monoxide, Carbon dioxide,***

- ***Nitrogen dioxide***
- At high temperatures, nitrogen from the intake air will react with oxygen and hydrocarbons to form nitrogen oxide compounds (NO_x), primarily nitric oxide and nitrogen dioxide. In the combustion chamber, these compounds form outside the fuel-rich region of the fuel plume, where the conditions are optimal.
- The formation of NO_x increases at higher combustion temperatures and lean conditions, whereas DPM mass formation increases at lower combustion temperatures and richer conditions. Therefore lowering NO_x emissions through in-cylinder techniques increases DPM.

- ***Sulphur dioxide***
- Sulphur dioxide forms when sulphur in the fuel and lubrication oil oxidises during the combustion process. This gaseous emission can damage or poison exhaust catalysts in modern diesel engines.

- ***Other irritant gases***
- Other irritant gases, including aldehydes, may be present in varying levels in raw diesel emissions depending on engine operation, and fuel and lubrication quality. Acrolein is the strongest irritant of the aldehydes produced in diesel emissions.

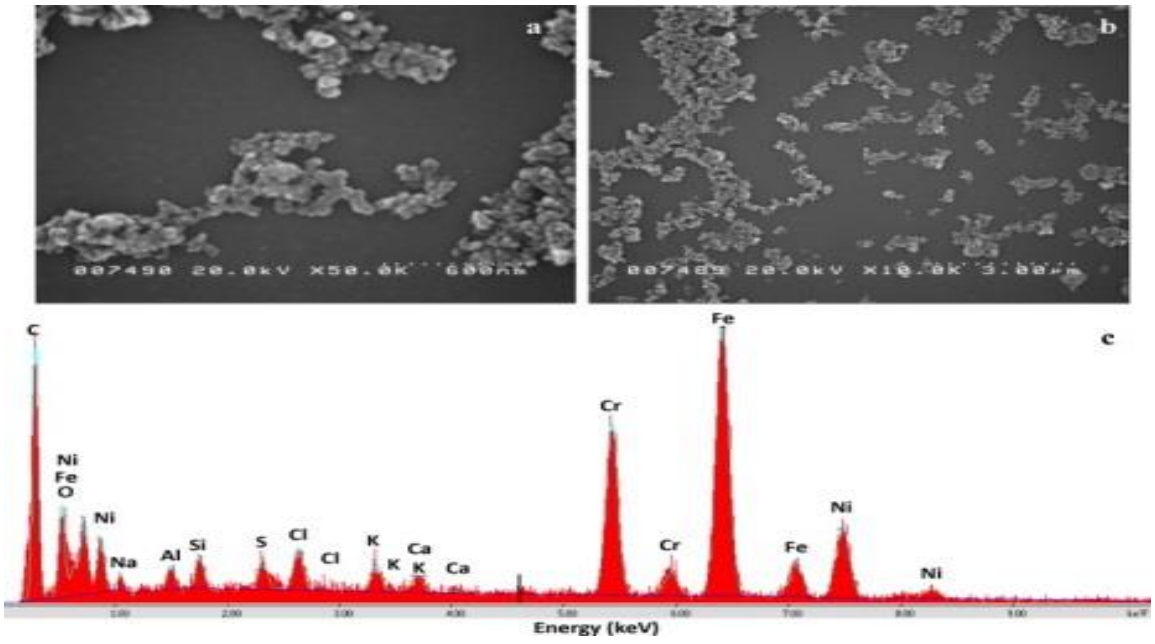


Fig. 1. Representative SEM images (a and b) and energy-dispersive X-ray spectroscopy (c) of diesel exhausted particles used in this study.**

Forty Years of International Cancer Research

The first Working Group of internationally recognised experts met in Lyon in December 1970 to prepare the scientific criteria that would be used in the Monographs and to make preliminary evaluations of the data on 5 substances.

Human Carcinogens

SUMMARY

>>Cancer prevention begins with identifying known and suspected human carcinogens

>>Carcinogen identification involves the scientific evaluation of epidemiological studies, animal bioassays, and mechanistic and other relevant data

>>Carcinogen identification is an important activity at IAR C (the IARC Monographs) and at several national health agencies

>>National and international health agencies use carcinogen identifications to guide their actions to prevent human exposure to known or suspected human carcinogens

>>Carcinogen identification programmes should avoid real or apparent conflicts of interests in order to maintain public confidence in the integrity of their evaluations

Under this paradigm, a cancer hazard is an agent that is capable of causing cancer while a cancer risk is an estimate of the incidence of cancer expected from exposure to a cancer hazard.

RISK

Epidemiologists have found useful guidance in a set of factors known as the Hill criteria [3]. These assess:

—Consistency of the observed association
—Strength of the observed association
—Specificity of the observed association
—Temporal relationship of the observed association
—Biological gradient (exposure-response relationship)
—Biological plausibility
—Coherence
—Experimental evidence (from human populations)
—Analogy

Cancer's latent period implies that many years of preventable human exposure could pass before informative epidemiological studies become available.

The 5 substance evaluations, together with those of 14 more substances, were considered by a Working Group that met in December 1971, and made up the first volume of the IARC Monographs Series, published in 1972 and covering organic, inorganic and natural products.

The IARC Monographs on the Evaluation of Carcinogenic Risks to Humans are a series of scientific reviews that identify agents, mixtures or exposures that can increase the risk for cancer in humans. Each Monograph includes a critical review of the pertinent scientific literature and an evaluation of the weight of the evidence that the agent can alter the risk for cancer in humans.

In June 2012 after 24 years of Diesel Exhaust Research; the IARC panel wrote:-

"The scientific evidence was reviewed thoroughly by the Working Group and overall it was concluded that there was sufficient evidence in humans for the carcinogenicity of diesel exhaust. The Working Group found that diesel exhaust is a cause of *lung cancer* (sufficient evidence) and also noted a positive association (limited evidence) with an increased risk of *bladder cancer.*"

"The *IARC Monographs* Program identifies environmental factors that can increase the risk of human cancer. These include chemicals, complex mixtures, occupational exposures, physical agents, biological agents, and personal habits. An *IARC Monograph* is not "a new study" but the comprehensive and critical review and evaluation of the published scientific evidence on the carcinogenicity of human exposures; this includes data on cancer in humans, cancer bioassays and data on the mechanisms of carcinogenesis".

"Since 1971, more than 900 agents have been evaluated, of which more than 100 have been identified as *carcinogenic* to humans (Group 1), and more than 300 as *probably carcinogenic*, or *possibly carcinogenic* to humans (Groups 2A, 2B)".

Some examples of carcinogenic agents		
	Some agents that are *carcinogenic to humans*	**Some agents that are *probably carcinogenic to humans***
Chemicals	Benzene, 1,3-butadiene, formaldehyde, vinyl chloride	Trichloroethylene, styrene oxide
Complex mixtures	Aflatoxins, coal-tar, soots	PCBs, creosote, emissions from high-temperature frying
Occupations	Painting, chimney sweeping, coal gasification, coke production	Petroleum refining, hairdressing
Metals	Arsenic and compounds, beryllium and compounds, cadmium and compounds, chromium [VI]	Inorganic lead compounds, cobalt metal with tungsten carbide
Particles and fibres	Asbestos, crystalline silica, wood dust	Diesel engine exhaust
Pharmaceuticals	DES, estrogen-progestogen menopausal therapy, tamoxifen, phenacetin	Androgenic (anabolic) steroids, chloramphenicol
Radiation	Radon, solar radiation, X- and Gamma-radiation	
Biological agents	Hepatitis B and C, human papillomaviruses (type 16 and several others), *Helicobacter pylori*	
Lifestyle factors	Tobacco smoke (active and passive smoking), areca nut, alcoholic beverages, household combustion of coal	Shiftwork that involves circadian disruption, household combustion of biomass fuel (primarily wood)

Table 2.1.1 Some examples of carcinogenic agents
Source: IARC Monographs, http://monographs.iarc.fr/

Attachment S26

Physicochemical characterisation of diesel exhaust particles: Factors for assessing biological activity

- K.A. Bérubé[a], T.P. Jones[b], B.J. Williamson[c], C. Winters[a], A.J. Morgan[a], R.J. Richards[a]

- Abstract
- A range of microscopy and analytical techniques have been used to investigate the physicochemical properties of diluted DEP that may be important in determining its biological activity. Transmission electron microscopy demonstrated four basic categories of particle morphology: (1) " spherulites" [individual particles]; (2) " chains" or " clusters" of spherulites; (3) " spherules" , [large bodies of spherulites]; (4) " flake-like bodies" . Image analysis of TEM photomicrographs determined empirical morphological parameters (30 nm mean spherulite diameter, aspect ratio 1.5, mean particle area 0.078 μ m, equivalent spherical diameter 0.23 μ m, roundness 2.76) and derived parameters (0.313 μ m^2 surface area, 3.7 μ m^2 pg surface area per mass and 0.042 μ m^3 volume) of DEP. Distributions of the particle sizes by number showed 10.1% were ultrafine (<0.1 μ m), 89.5% fine (0.1– 2.0 μ m), 0.4% coarse (>2.5 μ m), but distributions based on a mass value were different (0.01% ultrafine; 52.6% fine, 47.4% coarse). In contrast, impacted DEP contained 60.87% ultrafine, 39.13% fine and 0% coarse particles by number. Field emission scanning electron microscopy of spherulites revealed smooth surfaces and flocculated spherules with large surface areas. Electron probe X-ray micro-analysis demonstrated the presence of C, O, Na, Mg, K, Al, Si, P, S, Cl, Ca along with a range of metals (Ti, Mn, Fe, Zn, Cr), that were heterogeneous in distribution. Inductively coupled plasma mass and atomic emission spectrometry identified Mg, P, Ca, Cr, Mn, Zn, Sr, Mo, Ba, Na, Fe, S, and Si as the mobile sorbed metals readily removed during sonication in water from DEP suspensions. X-ray Diffraction confirmed previous observations of the presence of nanometer sized crystallites of disordered graphite. Comparison of microscopy and analytical results between sonicated and impacted DEP revealed a physicochemical difference that must be taken into account in any toxicological investigations.

Attachment S27

The Toxicity of Diesel Exhaust: Implications for Primary Care

Table 2.

Composition, breakdown, and carcinogenicity of diesel exhaust

Gas-Phase Emission Components	Atmospheric Reaction Products	Biological Impact
Carbon dioxide	–	Global warming
Carbon monoxide	–	Asphyxiation
Nitrogen oxides	Nitric acid, ozone	Respiratory tract irritants, acid rain
Sulfur dioxide	Sulfuric acid	Respiratory tract irritant, acid rain
Hydrocarbons		
Alkanes	Aldehydes, alkyl nitrates, ketones	Respiratory tract irritants
Alkenes	Aldehydes, ketones	Respiratory tract irritants, mutagenic and carcinogenic
Aldehydes		
Formaldehyde	Carbon monoxide, hydroperoxyl radicals	Carcinogenic
Higher aldehydes (eg, acetaldehyde, acrolein)	Peroxyacyl nitrates	Respiratory tract and eye irritants, plant damage
Monocyclic aromatic compounds (eg, toluene)	Hydroxylated-nitro derivatives	Carcinogenic
Benzene	Nitro-PAH	Mutagenic and carcinogenic
Particle-phase emission components		
Elemental carbon	–	Nuclei adsorb organic compounds
Inorganic sulfate and nitrate	–	Respiratory tract irritant
Hydrocarbons (C14–C35)	Aldehydes, ketones, and alkyl nitrates	Unknown
PAH	Nitro-PAH and nitro-PAH lactones	Mutagenic and carcinogenic

Attachment S28: The risks posed by mining-related Diesel Emissions

Our SSHEG submission made on 5th March 2013 listed diesel combustion products as significant components of emissions by the coal industry. Since making the submission, we have become aware that off-road diesel engines are subject to *lesser* emissions standards compared to diesel burned by on-road vehicles. Tightening regulations for on-road vehicles have been, we understand, significant in gradually improving air quality in capital cities. That has not occurred in diesel engines used in coal mines, diesel locomotives, and agricultural diesel machinery where dirty diesel continues to be used.

The importance of this information cannot be overstated. In 2012, the International Agency for Research on Cancer officially pronounced diesel emissions as carcinogenic. The significance of this has not escaped the notice of the mining industry: the journal, "Australian Mining" in its August 2012 edition, page 61 and following, noted that workers in close proximity to diesel engines have a threefold chance of contracting lung cancer. What does this mean for people working and living near coal mines and railways carrying near-continuous processions of coal trains, most passing through Residential Areas ? Because reliable information is not available publicly on this and other essential questions, we cannot know the answer.

Although we do not have access to accurate information about the volumes of diesel burned in the coal mines and by diesel locomotives hauling coal wagons, anecdotal reports indicate they are enormous. Moreover, they are growing rapidly in line with expansion of the industry. Any objective consideration of the numbers of huge earth-moving equipment and dump trucks used in mining, and the numbers of diesel locomotives plying the tracks, points to many, many millions of litres of diesel being burned in the air of the Hunter Valley.

Visible emissions, often described as dust, generally fall in the PM10 range i.e. particles of 10 microns and below (Figure 1). These are damaging to health but it is generally recognized that the risk to health increases as particles reduce in size. The larger particles fall out of the airshed relatively quickly and, if breathed in, are flitered out in the upper respiratory tract where they can and do contribute to illness, especially respiratory (Figure 2). It appears that the majority of diesel emissions entering the airshed may be in the range of PM 2.5 i.e. particles of 2.5 microns or less in size. These spread out over much bigger distances and are not filtered out in the upper respiratory tract, but enter the lungs. When they are below PM 1 they may also enter the bloodstream. It is easy to see how a wide range of respiratory diseases, cancers and metabolic disorders have been implicated as consequences of coal mining.

This is particularly so when the complex chemical nature of the Diesel Exhaust Particles are understood as illustrated in Figure 3.

The Senate Committee should be aware that many attempts have been made by State governments over the years to persuade the Commonwealth Government to lead regulation of the quality of off-road diesel. The Commonwealth's failure to address the issue has, thereby, put

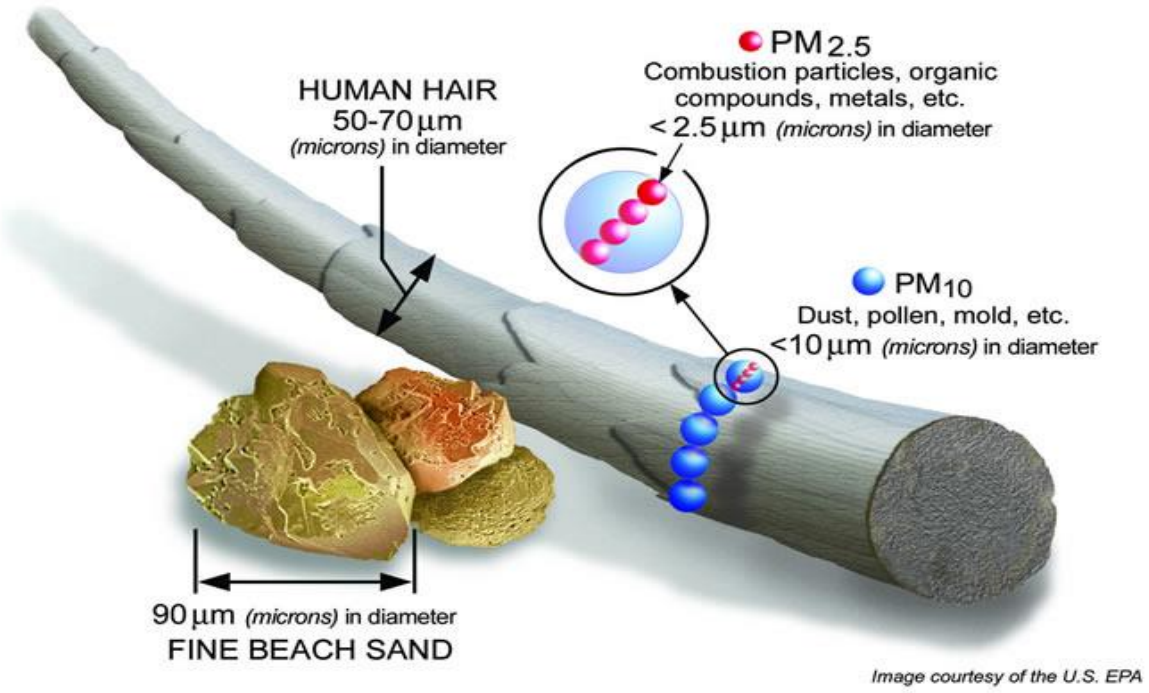
many lives at risk and has undoubtedly caused much unnecessary illness to innocent residents of areas with concentrated diesel use.

At the very least, the Senate Committee should press the Australian Government to require *one* high standard for diesel used for all purposes across the nation. Further, we encourage the Committee to press for urgent research to:

1. **Quantify the diesel used in mining regions;**
2. **Quantify the diesel emissions entering the atmosphere of mining regions;**
3. **Determine the distance over which diesel emissions travel under regional atmospheric conditions;**
4. **Determine distances at which it is safe to locate residences and workplaces, free from the risks of diesel particulates.**

16 March 2013 Dr John Drinan SSHEG

Figure 1: Relative sizes of particles in mining-related emissions



Note: This illustration demonstrates the sense of using the term "emissions", not "dust", to describe the pollutants entering the airshed. Dust usually refers to visible particles seen in haze and is misleading because it does not recognize the presence and significance of the invisible particles.

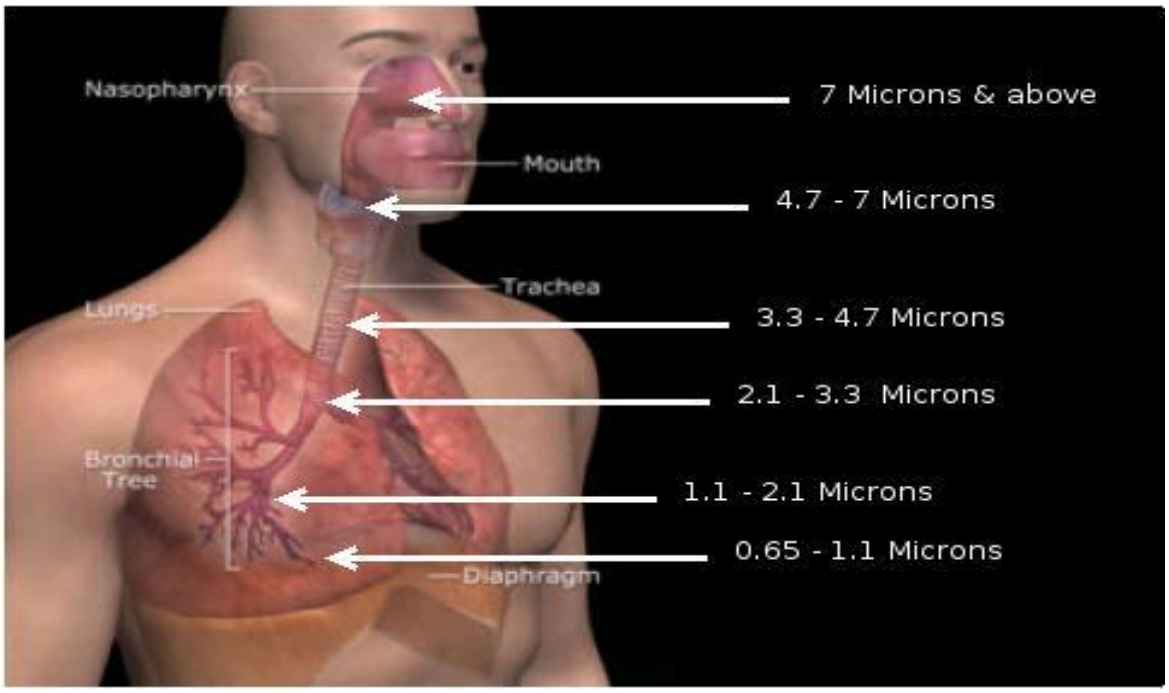
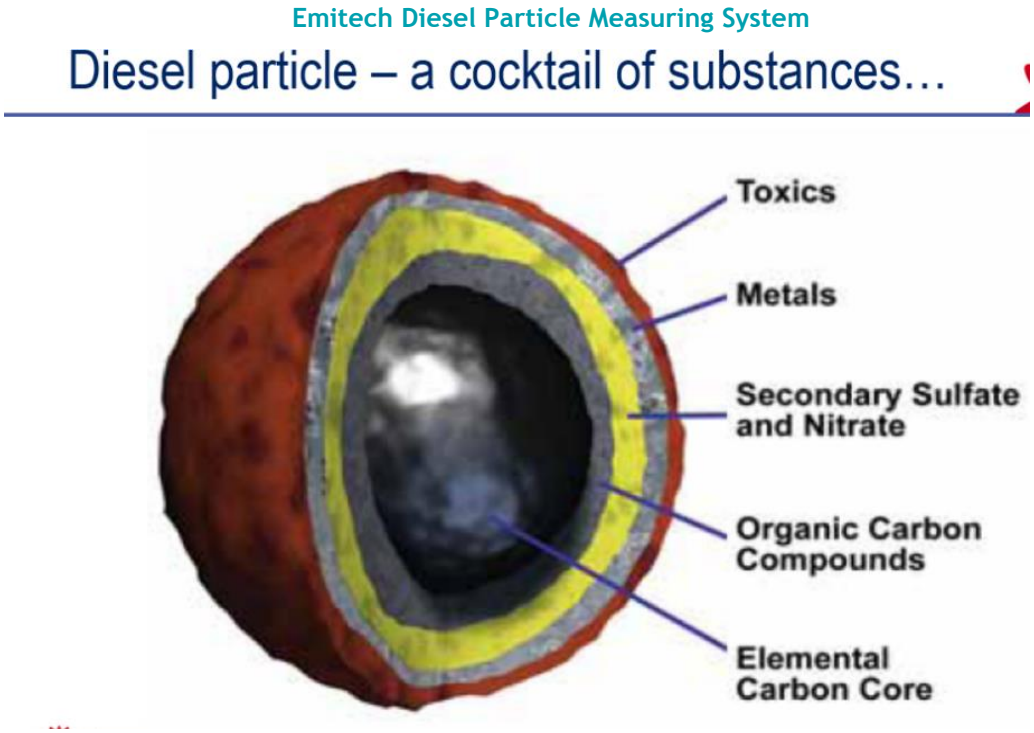


Figure 2: Distribution of mining-related particulates in the body



http:www.catf.ws/publications/reporte/Diesel_health_in_America.phf

Figure 3 Illustration of Diesel Particle which is dramatically different from the common perception of black diesel Exhaust fumes being like charcoal or soot.

Attachment S29 Particulate Matter Synergy Mechanisms in Hunter Valley

The ramifications of Diesel Engine Emission Pollution Classification as Carcinogenic leads directly to the Hunter Valley Independent Health Study sought by the Singleton Community warranting a detailed research focus:-

The questions to be answered are: -

"Is there a Toxicity Synergy between Diesel Exhaust Particulates and Coal Mining and Power Station Pollution Particulates"?

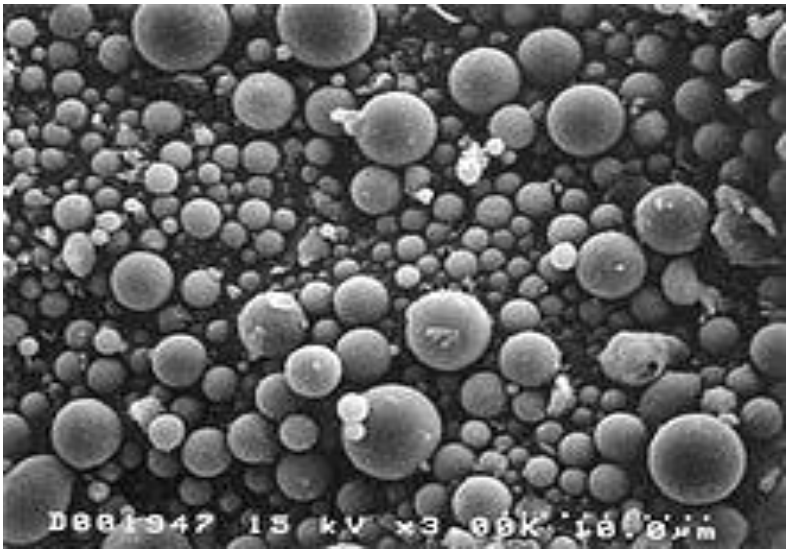
"Do Mining Dust Particulates and Power Station Plume Particulates act as Kernels to form Toxic Smog Particulates in the same way 'Carbon' acts in Diesel Emission Particulates (DEP) form" ?

"What role do Atmospheric Allergenic Molecules play as 'Kernels' to create even more Inflammatory Allergens"?

Fundamentally, the formation of the Toxic Pollutants in Diesel Emissions possible holds the key to understanding what and where to look for in terms of host Kernel Particulates; their size, suitability and chemical and physical affinity to absorbing and or adsorbing more concentrated but less voluminous Toxic substances.

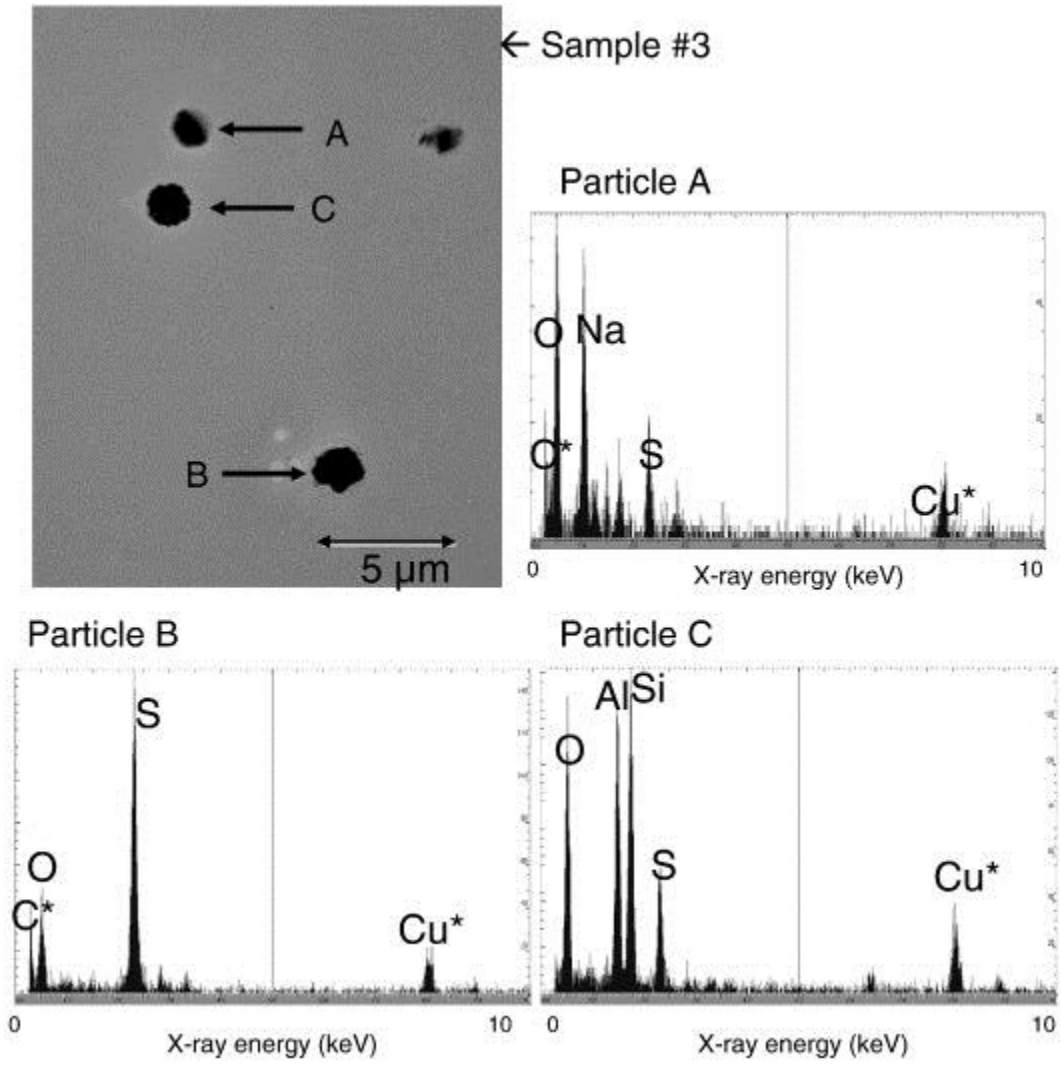
Such a Cocktail of Substances with a Carbon Kernel is illustrated below and in Figure S1 Page 2; in this case formed during the Diesel Combustion Process.

The Synergy Process may also be present in Power Station Plumes as Hot Boiler Gases cool and substances most likely "attach" to Fly Ash Particulates, for example. A simular but more rapid Combustion process may be involved in Coal Mining Blast Plumes, where Diesel Explosions are released into the Air.



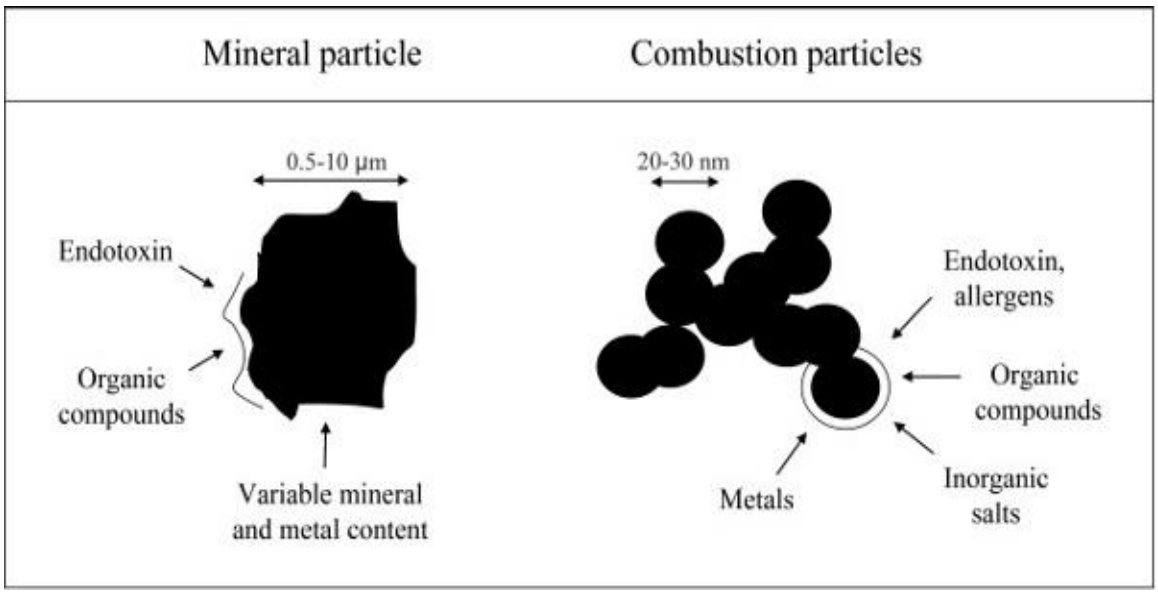
Photomicrograph , a Scanning Electron Microscope (SEM):
Fly ash particles at 2,000x magnification. Most of the particles in this aerosol are nearly spherical.

The same cocktail of chemicals present in Diesel Exhausts, for instance are present in Power Station Stack Plumes as in Diesel Exhausts, however the Fly Ash Particulate Matter would be expected to act similarly to the elementary carbon core of Diesel Exhaust Fumes. These concepts need to be now investigated.

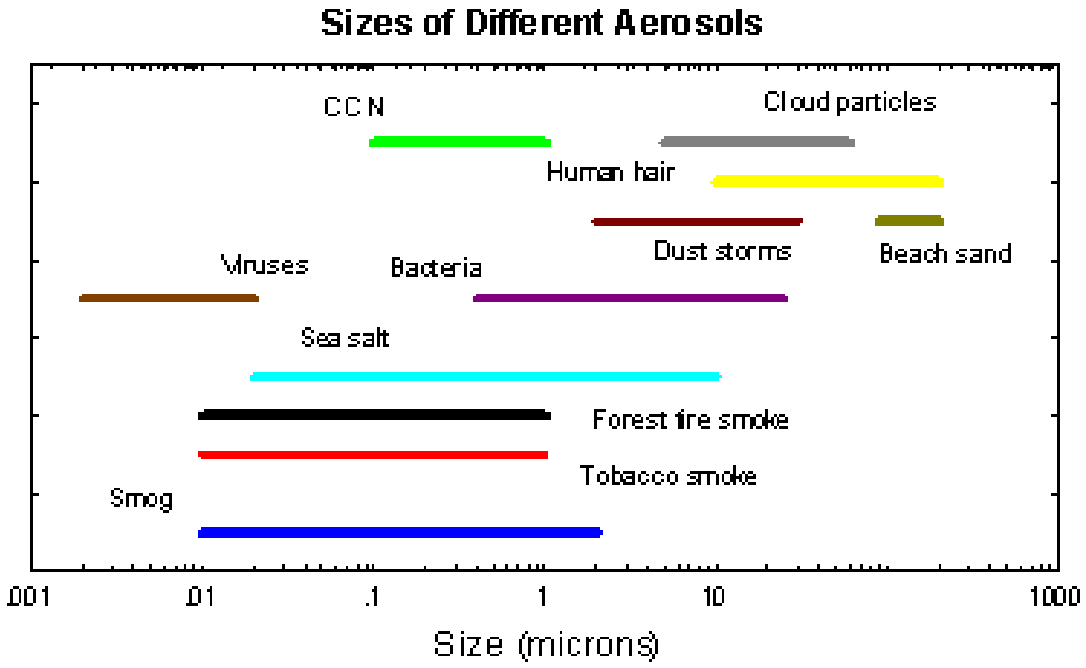


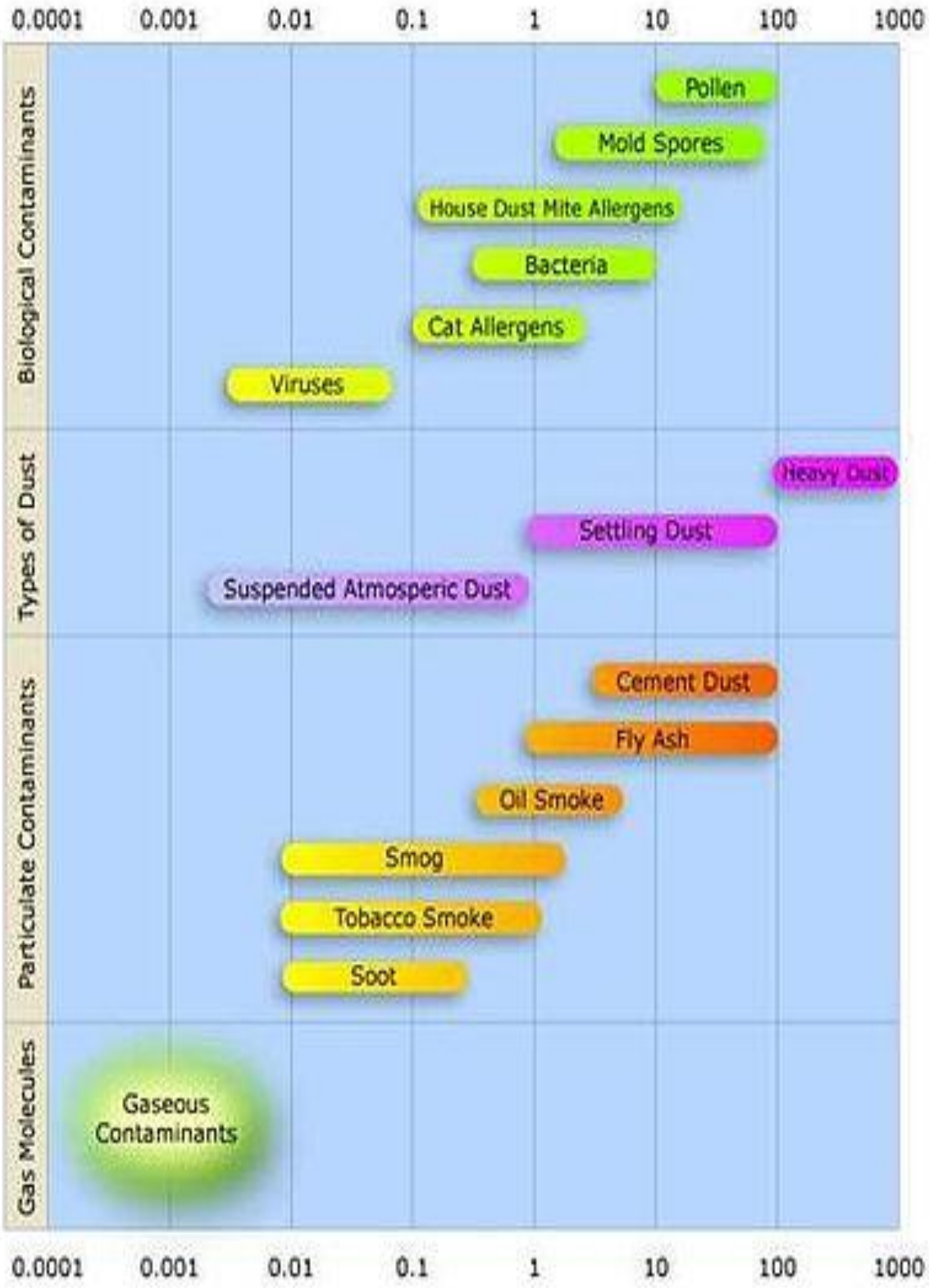
A novel silica alumina-based backfill material composed of coal refuse and fly ash

It is clear however that the Particulate size fractions of " Atmospheric Aerosols" are small sized as illustrated below; however when the Particulate Mass and Volume and Surface Area are considered, the Aerosol formation Mechanisms are clearly more complex.

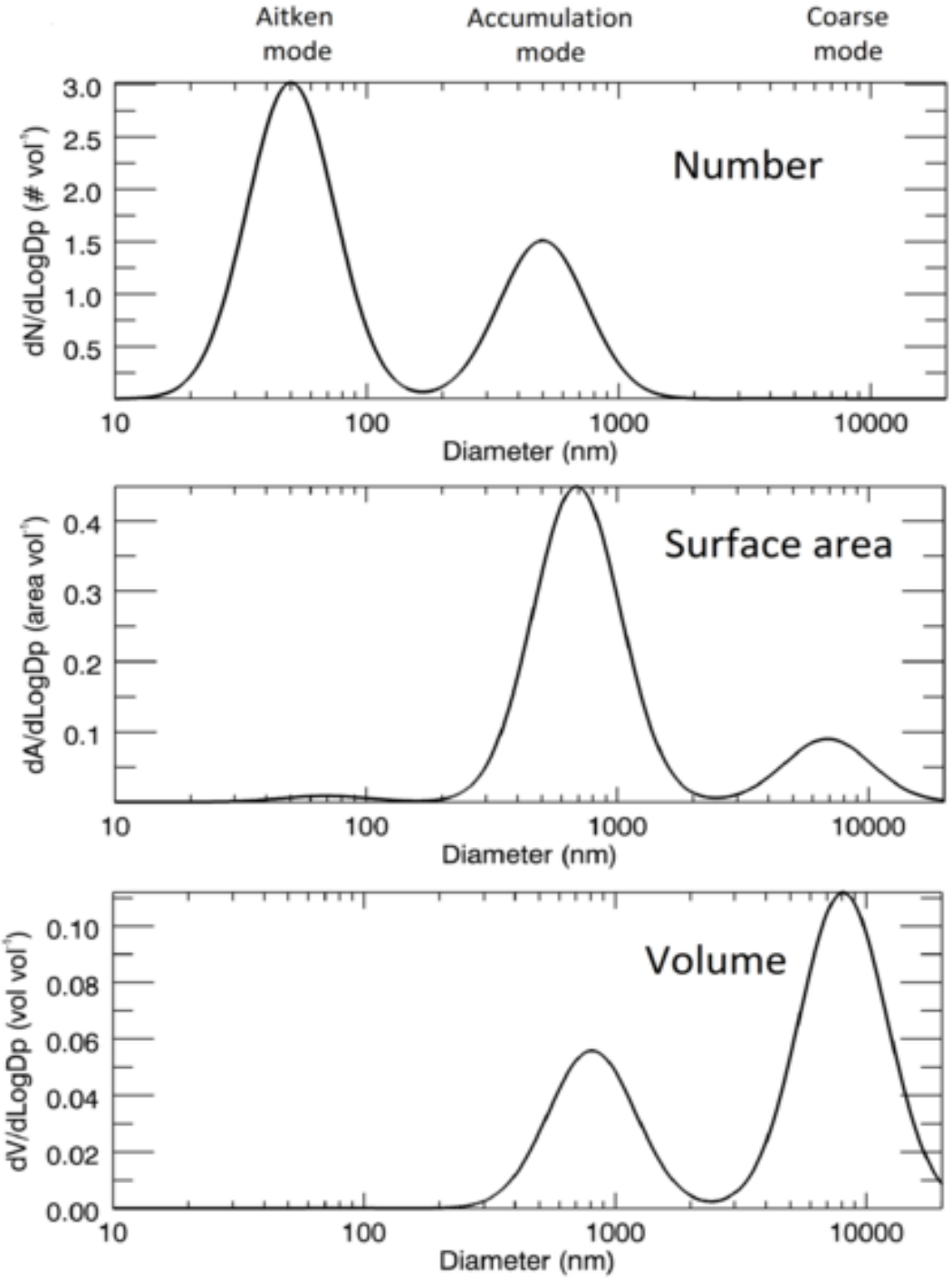


Although much is known of the Aerosol Particulate Matter that forms as "Brown Haze or Smog" from the Gaseous Pollutants (SOx & NOx ; the largest Mass and Volume Emissions), the Earths Solar influences, and the expected chemical interchange with fine and ultrafine Particulate Matter; the Human Disease Risk of these "Aerosol Particulate Matter" involves such a cocktail of substances that their degree of complexity and the accepted view of widespread dispersion and dilution in

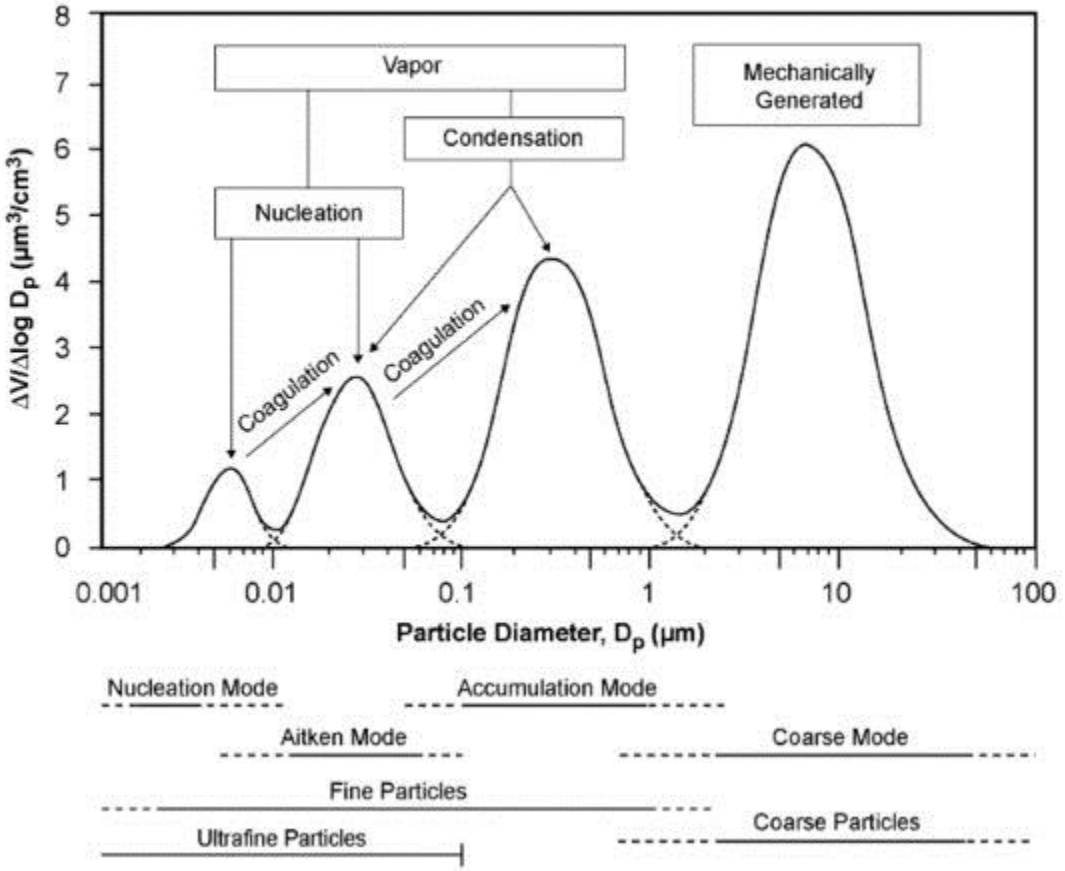




This diagram shows the size distribution in micrometres of various types of atmospheric particulate matter. It also shows the different types of particulates in the atmosphere. Wikipedia 'Particulates'

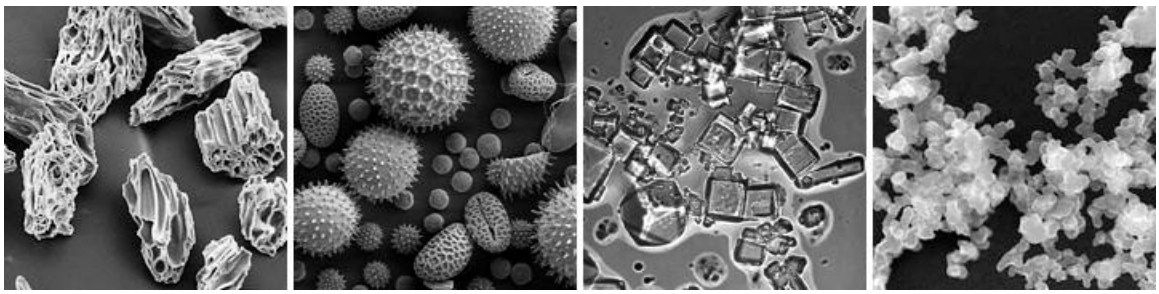


The same hypothetical log-normal aerosol distribution plotted, from top to bottom, as a number vs diameter distribution, a surface area vs diameter distribution, and a volume vs diameter distribution. Typical mode names are shows at the top. Each distribution is normalise so that the total area is 1000

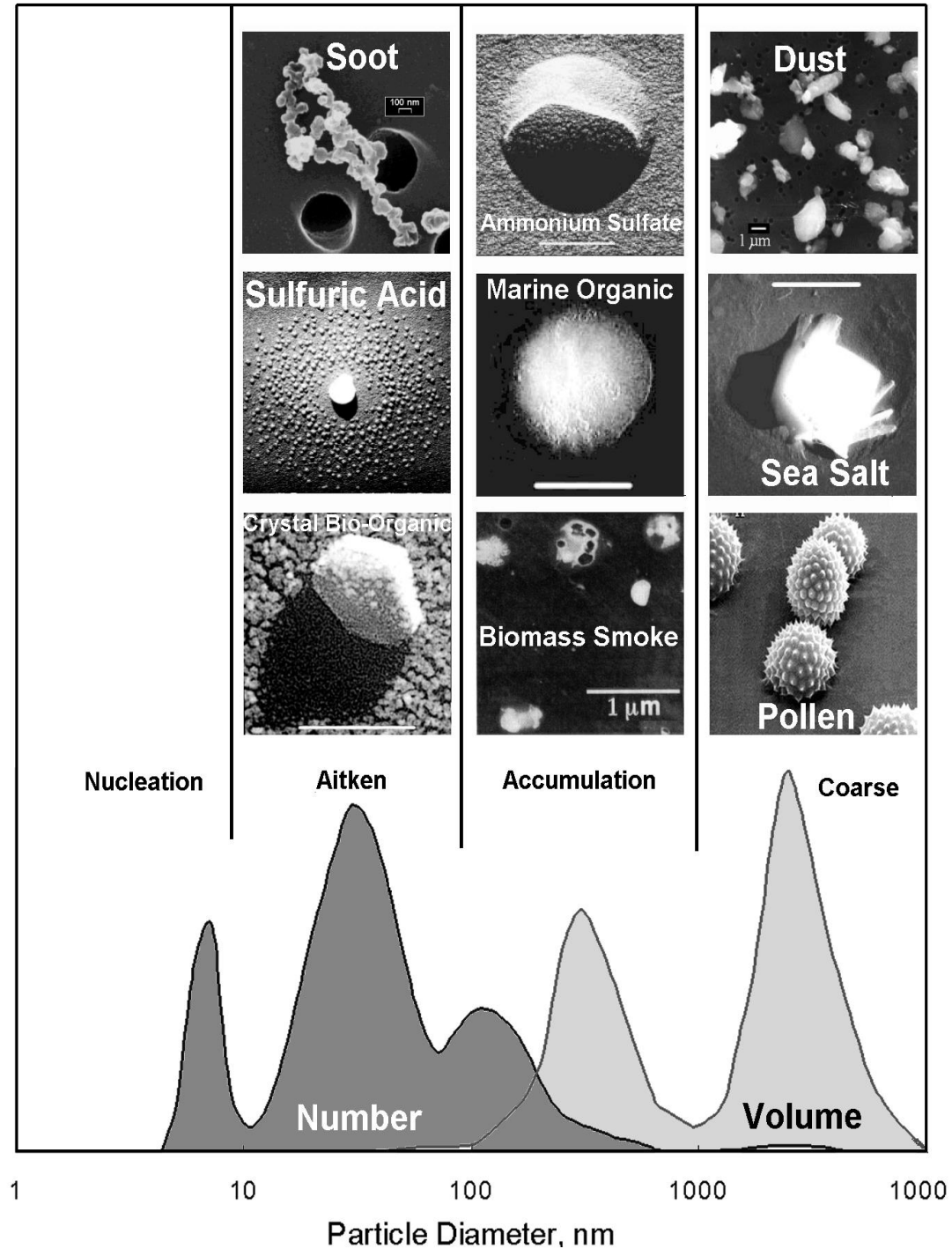


Idealized particle size distribution that might be observed in traffic. Particles from different sizes are generated by four modes: nucleation, aitken, accumulation and coarse mode. Also shown are the major formation and growth mechanisms of the four modes of ambient particles. V = volume, D_p = particle diameter. Source: U.S. EPA [8].

Araujo and Nel *Particle and Fibre Toxicology* 2009 **6**:24 doi:10.1186/1743-8977-6-24



These scanning electron microscope images (not at the same scale) show the wide variety of aerosol shapes. From left to right: volcanic ash, pollen, sea salt, and soot. [Images: NASA, compiled from USGS, UMBC (Chere Petty), and Arizona State University (Peter Buseck)


Soot
100 nm
Ammonium Sulfate
Dust
1 µm
Sulfuric Acid
Marine Organic
Sea Salt
Crystal Bio-Organic
Biomass Smoke
1 µm
Pollen
Nucleation
Aitken
Accumulation
Coarse
Number
Volume
1
10
100
1000
1000
Particle Diameter, nm

Currently Human Health focus involves the entry of fine and ultrafine Toxic Particulates with Pathways into the Lungs, thus establishing that Particle sizes are generally less than PM2.5, and with a further focus mainly in the PM1 through to the PM0.1 range.

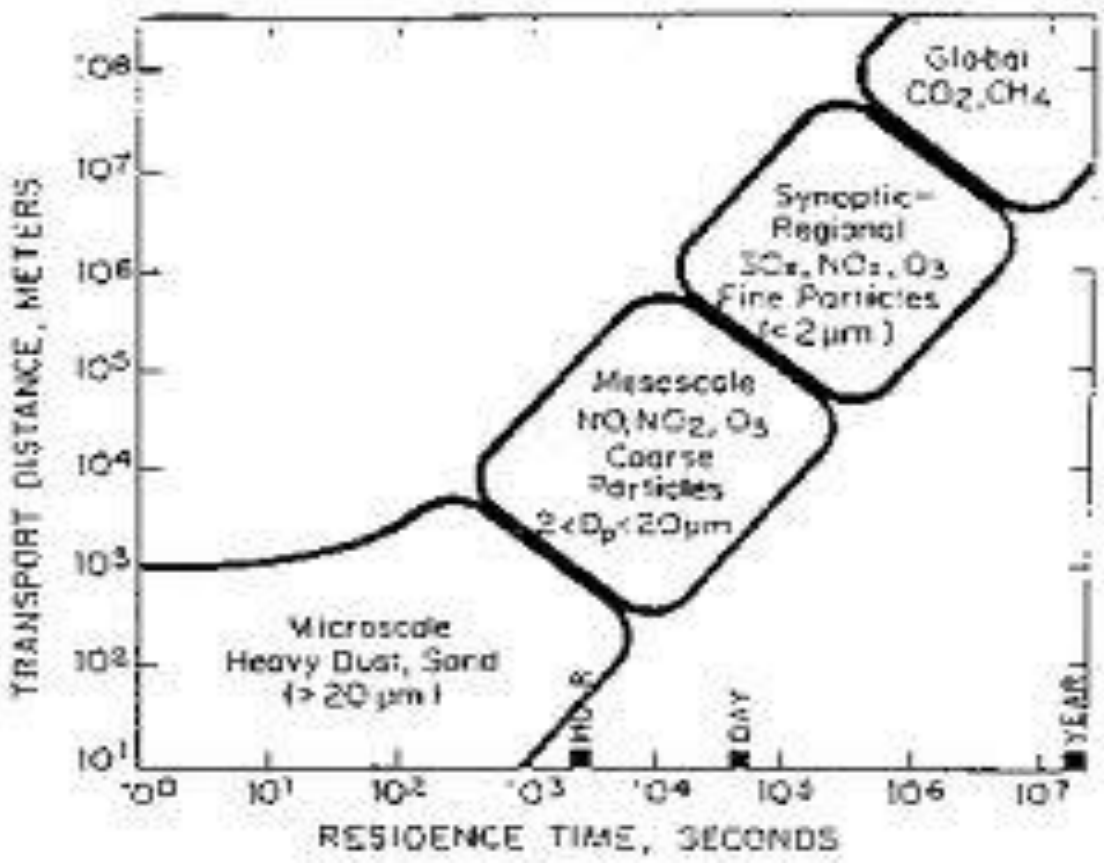
Two stages of Cocktail Pollutants formation of adsorption and or attachment to Host Particulates Kernels are evident.

(1) Attachment during the initial Combustion Process and during the Emission Source release into the Atmosphere.

(2) Secondary formation as atmospheric flows patterns allow mixing with various Air Pollutants under varying meteorological conditions.

It will be the ease with which known Toxic and Carcinogenic properties of substances such as Polycyclic Aromatic Hydrocarbons (PAH) adhere to the surface of the Host Kernel Particulates of Fly Ash Particulates for instance, that determine the extent of the Synergy to Diesel Emissions.

During this latter process, as time from Emission increases so too does the range of Particles that dissociate with transported distance, as illustrated below:-



Health Risk Synergy between Diesel Exhaust Emission,

Passive Smoking, and Hunter Valley Air Quality.

"Organic Compounds from Diesel Exhaust with known Toxic and Carcinogenic properties, such as Polycyclic Aromatic Hydrocarbons (PAH) adhere easily to the surface of the carbon particles and are these are carried deep into Lungs.

The majority of these particles tend to be found in the greatest concentration within the immediate vacinity of busy streets or highways.

Diesel engines emit other toxic compounds in disproportunately higher concentrations than gasoline engines, including nitrogen oxides, sulphur oxides, ozone, formaldahyde, benzene, and small organic molecules.

Nitrogen oxides are a major contribution to ozone production and Smog."

" More attention has been focused on the hundreds of different types of organic molecules created from the high-compression ratios of Diesel engines because many are toxic" as in Table 2 in Attachment S30.

The detailed Diesel Emision Particulates (DEP's) Health Risks are also outlined in Attachment S30 entitled "The Toxicity of Diesel Exhausts: Implications for Primary Care" Irina Krivoshto, et al JABFM Aug 2007; refer extracts below:-

1. ***Cardiac effects* – Acute coronary Syndrome and other Thrombotic effects.**
2. ***Pulmonary effects* – Exacetated Asthma including DEP's combining with atmopheric allergenic molecules to create even more inflaminatory allergens.**
3. ***Cancer* – DEP's have been shown to directly damage DNA and result incarcinogenesis in several animal Lung studies.**
4. ***Hypertension* – Transient Hypertension has been associated with brief periods of severe pollution and is possibly related to the effect of DEP's on Cardiovascular Autonomic Control . The sudden incrase in blood pressure may be a cofactor in the development of myocardial ischenia.**
5. ***Neurotoxicity* – Volatile Hydrocarbons such as PAH attached to DEP's and are rapidly absorbed through the Lungs into the central nervous system.**

- **Association decrease the number of dopaminergic neurons in thr Brain tissue of mice – with Parkinsons' Disease.**

- **Associated Brain Inflamination and Histopathologic changes simular to those seen in Alzheimers' Disease.**

- **Affects learning ability, coordination, memory, judgement etc.**

6. ***Perinatal Health & Infertility* – Low birth weight, perinatal births, congenital abnormalities and elevate infant mortality rate.**

    - **Accumulation in Air, Water and Soil may be a factor**

Passive Smoking Synergy

Besides Diesel Emissions, Passive Smoking also has been classified by International Agency for Research on Cancer IARC and World Health Organisation WHO as the *Group 1 Carcinogenic for Lung Cancer in 2002.*

(Attachment S32)**

IARC 2002 "Evaluation**

There is sufficient evidence that involuntary smoking (exposure to secondhand or 'environmental' tobacco smoke) causes lung cancer in humans

There is limited evidence in experimental animals for the carcinogenicity of mixtures of mainstream and sidestream tobacco smoke.

There is sufficient evidence in experimental animals for the carcinogenicity of sidestream smoke condensates.

In addition, the Working Group noted that there are published reports on possible carcinogenic effects of secondhand tobacco smoke in household pet dogs.

Overall evaluation Involuntary smoking (exposure to secondhand or 'environmental' tobacco smoke) is carcinogenic to humans (Group 1)".
IARC Vol 83 2002

The Synergy between Passive Smoking and Diesel Emissions should provide a further basis for the Toxic substances and the Pathway Mechanisms that facilitates the Human Lung Disease outcomes identfied by the IARC determinations.

Reviewing both the Cancer risk from Passive Smoking and the Toxic constituents of both Diesel Emissions and second hand Tobacco Smoke provides a first order Synergy basis comparison; as follows:-

The following is referenced from "Etiology of Cancer 2 2008[##]

www.iarc.fr/en/publication

"Tobacco smoke is the most common source of carcinogens to human, including polycyclic aromatic hydrocarbons (i.e. benzo[a]pyrene) , 1,3-butadiene, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and many others and tobacco specific nitrosamines (i.e. nnK).

Secondhand tobacco smoke consists of a gas phase and a particulate phase; it changes during its dilution and distribution in the environment and upon ageing.

Secondhand tobacco smoke contains Nicotine concentrations in the air in homes of smokers and in workplaces where smoking is permitted typically range on average from 2 to 10 micrograms/m3."**

Table 1.1 Concentration of selected constituents in second-hand tobacco smoke[##]

Constituent	Concentration
Nicotine	10–100 μg/m3
Carbon monoxide	5–20 ppm
Benzene	15–30 μg/m3
Formaldehyde	100–140 μg/m3
Acetaldehyde	200–300 μg/m3
1,3-Butadiene	20–40 μg/m3
Benzo[*a*]pyrene	0.37–1.7 ng/m3
NNK	0.2–29.3 ng/m3

Comparing the Carcinogens where Benzene, PAH and Formaldehyde are common to both Diesel Emissions and Passive Smoking, with the more complex Nitrocomplexes while with a different Chemical base but apparently lead to the same Human Health impacts, suggesting the chemical "unbonding" still provides a pathway to Disease Risk.

For this reason this Attachment S29 "Particulate Matter Synergy Mechanisms in Hunter Valley" outlines the preliminary comparison of the various IARC judgements for Passive Smoking in 2002 (Attachment S32), with the Diesel Exhaust Carcinogens in 2012 (Attachment S25,S26,S27,S30); and now includes details of the Hunter Valley Cocktail of Pollutants (Attachment S29,S31) with a particular focus on the Electron Microscopy Imagery to highlight the future level of targeted Research that is needed to understand the extent of these Pollution issues.

Table 1.1: Strength of evidence for an increased risk of cancer due to tobacco consumption

Tobacco smoking	Sufficient:	Bladder, bowel, cervix, kidney, larynx, liver, lung, myeloid leukaemia, nasal cavity and sinuses, oesophagus, oral cavity, ovary (mucinous), pancreas, pharynx, stomach
	Possible:	Breast
Environmental tobacco smoke	Sufficient:	Lung
	Possible:	Larynx, pharynx
Parental smoking (cancer in the offspring)	Sufficient:	Hepatoblastoma
	Possible:	Childhood leukaemia
Smokeless tobacco	Sufficient:	Oesophaus, oral cavity, pancreas
Betel quid* with tobacco	Sufficient:	Oesophagus, oral cavity, pharynx
Betel quid* without tobacco	Sufficient:	Oesophagus, oral cavity

*Betel quid, also known as paan, consists of a mixture of betel nut (or areca nut), slaked lime and various herbs and spices, wrapped in a betel leaf

"Tobacco smoking causes 13 different cancers: lung, oral cavity, nasal cavity and nasal sinuses, pharynx, larynx, oesophagus, stomach, pancreas, liver, urinary bladder, kidney, uterine cervix and myeloid leukaemia. In high-resource countries, tobacco smoking accounts for approximately 30% of all human cancers.

Lung cancer has the highest smoking attributable fraction among all cancers induced by smoking. duration of smoking is the strongest determinant of excess lung cancer risk in smokers, with risk increasing proportionally with the number of cigarettes smoked. tobacco smoking raises the excess risk of all histological types of lung cancer".

The chronic presentation of Passive Smoke Carcinogens to the airway epithelial cells, through sustained smoking, can lead to molecular lesions which, in the presence of reduced metabolic detoxification, can diminish repair capability, overwhelming cellular defences and leading to lung cancer."

"Mechanisms of carcinogenesis**

Tobacco smoke is the most common source of carcinogens to humans. It includes about 1010 particles per ml and 4800 compounds, of which 66 are carcinogens [19,20]. Of these, polycyclic aromatic hydrocarbons and tobacco specific nitrosamines are the most important. In addition, inducers of reactive oxygen species like NO, NO2, peroxynitrite and nitrosamines initiate, promote or amplify oxidative DNA damage [21-23]. Chemicals such as aromatic amines, benzene and heavy metals, independently established as carcinogenic to humans, of reduced metabolic detoxification can diminish repair capability, overwhelming cellular defenses and leading to lung cancer [22].

Most carcinogens are oxygenated by cells using cytochrome P54 enzymes to be transformed into excretable forms. Electrophilic oxygenated carcinogens can form covalently bound DNA adducts. Six carcinogens present in tobacco smoke are known to form DNA adducts in human tissue: benzo[a]pyrene (BaP), NNK, NDMA (N-nitrosodimethylamine), NNN (N'-nitrosonornicotine), ethylene oxide and 4-aminobiphenyl [22]. Cells can remove adducts and repair DNA.

Table 2.2.4 Concentration of carcinogenic agents in mainstream tobacco smoke of non-filtered cigarettes and in smokeless tobacco

Substances	Tobacco smoke	Smokeless tobacco ng / g
Volatile aldehydes		
Formaldehyde	70 - 100 µg	1600 - 7400
Acetaldehyde	500 - 1400 µg	1400 - 27 400
Crotonaldehyde		200 - 2400
N-Nitrosamines		
N-Nitrosodimethylamine	2 - 1000 ng	nd - 270
N-Nitrosodiethylamine	nd - 2.8 ng	
N-Nitrosopyrrolidine	3 - 110 ng	nd - 860
Tobacco specific nitrosamines		
N'Nitrosonornicotine (NNN)	45 - 58 000 ng/g	400 - 3 085 000
4-(Methylnitrosamino)-1-(3-pyrydyl)-1-butanone (NNK)	nd - 10 745 ng/cigarette	0.07 - 22 900
4-(Methylnitrosamino)-1-(3-pyrydyl)-1-butanol (NNAL)		
N'Nitrosoanabasine (NAB)		present - 2 370 000
Metals		
Nickel	nd - 600 ng	180 - 2700
Cadmiun	7 - 350 ng	
Polonium 210	0.03 - 1.0 pCi/g	0.16 - 1.22
Uranium 235 and 238		2.4 and 1.91
Arsenic	40 - 120 µg	500 - 900
Polycyclic aromatic hydrocarbons		
Benzo[a]pyrene	20 - 40 ng	> 0.1 - 90 ng/g
Benzo[a]anthracene	20 - 70 ng	
Benzo[b]fluoranthene	4 - 22 ng	
Chrysene		
Dibenzo[a,l]pyrene	1.7 - 3.2 ng	
Dibenzo[a,h]anthracene	4 ng	

Table 2.2.4 *Concentration of carcinogenic agents in mainstream tobacco smoke of non-filtered cigarettes and in smokeless tobacco*
Numbers in black derived from IARC Monographs volumes 83 and 89, numbers in red from Hoffman, Hoffman and El-Bayoumy, 2001

The balance between metabolic activation and metabolic detoxification and the efficiency of DNA repair pathways may define cancer risk in individuals exposed to polycyclic aromatic compounds, for example [22].

In summary, the chronic presentation of carcinogens through sustained smoking can lead to molecular lesions which in the presence of reduced metabolic detoxification can diminish repair capability, overwhelming cellular
defenses and leading to lung cancer [22]."

Chemical composition **

"Many studies have examined the concentrations of cigarette smoke constituents in mainstream and sidestream smoke. The composition of mainstream and sidestream smoke is qualitatively similar but quantitatively different. The ratios of sidestream to mainstream smoke vary greatly depending on the constituent. Some representative SS:MS ratios are: nicotine, 7.1; carbon monoxide, 4.8; ammonia, 455; formaldehyde, 36.5; acrolein, 18.6; benzo[*a*]pyrene, 16.0; *N*′-nitrosonornicotine (NNN), 0.43; (methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 0.40 (Jenkins ***et al.***, 2000; IARC, 2004)."

Attachment S30 **"The Toxicity of Diesel Exhausts"**

JABFM
JOURNAL OF THE AMERICAN BOARD OF FAMILY MEDICINE

The Toxicity of Diesel Exhaust: Implications for Primary Care

Irina N. Krivoshto, BA, John R. Richards, MD, Timothy E. Albertson, MD, MPH, PhD and Robert W. Derlet, MD

+ Author Affiliations

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Abstract

Diesel fuel and the products of its combustion represent one of the toxins most commonly encountered by people living in both urban and rural areas of the world. As nations become more heavily populated, there will be increasing reliance on diesel fuel to power mass transportation and commercial vehicles, as well as heavy machinery involved in construction, farming, and mining. The majority of patients who present to urban primary care clinics and emergency departments will have had significant chronic exposure to diesel exhaust because most use and/or live near busy streets and highways. Furthermore, those who operate or work or live near diesel-powered machinery will have even more toxic exposure. Primary care physicians should be aware of the acute and chronic deleterious clinical effects of diesel exhaust. In this article we review the toxicity and myriad health problems associated with diesel exhaust.

The compression-ignition diesel engine was invented by Rudolph Diesel in 1892 as an alternative to the spark-ignition gasoline engine.[1] The engine's popularity expanded because it had excellent fuel economy and durability and it required less maintenance. Diesel is the fuel of choice for use in mass transportation vehicles such as trucks, buses, and trains. Diesel fuel and the products of its combustion represent one of the most common toxins to which people living in both urban and rural areas of the world are exposed. On an equal horsepower basis, diesel exhaust is 100 times more toxic than gasoline exhaust, even when carbon monoxide is considered.[2] The Environmental Protection Agency estimates truck exhaust accounts for 20% of all vehicle-produced microscopic soot and 30% of all smog-causing chemicals in the

United States.[1] As for passenger cars, fewer than 1% of new American cars hav diesel engines. In contrast, diesel engines power 37% of all new cars sold in Europe, with rates as high as 62% in France.[3] One reason for this discrepancy is the suboptimal quality of diesel fuel sold in the United States; roughly half of the supply has been found to be below the standards recommended by equipment manufacturers.[1]

The majority of patients who present to urban primary care clinics and emergency departments may have had a potentially significant chronic exposure to diesel exhaust because many of them live near busy streets and highways. In Japan and Europe, epidemiologic surveyors have demonstrated high acute and chronic respiratory disease morbidity rates from occupational and proximity exposure to diesel exhaust.[4] The National Institute for Occupational Safety and Health estimates millions of workers are occupationally exposed to the combustion products of diesel fuel in their respective workplaces. Diesel exhaust is a complex mixture of toxic compounds with wide variability of deleterious effects in human and animal studies. This represents a significant limitation to epidemiologic research on diesel exhaust because the over-reporting of exposure may affect study outcomes.[5] Thus, no standard for exposure limits exists at this time.

Patients most likely to be in proximity to diesel exhaust on the job and thus suffer from occupational exposure include (1) shipping, receiving, and loading dock workers; (2) bus, truck, and forklift drivers; (3) railroad workers; (4) mine workers; (5) diesel engine repair and maintenance garage workers; (6) construction site, tunnel, and bridge workers. In 2006 the California Air Resources Board estimated that diesel exhaust pollution directly accounts for 2400 deaths and, annually, nearly 3000 hospital admissions for respiratory and cardiac-related diseases, at a total cost of $19 billion.[6] Besides on-the-job exposure to diesel exhaust, patients may be exposed to diesel exhaust from myriad and commonplace sources (Table 1). Primary care physicians should be aware of the acute and chronic deleterious health effects from diesel exhaust and its potential to exacerbate other chronic disease states. We thoroughly searched medical and scientific literature databases to identify those articles that specifically addressed the relationship between diesel exhaust pollution and illness. Here we review the myriad health problems associated with this commonly encountered substance.

View this table:
» In this window » In a new window

Table 1.

Potential sources of clinically significant exposure to diesel exhaust

Diesel Exhaust Composition

There are many components of diesel exhaust, including (1) carbon monoxide and carbon dioxide; (2) nitrogen oxides; (3) sulfur oxides; (4) hydrocarbons; (5) unburned carbon particles (soot); and (6) water.[2] Exhaust from diesel engines is considered to contribute to more than 50% of ambient particulate matter with a mass median aerodynamic diameter less than 10 µm (PM10), greatly contributing to overall air pollution. For fine particulate matter with a diameter below 2.5 µm (PM2.5) and ultra-fine particles with a diameter below 0.1 µm, this contribution is even higher.[1] These carbon particles are small enough to be inhaled and deposited in the lungs but have a large surface area. Organic compounds from diesel exhaust with known toxic and carcinogenic properties, such as polycyclic aromatic hydrocarbons (PAH), adhere easily to the surface of the carbon particles and are carried deep into the lungs.[4] The majority of these particles tend to be found in the greatest concentration within the immediate vicinity of busy streets or highways.[7,8] Diesel engines emit other toxic compounds in disproportionately higher concentrations than gasoline engines, including nitrogen oxides, sulfur oxides, ozone, formaldehyde, benzene, and smaller organic molecules. Diesel engines also produce 26% of the total nitrogen oxides in outdoor air. Nitrogen oxides are a major contributor to ozone production and smog. More attention has been focused on the hundreds of different types of organic molecules created from the high-compression ratios of diesel engines because many are highly toxic.[1] A summary of the composition of diesel exhaust and its biological effects are detailed in Table 2.

View this table:
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Table 2.

Composition, breakdown, and carcinogenicity of diesel exhaust

Cardiac Effects

Acute coronary syndrome (ACS) and other thrombotic effects have been associated with acute exposure to diesel exhaust.[9,10] A recent study by Mills and associates evaluated men with previous myocardial infarction who were exposed to diesel exhaust during moderate exercise. Significant ST-segment depression was noted, as well as diminished release of endothelial tissue plasminogen activator.[11] Possible mechanisms to explain these results include diesel exhaust-induced coronary vasoconstriction, transient thrombus formation, carbon monoxide exposure, and altered myocardial energetics.[12] Another recent study of 1816 postmenopausal women with long-term exposure to air pollution, of which diesel exhaust represented a significant proportion, concluded there was an increased risk of cardiovascular disease and death proportional to the level of exposure.[13] One European study group examined the association between exposure to diesel exhaust and hospital admission for ischemic heart disease in 8 cities and found that patients 65 years and older had a significantly increased risk of ACS after exposure to diesel pollution.[14] In a study performed in a major European city, Peters et al determined that exposure to traffic, with its high levels of diesel exhaust, was associated with the onset of myocardial infarction within 1 hour. They concluded the time spent in traffic was consistently linked with an increased risk of myocardial infarction.[15]

Diesel exhaust particles (DEPs) have been shown to be cardiotoxic in animal studies. Minami and colleagues demonstrated in a guinea pig model that DEPs had a negative inotropic effect, induced arrhythmias, and caused sudden cardiac death.[16] Another animal study by Sakakibara et al determined that DEP-induced cardiotoxicity could not be prevented with propranolol, atropine, verapamil, diltiazem, diphenhydramine, indomethacin, superoxide dismutase, or catalase.[17] Diesel exhaust induces heart rate variability, ventricular arrhythmia, a significant decrease in left-ventricular systolic pressure, and an increase in left-ventricular end-diastolic pressure in animal models.[18,19] It is postulated that DEP produces superoxide radicals, which cause irreversible myocardial damage leading to cardiac arrest.[20]

DEPs also have been shown to induce immunoglobulin E synthesis and cause histamine release.[21] Histamine is a potent coronary vasoconstrictor and platelet and thrombin activator, and it up-regulates P-selectin on endothelial cell surfaces.[22] A high incidence of serious cardiac arrhythmias was noted in patients with implanted cardioverter defibrillators who had significant exposure to air pollution.[23] Zanobetti and Schwartz reported that diabetics have twice the risk of ACS-related admission because of particulate air pollution exposure.[24] Another study from Finland found that patients undergoing serial cardiac exercise testing had a higher incidence of ST-segment depression during days of high particulate air pollution.[25] Progression of atherosclerosis has also been linked to air pollution exposure.[26]

Occupational hazards may also be a factor in development of coronary artery disease. Finkelstein et al, after controlling for smoking, reported higher incidence of ischemic heart disease in heavy equipment operators chronically exposed to DEPs.[27] It may then be important for primary care physicians to inquire about occupational or environmental exposure to diesel exhaust from patients presenting with chest pain and dyspnea. For patients whose ACS was indeed precipitated by acute exposure to diesel exhaust, it will be important to counsel them about avoiding diesel fumes in the future.

Pulmonary Effects

DEPs have been demonstrated to increase the production of inflammatory cytokines such as interleukin 1β, interleukin 8, and granulocyte–macrophage colony–stimulating factor from cyclo–oxygenase stimulation in bronchial epithelial cells.[28] This in turn results in decreased adhesion between cells, reduction of structural integrity, and inhibited repair. Pulmonary damage incurred from DEP exposure may resemble that caused by bacterial endotoxin.[29] Asphyxiation from diesel exhaust is more likely to be caused by acute lung injury from soot particles, nitrogen dioxide, and sulfur dioxide than by carbon monoxide. This is different from gasoline exhaust, which contains 28 times more carbon monoxide than diesel exhaust.[30] Nevertheless, in patients with significant acute and/or chronic diesel exhaust exposure, carbon monoxide levels should be checked. In the absence of deliberate exposure, elevated carbon monoxide levels may represent a marker for serious exposure to diesel exhaust and should be further investigated. Patients with reactive and/or obstructive airway diseases such as asthma and emphysema may have their underlying disease exacerbated as a result of exposure to diesel exhaust.[31-33] Visits to the emergency department for pulmonary complaints have been shown to increase during periods of severe air pollution.[34] One possible explanation is DEPs combining with atmospheric allergenic molecules to create even more inflammatory allergens.[35] Admission rates for pediatric asthma exacerbation have been shown to be higher in areas with greater–than–average diesel emissions.[36] DEPs have been shown to directly induce degranulation of mast cells with subsequent histamine release.[37] Histamine release–induced by exposure to DEPs may result in allergic conjunctivitis, rhinosinusitis, pharyngitis, laryngitis, and chronic cough.[38] Macrophages, the first line of immunologic defense within the lung, are severely impaired from exposure to high concentrations of DEPs, resulting in an increased risk of bacterial and viral bronchitis and pneumonia.[39] Although no relevant clinical studies have been published, primary care physicians may consider the inclusion of antihistamines in addition to β–agonists and corticosteroids for the care of patients with acute exacerbation of reactive airway disease precipitated by diesel exhaust exposure.

Many substances in diesel exhaust, such as ozone, can contribute to lung tissue destruction. Ozone is formed from nitrogen oxides, which diesel engines emit in disproportionately higher amounts compared with catalytic converter–equipped gasoline engines. Many of the hydrocarbon molecules emitted by diesel engines, such as PAH, are quite toxic to the lung. Living in areas with high DEPs accelerates pulmonary disease. Chronic exposure to DEPs is associated with an increased risk for the development of asthma. Churg et al compared postmortem lung histology of nonsmoking inhabitants of Mexico City, Mexico, with those of Vancouver, British Columbia, Canada.[40] The lungs of the Mexico City inhabitants were significantly more diseased, with smaller airways consistent with an obstructive pattern and ultra-fine particles embedded in the airway mucosa. A similar study comparing young, recently deceased patients in Los Angeles and Miami found higher levels of pulmonary centriacinar inflammation in the Los Angeles residents.[41] A large study of children demonstrated a significant decrease in the forced expiratory volume in 1 second (FEV1) in those patients living in areas with high concentrations of DEPs.[42] Another pediatric study concluded a dose-dependent inverse association exists between the carbon content of airway macrophages and FEV1 for children living in urban areas with significant diesel exhaust exposure.[43] Workers in enclosed spaces such as mines and ships are especially at risk from DEP-induced pulmonary disease. Jorgensen and Svensson reported that underground miners had productive cough and frequent respiratory infections,[44] and Wade and Newman attributed asthma in train crews to diesel exhaust.[45]

Cancer

In 1989, the International Agency for Research on Cancer concluded that there is sufficient evidence for the carcinogenicity of diesel exhaust in experimental animals but limited evidence for carcinogenicity in humans. In 1990, California identified diesel exhaust as a substance known to cause cancer. Diesel exhaust particles have been shown to directly damage DNA and result in carcinogenesis in several animal lung studies.[46] Diesel exhaust particles have been shown to generate reactive oxygen species, which lead to oxidative stress and DNA damage. PAH associated with diesel exhaust are genotoxic, forming PAH-DNA adducts and resulting in mutation and DNA strand breakage.[47] Occupational studies of railroad workers, heavy equipment operators, and truck drivers have demonstrated a significantly higher-than-normal incidence of death from lung cancer.[48,49] A more recent case-control study of occupational diesel exhaust exposure in Montreal, Quebec, Canada found a limited association with lung cancer in both smokers and nonsmokers.[50] Gustavsson et al reported that workers exposed to combustion products had a higher incidence of esophageal cancer.[51] In a study by Guo et al, human exposure to DEPs was associated with a higher risk of ovarian cancer but not with esophageal, testicular, or urinary tract cancers or leukemia.[52] A possible causal relationship between DEPs and multiple myeloma was reported by Lee et al.[53]

Hypertension

A link between hypertension and diesel exhaust exposure seems to exist, based on several studies.[54-57] Transient hypertension has been associated with brief periods of severe pollution and is possibly related to the effect of DEPs on cardiovascular autonomic control. This sudden increase in blood pressure may be a cofactor in the development of myocardial ischemia precipitated by diesel exhaust exposure. At levels encountered in an urban environment, inhalation of dilute diesel exhaust impairs regulation of vascular tone and endogenous fibrinolysis.[58]

Neurotoxicity

Volatile hydrocarbons such as PAH attach to DEPs and are rapidly absorbed through the lungs into the central nervous system. A possible association between chronic DEP exposure and Parkinson's disease has been explored because DEPs have been shown to decrease the number of dopaminergic neurons in the brain tissue of mice.[59] Another study group demonstrated that brain inflammation induced by DEPs resulted in histopathologic changes similar to those seen in patients with Alzheimer's disease.[60] The result of chronic DEP exposure may affect learning ability, coordination, memory, and judgment in both children and adults.[61] Kilburn demonstrated slowness of response, memory loss, and disordered sleep suggestive of neurobehavioral impairment in workers whose occupations involved significant indoor diesel exhaust exposure. Abnormalities such as visual field defects, delayed blink reflex latency, and balance impairment, as well as impaired recall memory, problem solving, and perceptual motor speed tests were also detected.[62]

Perinatal Health and Infertility

Several worldwide studies have linked diesel exhaust exposure to low birth weight in infants, premature births, congenital abnormalities, and elevated infant mortality rate.[63-66] DEPs caused a significant decrease in adult sperm production and a diminished number of Sertoli cells in an animal model.[67] Other studies have shown aberration of sex hormone production and effect in chronically exposed female rats, with increased levels of testosterone and subsequent masculinization.[68] Pregnant rats exposed to DEPs had higher rates of spontaneous abortions. There are few human epidemiologic studies, but one study demonstrated a negative effect of DEPs on human sperm motility.[69] Another compound isolated from DEPs, 4–nitrophenol (PNP), has been identified as a vasodilator. One study group demonstrated that PNP has estrogenic and antiandrogenic activities in vivo, leading to sterility.[70] The accumulation of PNP in air, water, and soil may be one factor in the increasing incidence of sterility in humans and animals, but epidemiologic studies are pending.

The Future

In 2001 the Environmental Protection Agency proposed the Heavy-Duty Engine and Vehicle Standards and Highway Diesel Fuel Sulfur Control Requirements, to be implemented by 2008.[1] The production and distribution of low (<30 parts per million) sulfur content diesel fuel, which is widely available in Europe, is one of the most significant changes in policy. This cleaner diesel fuel is viewed as being essential to reducing tailpipe emissions from large trucks and buses; the current sulfur content prevents pollution control equipment from working properly.[71] After-treatment devices such as diesel particulate filters, traps, and nitrogen oxide-reducing catalysts are also being implemented. One study found that buses using diesel and compressed natural gas as well as clean diesel fuel and particulate traps were superior to standard diesel buses with regard to emissions.[72] A new generation of diesel engines developed for Europe should become available in the United States in the near future. The Environmental Protection Agency has issued a Notice of Proposed Rulemaking to implement onboard diagnostic systems to monitor diesel exhaust emissions on heavy-duty engines used in highway vehicles over 14,000 pounds by 2010. Individual states are also implementing "No Idling" policies with regard to diesel -powered vehicles that are not in active use.

Conclusions

As populations continue to grow worldwide, the expansion of mass transportation and the construction of new buildings for housing and commerce will occur concomitantly. Until alternative energy sources are fully developed and implemented, reliance on diesel fuel will increase. Acute and chronic exposure to diesel exhaust will continue to be a problem in the United States. This will ultimately increase the number of patients presenting to urban primary care clinics and emergency departments with cardiopulmonary disease, neurological disorders, and adverse perinatal events. If new regulations and technology to reduce DEP emissions are fully implemented and prove to be effective, this outcome may be averted. The omnipresence of diesel exhaust in urban areas may lead the clinician to preclude its query in the patient's history. A plethora of unexplained signs and symptoms may be caused by diesel exposure (Table 3). Although no specific screening guidelines exist, primary care physicians should question patients about potential exposure to diesel exhaust and be familiar with its myriad deleterious health effects.

View this table:
» In this window » In a new window

Table 3.

Unexplained signs and symptoms and potential diesel exhaust exposure

Notes

Notes

This article was externally peer reviewed.

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J Am Board Fam Med January 1, 2008 21:1–3

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The Toxicity of Diesel Exhaust: Implications for Primary Care

Table 2.

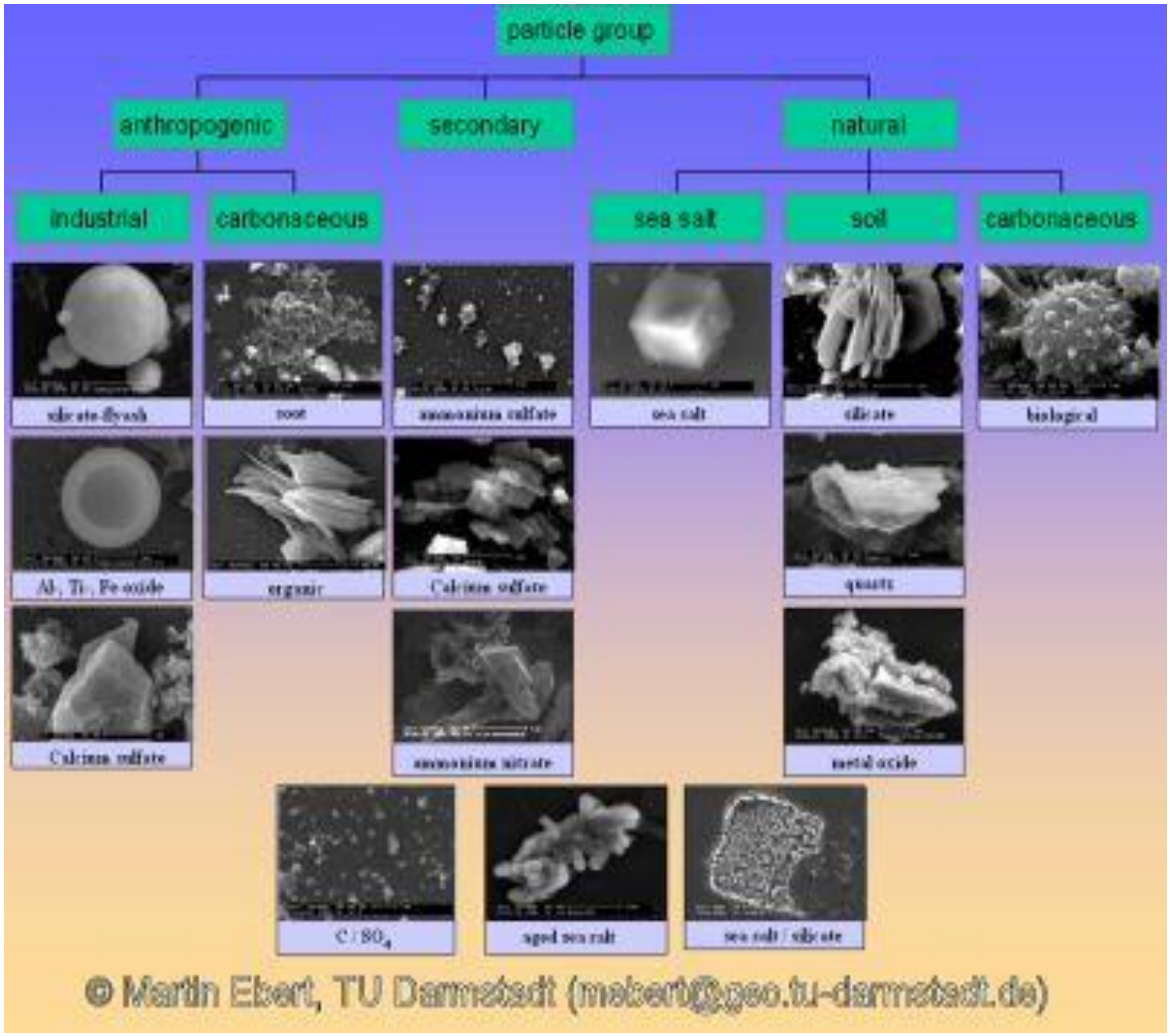
Composition, breakdown, and carcinogenicity of diesel exhaust

Gas-Phase Emission Components	Atmospheric Reaction Products	Biological Impact
Carbon dioxide	–	Global warming
Carbon monoxide	–	Asphyxiation
Nitrogen oxides	Nitric acid, ozone	Respiratory tract irritants, acid rain
Sulfur dioxide	Sulfuric acid	Respiratory tract irritant, acid rain
Hydrocarbons		
Alkanes	Aldehydes, alkyl nitrates, ketones	Respiratory tract irritants
Alkenes	Aldehydes, ketones	Respiratory tract irritants, mutagenic and carcinogenic
Aldehydes		
Formaldehyde	Carbon monoxide, hydroperoxyl radicals	Carcinogenic
Higher aldehydes (eg, acetaldehyde, acrolein)	Peroxyacyl nitrates	Respiratory tract and eye irritants, plant damage
Monocyclic aromatic compounds (eg, toluene)	Hydroxylated–nitro derivatives	Carcinogenic
Benzene	Nitro-PAH	Mutagenic and carcinogenic
Particle-phase emission components		
Elemental carbon	–	Nuclei adsorb organic compounds
Inorganic sulfate and nitrate	–	Respiratory tract irritant
Hydrocarbons (C14–C35)	Aldehydes, ketones, and alkyl nitrates	Unknown
PAH	Nitro-PAH and nitro-PAH lactones	Mutagenic and carcinogenic

- PAH, polycyclic aromatic hydrocarbons; C, carbon.

Attachment S31 Hunter Valley Aerosol Cocktail Smog

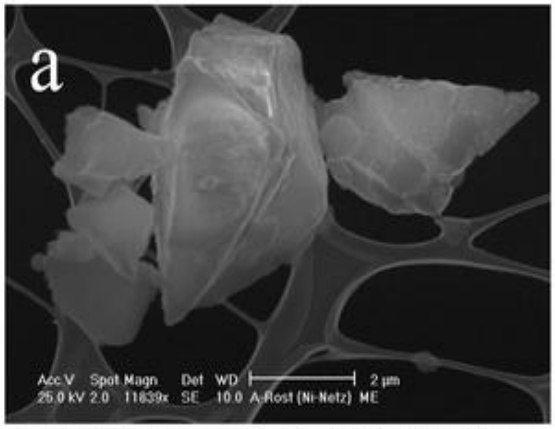
Electron Microscopy Images serve to identify the type of aerosol Particulates that would be expected to be present in the Hunter Valley Brown Smog.



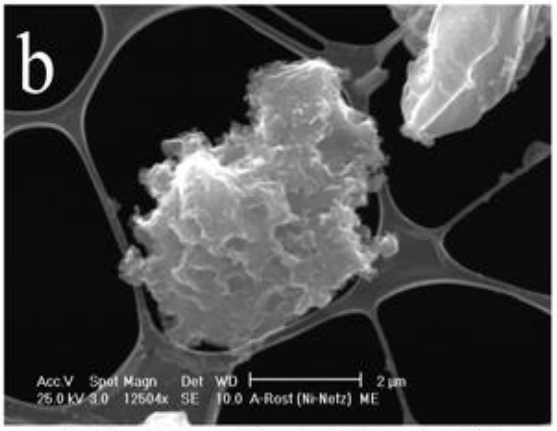
Environmental Scanning Electron Microscopy (ESEM

…www.geo.tu-darmstadt.de - 400 × 322 - More sizes

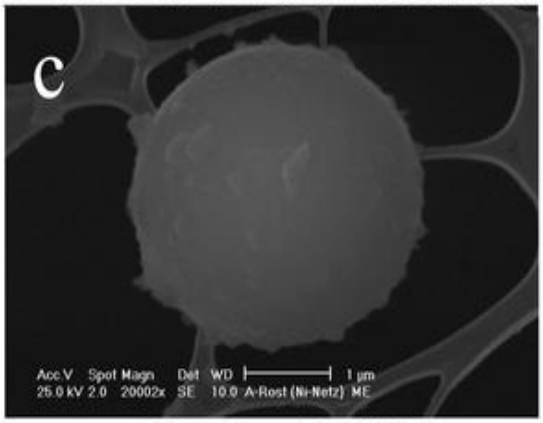
The heterogeneous composition of working place aerosols ...pubs.rsc.org



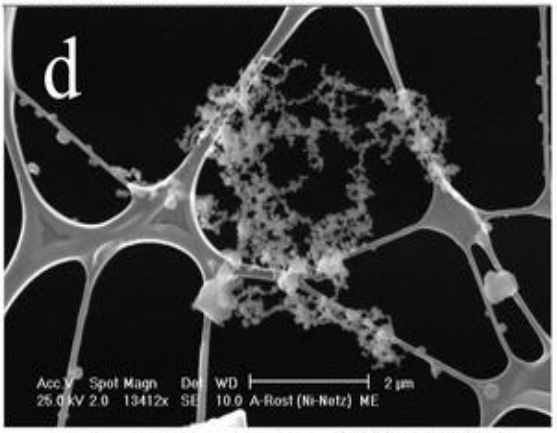
metal/metal oxides/sulfides/sulfates



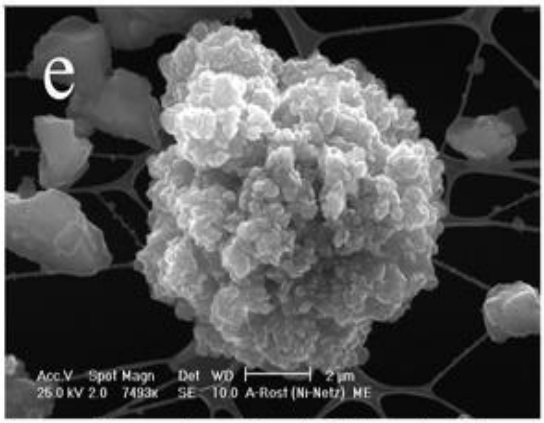
metal/metal oxides/sulfides/sulfates



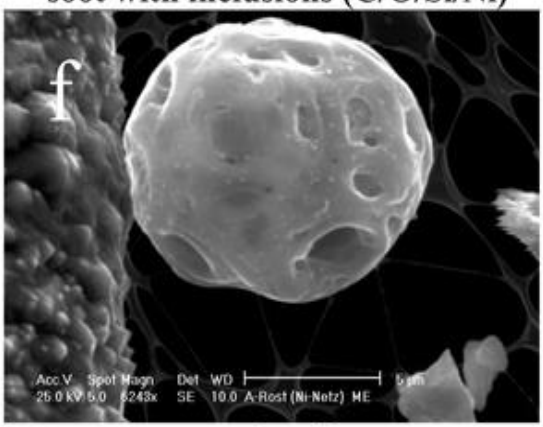
metal/metal oxides/silicates



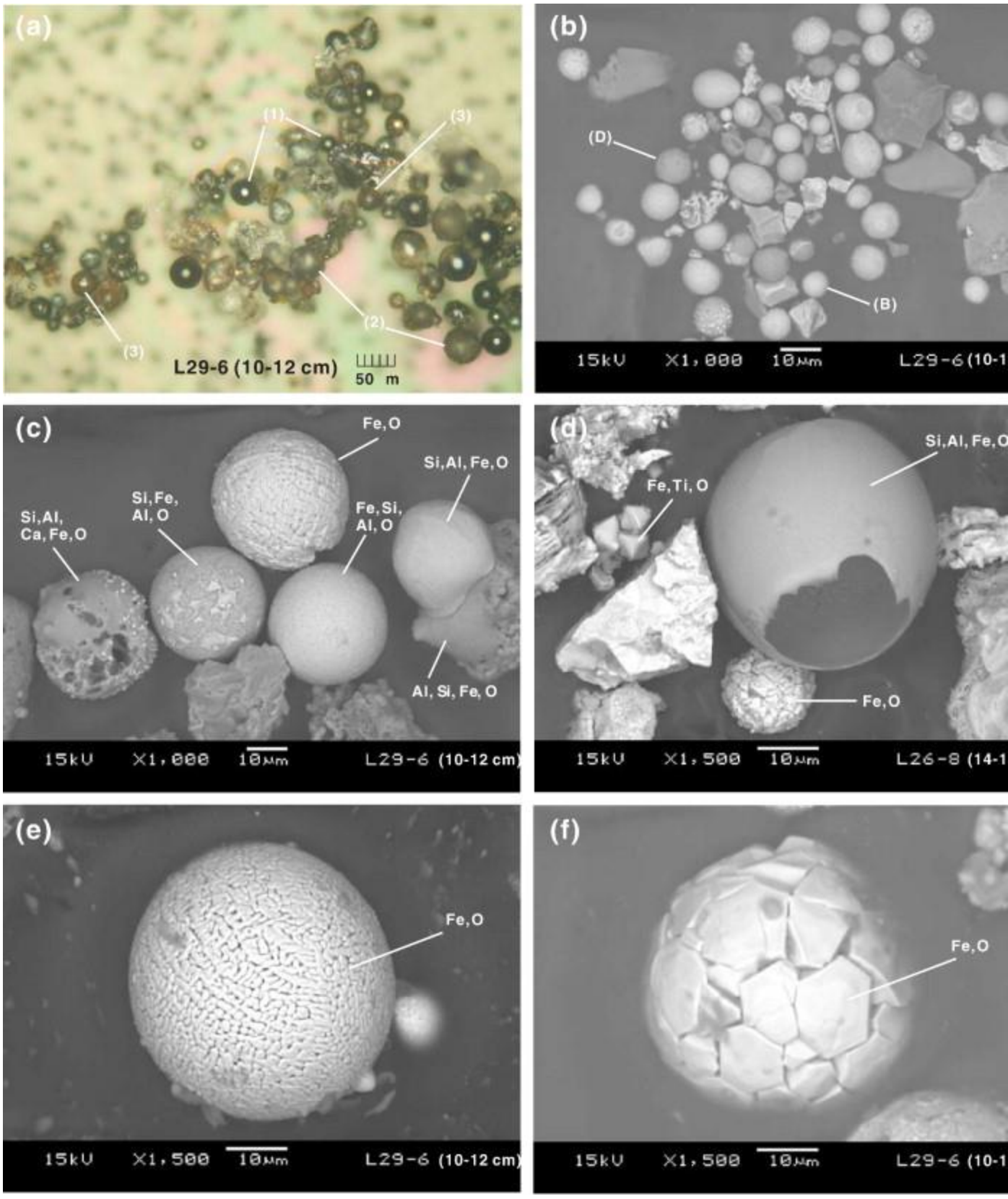
soot with inclusions (C/O/Si/Ni)



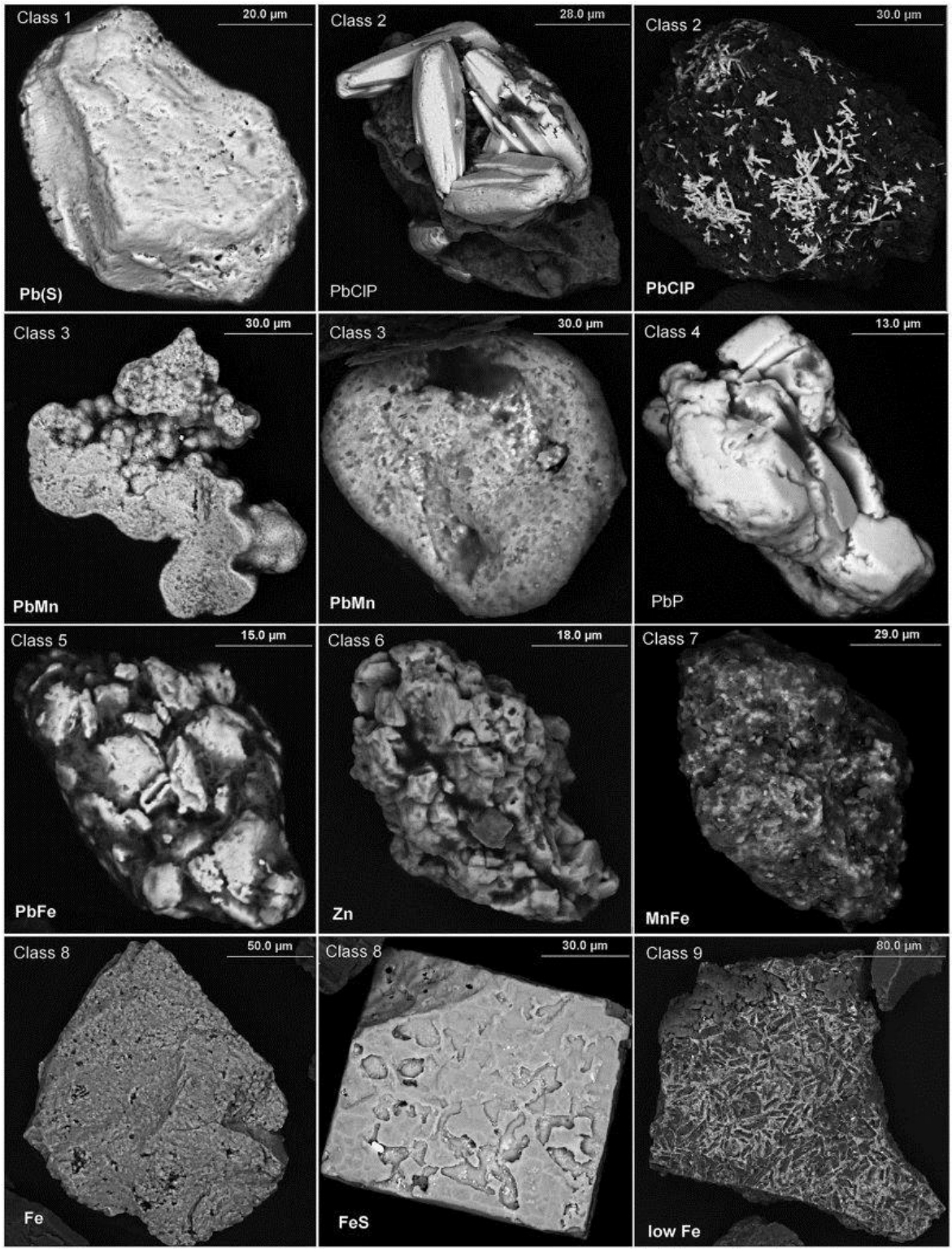
metal/metal oxides/sulfides/sulfates



metal oxides



Science Dust.com J Marine Sc. Air Pollution


Class 1
20.0 µm
Pb(S)
Class 2
28.0 µm
PbClP
Class 2
30.0 µm
PbClP
Class 3
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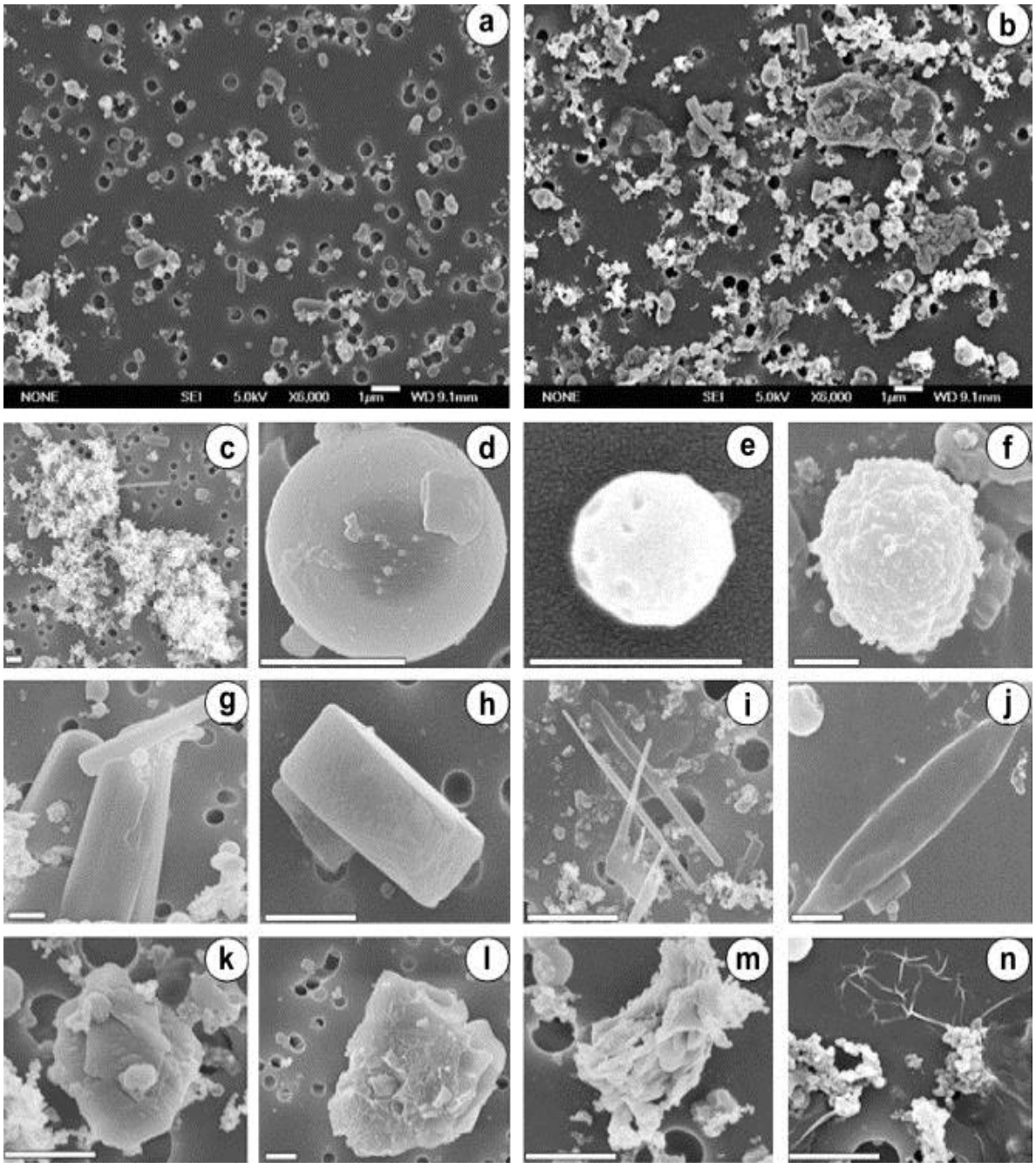
Class 3
30.0 µm
PbMn
Class 4
13.0 µm
PbP
Class 5
15.0 µm
PbFe
Class 6
18.0 µm
Zn
Class 7
29.0 µm
MnFe
Class 8
50.0 µm
Fe
Class 8
30.0 µm
FeS
Class 9
80.0 µm
low Fe

The relationship between physicochemical characterization and the potential toxicity of fine particulates ($PM_{2.5}$) in Shanghai atmosphere

- Lu Senlin[a, b],et al 2008



Particulate Matter consideration including ”New Diesel Technology - Changed Particulate Matter”

“The sometimes high correlation between PM and some gaseous components of ambient air pollution makes it difficult to statistically separate their effects on health. The one exception is ozone: in many areas and time series, the correlation between PM and ozone is weak or sometimes even negative.

A recent paper has shown that especially coarse-mode PM contains relatively high levels of bacterial endotoxin, and that the biological activity of these particles is clearly related to the endotoxin level (130). This is an interesting observation that may account for findings in epidemiological studies showing associations between coarse PM exposure and health effects.

Gamble and Nicolich have argued that the PM doses required to elicit adverse effects in humans by active smoking and various occupational exposures are orders of magnitude higher than doses obtained from ambient PM exposures (131). However, when ambient PM exposures are compared to environmental tobacco smoke (ETS) exposure, the doses are of comparable magnitude, and IARC has recently decided that ETS should be classified as a proven human carcinogen (132)”.

“Approximately 20% of all human cancers worldwide have been associated with infectious agents. This percentage is likely to be higher in low-resource countries where, due to socio-economic conditions, infections are more frequent and healthcare surveillance is less available than in high-resource countries. Based on a vast number of biological and epidemiological studies, the International Agency for Research on Cancer (IARC) has classified 6 viruses and one bacterium as human carcinogens-i.e. high-risk mucosal human papillomavirus (HPV) types, hepatitis C virus (HCV), hepatitis B virus, Human T-lymphotropic virus type I (HTLV-1), Epstein-Barr virus (EBV), Kaposi sarcoma-associated virus (KSHV) and the bacterium *Helicobacter pylori”*.

Attachment S32 Tobacco Smoking and Involuntary Smoking

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation

Of

Carcinogenic Risks to Humans

Volume 83

Tobacco Smoke and Involuntary Smoking

Summary of Data Reported and Evaluation

TOBACCO SMOKING AND TOBACCO SMOKE (Group 1)

5. Summary of Data Reported and Evaluation VOL.: 83 (2002)

5.1 Exposure data

Smoking of tobacco is practised worldwide by over one thousand million people. However, while smoking prevalence has declined in many developed countries, it remains high in others and is increasing among women and in developing countries. Between one-fifth and two-thirds of men in most populations smoke. Women's smoking rates vary more widely but rarely equal male rates.

Tobacco is most commonly smoked as cigarettes, both manufactured — which are a highly sophisticated nicotine delivery system — and hand-rolled. Pipes, cigars, bidis and other products are used to a lesser extent or predominantly in particular regions. Cigarettes are made from fine-cut tobaccos which are wrapped in paper or a maize leaf. Cigars consist of cut tobacco filler formed in a binder leaf and with a wrapper leaf rolled spirally around the bunch. Bidis contain shredded tobacco wrapped in non-tobacco leaves, usually dried temburni leaves.

The chemical composition of tobacco smoke, although influenced by the specific manner in which individuals smoke, is primarily determined by the type of tobacco. It is also influenced by the design of the smoking device or product and, for cigarettes, by the presence or absence of filters, and by other factors including ventilation, paper porosity and types of additives. As a result, concentrations of individual chemicals in smoke vary. Analysis of the ways in which people smoke modern cigarettes shows that actual doses of nicotine, carcinogens and toxins depend on the intensity and method of smoking and have little relation to stated tar

yields. The total volume of smoke drawn from cigarettes as a result of specific smoking patterns is the principal determinant of dose to the smoker. All presently available tobacco products that are smoked deliver substantial amounts of established carcinogens to their users.

The yields of tar, nicotine and carbon monoxide from cigarettes, as measured by standard machine-smoking tests, have fallen over recent decades in cigarettes sold in most parts of the world, but have remained higher in some countries. The tar and nicotine yields as currently measured are misleading and have only little value in the assessment of human exposure to carcinogens.

The regulation of smoking and smoke yields varies widely around the world in scope and degree of enforcement. Certain regulatory actions, such as taxes and workplace smoking bans, are effective in reducing smoking rates and protecting nonsmokers.

5.2 Human carcinogenicity data

In the previous 1986 IARC Monograph on tobacco smoking, cancers of the lung, oral cavity, pharynx, larynx, oesophagus (squamous-cell carcinoma), pancreas, urinary bladder and renal pelvis were identified as caused by cigarette smoking. Many more studies published since this earlier Monograph support these causal links. In addition, there is now sufficient evidence for a causal association between cigarette smoking and cancers of the nasal cavities and nasal sinuses, oesophagus (adenocarcinoma), stomach, liver, kidney (renal-cell carcinoma), uterine cervix and myeloid leukaemia.

In cancer sites that were causally linked to cigarette smoking in the previous IARC Monograph on tobacco smoking, the observed relative risks ranged generally from approximately 3 for pancreatic cancer to more than 20 for lung cancer. For those cancer sites that were now also linked to cigarette smoking in this Monograph, generally two- to threefold increased risks were observed.

Cigarettes

Lung

Lung cancer is the most common cause of death from cancer in the world. The total number of cases is now estimated to be 1.2 million annually and is still increasing. The major cause of lung cancer is tobacco smoking, primarily of cigarettes. In populations with prolonged cigarette use, the proportion of lung cancer cases attributable to cigarette smoking has reached 90%.

The duration of smoking is the strongest determinant of lung cancer in smokers. Hence, the earlier the age of starting and the longer the continuation of smoking in adulthood, the greater the risk. Risk of lung cancer also increases in proportion to the numbers of cigarettes smoked.

Tobacco smoking increases the risk of all histological types of lung cancer including squamous-cell carcinoma, small-cell carcinoma, adenocarcinoma (including bronchiolar/alveolar carcinoma) and large-cell carcinoma. The association between adenocarcinoma of the lung and smoking has become stronger over time. The carcinogenic effects of cigarette smoking appear similar in both women and men.

Stopping smoking at any age avoids the further increase in risk of lung cancer incurred by continued smoking. The younger the age at cessation, the greater the benefit.

Urinary tract

Tobacco smoking is a major cause of transitional-cell carcinomas of the bladder, ureter and renal pelvis. Risk increases with the duration of smoking and number of cigarettes smoked. As for lung cancer, stopping smoking at any age avoids the further increase in risk incurred by continued smoking.

Evidence from several cohort and case–control studies published since the previous IARC Monograph on tobacco smoking has indicated that renal-cell carcinoma is associated with tobacco smoking in both men and women. The association is not explained by confounding. A dose–response relationship with the number of cigarettes smoked has been noted in most studies, and a few also noted a reduction in risk after cessation.

Oral cavity

Tobacco smoking, including cigarette smoking, is causally associated with cancer of the oral cavity (including lip and tongue) in both men and women. Since the previous IARC Monograph on tobacco smoking, evidence from many more studies has accumulated that further confirms this association. Use of smokeless tobacco and/or alcohol in combination with tobacco smoking greatly increases the risk of oral cancer. Risk increases substantially with duration of smoking and number of cigarettes smoked. Risk among former smokers is consistently lower than among current smokers and there is a trend of decreasing risk with increasing number of years since quitting.

Nasal cavity and paranasal sinuses

An increased risk of sinonasal cancer among cigarette smokers has been reported in all nine case–control studies for which results are available. Of seven studies that have analysed dose–response relationships, a positive trend was found in five and was suggested in the other two. In all the five studies that have analysed squamous-cell carcinoma and adenocarcinoma separately, the relative risk was clearly increased for squamous-cell carcinoma.Nasopharynx

An increased risk for nasopharyngeal cancer among cigarette smokers was reported in one cohort study and nine case–control studies. Increased relative risks were reported in both high- and low-risk geographical regions for nasopharyngeal cancer. A dose–response relationship was detected with either duration or amount of smoking. A reduction in risk after quitting was also detected. The potential confounding effect of infection with Epstein–Barr virus was not controlled for in these studies; however, such an effect was not considered to be plausible. No important role was shown for other potential confounders.

Oropharynx and hypopharynx

Oropharyngeal and hypopharyngeal cancer are causally associated with cigarette smoking. The risk increased with increased duration of smoking and daily cigarette consumption and decreased with increasing time since quitting.

Oesophagus

Tobacco smoking is causally associated with cancer of the oesophagus, particularly squamous-cell carcinoma. Tobacco smoking is also causally associated with adenocarcinoma of the oesophagus. In most of the epidemiological studies, the risk for all types of oesophageal cancer increased with numbers of cigarettes smoked daily and duration of smoking. However, risk for oesophageal cancer remains elevated many years after cessation of smoking.

Tobacco and alcohol in combination with tobacco smoking greatly increase the risk for squamous-cell carcinoma of the oesophagus. In India, use of smokeless tobacco in combination with smoking also greatly increases the risk.

Larynx

Laryngeal cancer is causally associated with cigarette smoking. The risk increases substantially with duration and number of cigarettes smoked. Use of alcohol in combination with tobacco smoking greatly increases the risk for laryngeal cancer. A few studies also reported that relative risks for cancer of the larynx

increased with decreasing age at start of smoking. The relative risk decreased with increasing time since quitting smoking.

Pancreas

Cancer of the pancreas is causally associated with cigarette smoking. The risk increases with duration of smoking and number of cigarettes smoked daily. The risk remains elevated after allowing for potential confounding factors such as alcohol consumption. The relative risk decreased with increasing time since quitting smoking.

Stomach

The data available in 1986 did not permit the earlier IARC Working Group to conclude that the association between tobacco smoking and stomach cancer was causal. Since that time, further studies have shown a consistent association of cancer of the stomach with cigarette smoking in both men and women in many cohort and case–control studies conducted in various parts of the world. Confounding by other factors (e.g. alcohol consumption, Helicobacter pylori infection and dietary factors) can be reasonably ruled out. Risk increases with duration of smoking and number of cigarettes smoked, and decreases with increasing duration of successful quitting. In studies that had adequate numbers, the relative risks for men and women were similar.

Liver

In the previous IARC Monograph on tobacco smoking, a causal relationship between liver cancer and smoking could not be established, chiefly due to possible confounding from alcohol intake and hepatitis B and hepatitis C virus infections. Many cohort studies and case–control studies have provided additional information on smoking and liver cancer since then. Most of the cohort studies and the largest case–control studies (most notably those that included community controls) showed a moderate association between tobacco smoking and risk of liver cancer. In many studies, the risk for liver cancer increased with the duration of smoking or the number of cigarettes smoked daily. Former smokers who had stopped smoking for more than 10 years showed a decline in liver cancer risk. Confounding from alcohol can be ruled out, at least in the best case–control studies, by means of careful adjustment for drinking habits. An association with smoking has also been demonstrated among non-drinkers. Many studies, most notably from Asia, have shown no attenuation of the association between smoking and liver cancer after adjustment/stratification for markers of hepatitis B/hepatitis C virus infection. There is now sufficient evidence to judge the association between tobacco smoking and liver cancer as causal.

Cervix

An association of invasive cervical squamous-cell carcinoma with smoking has been observed in the large number of studies reviewed. The most recent studies have controlled for infection with human papillomavirus, a known cause of cervical cancer. The effect of smoking was not diminished by the adjustment for human papillomavirus infection, or analysis restricted to cases and controls both positive for human papillomavirus (as ascertained by human papillomavirus DNA or human papillomavirus serological methods).

There is now sufficient evidence to establish a causal association of squamous-cell cervical carcinoma with smoking. In the small number of studies available for adeno- and adeno-squamous-cell carcinoma, no consistent association was observed.

Leukaemia

Myeloid leukaemia in adults was observed to be causally related to smoking. Risk increased with amount of tobacco smoked in a substantial number of adequate studies. No clear evidence of any risk was seen for lymphoid leukaemia/lymphoma.

Support for a causal relationship of smoking with myeloid leukaemia is provided by the finding of known leukaemogens in tobacco smoke, one of which (benzene) is present in sufficient amounts to account for up to half of the estimated excess of acute myeloid leukaemia.

Colorectal cancer

There is some evidence from prospective cohort studies and case–control studies that the risk of colorectal cancer is increased among tobacco smokers. However, it is not possible to conclude that the association between tobacco smoking and colorectal cancer is causal. Inadequate adjustment for various potential confounders could account for some of the small increase in risk that appears to be associated with smoking.

Female breast

Most epidemiological studies have found no association with active smoking, after controlling for established risk factors (e.g. age at time of first birth, parity, family history of breast cancer and alcohol). The large multicentre pooled analysis of the association of smoking with breast cancer in non-drinkers confirms the lack of an increased risk of breast cancer associated with smoking.

Endometrium

Cigarette smoking is not associated with an increased risk for endometrial cancer. An inverse relationship of cigarette smoking with endometrial cancer is observed consistently in most case–control and cohort studies, after adjustment for major confounders. This pattern is stronger in postmenopausal women.

Prostate

No clear evidence of any risk for prostate cancer is seen in case–control studies or in studies of incident cases in cohort studies. The small excess observed in some analytical mortality studies can reasonably be explained by bias in the attribution of the underlying cause of death.

Other

There is inconsistent and/or sparse evidence for association between cigarette smoking and other cancer sites that were considered by the Working Group.

Cigars and pipes

Cigar and/or pipe smoking is strongly related to cancers of the oral cavity, oropharynx, hypopharynx, larynx and oesophagus, the magnitude of risk being similar to that from cigarette smoking.

These risks increase with the amount of cigar and/or pipe smoking and with the combination of alcohol and tobacco consumption. Cigar and/or pipe smoking is causally associated with cancer of the lung and there is evidence that cigar and/or pipe smoking are also causally associated with cancers of the pancreas, stomach and urinary bladder.

Bidi

Bidi smoking is the most common form of tobacco smoking in India and is also prevalent in other south-Asian countries and an emerging problem in the USA. Bidi smoke was considered as carcinogenic in the earlier IARC Monograph on tobacco smoking, and later studies have provided further evidence of causality.

Case–control studies demonstrated a strong association at various sites: oral cavity (including subsites), pharynx, larynx, oesophagus, lung and stomach. Almost all studies show significant trends with duration of bidi smoking and number of bidis smoked.

Synergy

For public health purposes, synergy should be characterized as a positive departure from additivity.

The epidemiological literature often inadequately describes combined effects of smoking with co-exposures to other carcinogenic agents and in many studies power is limited for characterizing combined effects. The issue of synergistic effects can be appropriately addressed by epidemiological studies that show stratified analysis and have sufficient power. The studies reviewed found evidence of synergy between smoking and several occupational causes of lung cancer (arsenic, asbestos and radon), and between smoking and alcohol consumption for cancers of the oral cavity, pharynx, larynx and oesophagus and between smoking and human papillomavirus infection for cancer of the cervix. Data were inadequate to evaluate the evidence for synergy between smoking and other known causes of cancer (e.g. hepatitis B and alcohol for liver cancer).

5.3 Animal carcinogenicity data

Cigarette smoke has been tested for carcinogenicity by inhalation studies in rodents, rabbits and dogs. The model systems for animal exposure to tobacco smoke do not fully simulate human exposure to tobacco smoke, and the tumours that develop in animals are not completely representative of human cancer. Nevertheless, the animal data provide valuable insights regarding the carcinogenic potential of tobacco smoke.

The most compelling evidence for a positive carcinogenic effect of tobacco smoke in animals is the reproducible increase observed in several studies in the occurrence of laryngeal carcinomas in hamsters exposed to whole tobacco smoke or to its particulate phase. In four of five studies in rats, exposure to whole smoke led to modest increases in the occurrence of malignant and/or benign lung tumours. Similarly, in four of eight studies in mice of varying susceptibility to lung tumour development, exposure to whole smoke led to a modest increase in the frequency of lung adenomas. An increased incidence of lung 'tumours' has also been reported in dogs exposed to tobacco smoke, but it is uncertain whether the histopathological features of the lesions are consistent with malignancy. In hamsters exposed to both cigarette smoke and chemical carcinogens (N-nitrosodiethylamine and 7,12-dimethylbenz[a]anthracene), the tumour response in the respiratory tract was higher than in hamsters exposed to either agent alone. The same is true in rats exposed simultaneously to cigarette smoke and radionuclides (radon progeny and plutonium oxide).

Cigarette smoke condensate both initiates and promotes tumour development in animals. It reproducibly induces both benign and malignant skin tumours in mice following topical application. Similarly, it produces skin tumours in rabbits following topical application. Topical application to the oral mucosa also produced an increased incidence of lung tumours and lymphomas in mice. In rats, cigarette smoke condensate produced lung tumours after intrapulmonary injection.

In initiation/promotion assays in mouse skin, a single topical application of cigarette smoke condensate followed by application of croton oil was sufficient to initiate both benign and malignant skin tumours. Smoke condensates of Indian bidi administered to mice by gavage were found to induce tumours in a number of organs. Collectively, these data provide evidence of the carcinogenic effect of mainstream tobacco smoke in experimental animals.

5.4 Other relevant data

Causal associations have been clearly established between active smoking and adverse reproductive outcomes and numerous non-neoplastic diseases, including chronic obstructive pulmonary disease and cardiovascular diseases.

Tobacco smoking is addictive, and nicotine has been established as the major addictive constituent of tobacco products. Measurement of the nicotine metabolite, cotinine, in human blood, urine or saliva provides a specific and sensitive test for exposure to tobacco smoke and can be used to distinguish active and passive smokers from nonsmokers.

Active smoking raises the concentrations of carbon monoxide, benzene and volatile organic compounds in exhaled air. The concentrations of urinary metabolites of some important tobacco smoke carcinogens and related compounds are consistently higher in smokers than in nonsmokers. These include metabolites of benzene, a known carcinogen in humans, as well as metabolites of several carcinogens that cause lung tumours in rodents. Covalent binding to blood proteins by carcinogens present in tobacco smoke has been demonstrated to occur at significantly higher levels in smokers than in nonsmokers. The adducts are derived from various compounds including aromatic amines (e.g. 4-aminobiphenyl), polycyclic aromatic hydrocarbons (e.g. benzo[a]pyrene), tobacco-specific nitrosamines (e.g. 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone), benzene, acrylamide and acrylonitrile.

Smoking-related DNA adducts have been detected by a variety of analytical methods in the respiratory tract, urinary bladder, cervix and other tissues. In many studies the levels of carcinogen-DNA adducts have been shown to be higher in tissues of smokers than in tissues of nonsmokers. Some but not all studies have demonstrated elevated levels of these adducts in the peripheral blood and in full-term placenta. Smoking related adducts have also been detected in cardiovascular tissues. Collectively, the available biomarker data provide convincing evidence that carcinogen uptake, activation and binding to cellular macromolecules, including DNA, are higher in smokers than in nonsmokers.

The exposure of experimental animals, primarily rodents, to mainstream tobacco smoke results in a number of biological effects that include (i) increases or decreases in the activities of phase I and phase II enzymes involved in carcinogen metabolism, (ii) increases in the activation of antioxidant enzymes, (iii) increased expression of nitric oxide synthase and of various protein kinases and collagenase, (iv) the formation of tobacco smoke-related DNA adducts in several tissues and (v) reduced clearance of particulate material from the lung. Smoking is known to have inhibitory or inducing effects on the activities of many enzymes in human tissues. These include xenobiotic metabolizing enzymes, which affect drug and carcinogen metabolism. Numerous studies have reported effects on enzymes in cells treated in culture with tobacco smoke or tobacco smoke condensates.

In humans, smoking produces gene mutations and chromosomal abnormalities. Urine from smokers is mutagenic. Relative to nonsmokers, lung tumours of smokers contain higher frequencies of TP53 and KRAS mutations, and the spectrum of mutations has unique features. Most of the genetic effects seen in smokers are also observed in cultured cells or in experimental animals exposed to tobacco smoke or smoke condensate. Tobacco smoke is genotoxic in humans and in experimental animals.

5.5 Evaluation

There is sufficient evidence in humans that tobacco smoking causes cancer of the lung, oral cavity, naso-, oro- and hypopharynx, nasal cavity and paranasal sinuses, larynx, oesophagus, stomach, pancreas, liver, kidney (body and pelvis), ureter, urinary bladder, uterine cervix and bone marrow (myeloid leukaemia).

There is evidence suggesting lack of carcinogenicity of tobacco smoking in humans for cancers of the female breast and endometrium.

There is sufficient evidence in experimental animals for the carcinogenicity of tobacco smoke and tobacco smoke condensates.

Overall evaluation

Tobacco smoking and tobacco smoke are carcinogenic to humans (Group 1).

For definition of the italicized terms, see Preamble.

INVOLUNTARY SMOKING (Group 1)

For definition of groups, see Preamble. VOL.: 83 (2002)

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Involuntary (or passive) smoking is exposure to secondhand tobacco smoke, which is a mixture of exhaled mainstream smoke and sidestream smoke released from the smouldering cigarette or other smoking device (cigar, pipe, bidi, etc.) and diluted with ambient air. Involuntary smoking involves inhaling carcinogens, as well as other toxic components, that are present in secondhand tobacco smoke. Secondhand tobacco smoke is sometimes referred to as 'environmental' tobacco smoke. Carcinogens that occur in secondhand tobacco smoke include benzene, 1,3-butadiene, benzo[a]pyrene, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and many others.

Secondhand tobacco smoke consists of a gas phase and a particulate phase; it changes during its dilution and distribution in the environment and upon ageing. The concentrations of respirable particles may be elevated substantially in enclosed spaces containing secondhand tobacco smoke.

The composition of tobacco smoke inhaled involuntarily is variable quantitatively and depends on the smoking patterns of the smokers who are producing the smoke as well as the composition and design of the cigarettes or other smoking devices. The secondhand tobacco smoke produced by smoking cigarettes has been most intensively studied.

Secondhand tobacco smoke contains nicotine as well as carcinogens and toxins. Nicotine concentrations in the air in homes of smokers and in workplaces where smoking is permitted typically range on average from 2 to 10 micrograms/m3.

5.2 Human carcinogenicity data

Lung cancer

Involuntary smoking involves exposure to the same numerous carcinogens and toxic substances that are present in tobacco smoke produced by active smoking, which is the principal cause of lung cancer. As noted in the previous IARC Monograph on tobacco smoking, this implies that there will be some risk of lung cancer from exposure to secondhand tobacco smoke.

More than 50 studies of involuntary smoking and lung cancer risk in never-smokers, especially spouses of smokers, have been published during the last 25 years. These studies have been carried out in many countries. Most showed an increased risk, especially for persons with higher exposures.

To evaluate the information collectively, in particular from those studies with a limited number of cases, meta-analyses have been conducted in which the relative risk estimates from the individual studies are pooled together. These meta-analyses show that there is a statistically significant and consistent association between lung cancer risk in spouses of smokers and exposure to secondhand tobacco smoke from the spouse who smokes. The excess risk is of the order of 20% for women and 30% for men and remains after controlling for some potential sources of bias and confounding. The excess risk increases with increasing exposure. Furthermore, other published meta-analyses of lung cancer in never-smokers exposed to secondhand tobacco smoke at the workplace have found a statistically significant increase in risk of 12–19%. This evidence is sufficient to conclude that involuntary smoking is a cause of lung cancer in never-smokers.

The magnitudes of the observed risks are reasonably consistent with predictions based on studies of active smoking in many populations.

Breast cancer

The collective evidence on breast cancer risk associated with involuntary exposure of never-smokers to tobacco smoke is inconsistent. Although four of the 10 case–control studies found statistically significant increases in risks, prospective cohort studies as a whole and, particularly, the two large cohort studies in the USA of nurses and of volunteers in the Cancer Prevention Study II provided no support for a causal relation between involuntary exposure to tobacco smoke and breast cancer in never-smokers. The lack of a positive dose–response also argues against a causal interpretation of these findings. Finally, the lack of an association of breast cancer with active smoking weighs heavily against the possibility that involuntary smoking increases the risk for breast cancer, as no data are available to establish that different mechanisms of carcinogenic action operate at the different dose levels of active and of involuntary smoking.

Childhood cancer

Overall, the findings from studies of childhood cancer and exposure to parental smoking are inconsistent and are likely to be affected by bias. There is a suggestion of a modest association between exposure to maternal tobacco smoke during pregnancy and childhood cancer for all cancer sites combined; however, this is in contrast with the null findings for individual sites. Studies on paternal tobacco

smoking suggest a small increased risk for lymphomas, but bias and confounding cannot be ruled out.

Other cancer sites

Data are conflicting and sparse for associations between involuntary smoking and cancers of the nasopharynx, nasal cavity, paranasal sinuses, cervix, gastrointestinal tract and cancers at all sites combined. It is unlikely that any effects are produced in passive smokers that are not produced to a greater extent in active smokers or that types of effects that are not seen in active smokers will be seen in passive smokers.

5.3 Animal carcinogenicity data

Secondhand tobacco smoke for carcinogenicity studies in animals is produced by machines that simulate human active smoking patterns and combine mainstream and sidestream smoke in various proportions. Such mixtures have been tested for carcinogenicity by inhalation studies in rodents. The experimental model systems for exposure to secondhand tobacco smoke do not fully simulate human exposures, and the tumours that develop in animals are not completely representative of human cancer. Nevertheless, the animal data provide valuable insights regarding the carcinogenic potential of secondhand tobacco smoke.

A mixture of 89% sidestream smoke and 11% mainstream smoke has been tested for carcinogenic activity in mouse strains that are highly susceptible to lung tumours (strains A/J and Swiss). In strain A/J mice, this mixture consistently produces a significant, modest increase in lung tumour incidence and lung tumour multiplicity when the mice are exposed for 5 months followed by a 4-month recovery period. These lung tumours are predominantly adenomas. Continuous exposure of strain A/J mice to the above mixture of mainstream and sidestream tobacco smoke for 9 months with no recovery period did not increase the incidence of lung tumours. In Swiss strain mice, the same mixture induced lung tumours by both protocols, i.e. when the animals were exposed for 5 months followed by a 4-month recovery period and when they were exposed continuously for 9 months with no recovery period. In addition, exposure of Swiss mice to the tobacco smoke mixture for a shorter period was sufficient to induce lung tumours.

Condensates of sidestream and of mainstream cigarette smoke have been tested for carcinogenicity. Both kinds of condensates produced a spectrum of benign and malignant skin tumours in mice following topical application, and the sidestream condensate exhibited higher carcinogenic activity. Sidestream smoke condensate was shown to produce a dose-dependent increase in lung tumours in rats following implantation into the lungs.

Increased relative risks for lung and sinonasal cancer have been reported in companion animals (dogs) exposed to secondhand tobacco smoke in homes.

5.4 Other relevant data

Involuntary smoking has been associated with a number of non-neoplastic diseases and adverse effects in never-smokers, including both children and adults. Epidemiological studies have demonstrated that exposure to secondhand tobacco smoke is causally associated with coronary heart disease. From the available metaanalyses, it has been estimated that involuntary smoking increases the risk of an acute coronary heart disease event by 25–35%. Adverse effects of involuntary smoking on the respiratory system have also been detected.

In adults, the strongest evidence for a causal relation exists for chronic respiratory symptoms. Some effects on lung function have been detected, but their medical relevance is uncertain.

Data on the hormonal and metabolic effects of involuntary smoking are sparse. However, female involuntary smokers do not appear to weigh less than women who are not exposed to secondhand tobacco smoke, a pattern that contrasts with the findings for active smoking. No consistent association of maternal exposure to secondhand smoke with fertility or fecundity has been identified. There is no clear association of passive smoking with age at menopause.

Maternal cigarette smoking has repeatedly been associated with adverse effects on fetal growth; full-term infants born to women who smoke weigh about 200 g less than those born to nonsmokers. A smaller adverse effect has been attributed to maternal passive smoking.

Cotinine, and its parent compound nicotine, are highly specific for exposure to secondhand smoke. Because of its favourable biological half-life and the sensitivity of techniques for quantifying it, cotinine is currently the most suitable biomarker for assessing recent exposure to secondhand tobacco smoke uptake and metabolism in adults, children and newborns.

Several studies in humans have shown that concentrations of adducts of carcinogens to biological macromolecules, including haemoglobin adducts of aromatic amines and albumin adducts of polycyclic aromatic hydrocarbons, are higher in adult involuntary smokers and in the children of smoking mothers than in individuals not exposed to secondhand tobacco smoke. Protein adduct concentrations in fetal cord blood correlate with those in maternal blood but are lower. Fewer studies have investigated DNA adduct levels in white blood cells of

exposed and unexposed nonsmokers, and most studies have not shown clear differences.

In studies of urinary biomarkers, metabolites of the tobacco-specific carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, have been found to be consistently elevated in involuntary smokers. Levels of these metabolites are 1–5% as great as those found in smokers. The data demonstrating uptake of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, a lung carcinogen in rodents, by nonsmokers are supportive of a causal link between exposure to secondhand tobacco smoke and development of lung cancer.

The exposure of experimental animals, primarily rodents, to secondhand tobacco smoke has several biological effects that include

(i) increases or decreases in the activity of phase I enzymes involved in carcinogen metabolism;

(ii) increased expression of nitric oxide synthase, xanthine oxidase and various protein kinases;

(iii) the formation of smoke-related DNA adducts in several tissues; and (iv) the presence of urinary biomarkers of exposure to tobacco smoke.

In adult experimental animals, sidestream tobacco smoke has been found to produce changes that are similar to those observed with exposure of humans to secondhand tobacco smoke. These include inflammatory changes in the airways and accelerated formation of arteriosclerotic plaques. Although the changes are often comparatively minor and require exposure to rather elevated concentrations of sidestream smoke, they support the results of human epidemiological studies.

During pre- and postnatal exposure, sidestream smoke produces intrauterine growth retardation, changes the pattern of metabolic enzymes in the developing lung, and gives rise to hyperplasia of the pulmonary neuroendocrine cell population. In addition, it adversely affects pulmonary compliance and airway responsiveness to pharmacological challenges.

In humans, involuntary smoking is associated with increased concentrations of mutagens in urine. Some studies have shown a correlation of urinary mutagenicity with concentrations of urinary cotinine.

Increased levels of sister chromatid exchanges have not been observed in involuntary smokers; however, there is some indication of elevated levels in exposed children.

Lung tumours from nonsmokers exposed to tobacco smoke contain TP53 and KRAS mutations that are similar to those found in tumours from smokers.

The genotoxicity of sidestream smoke, 'environmental' tobacco smoke, sidestream smoke condensate or a mixture of sidestream and mainstream smoke condensates has been demonstrated in experimental systems in vitro and in vivo.

5.5 Evaluation

There is sufficient evidence that involuntary smoking (exposure to secondhand or 'environmental' tobacco smoke) causes lung cancer in humans.

There is limited evidence in experimental animals for the carcinogenicity of mixtures of mainstream and sidestream tobacco smoke.

There is sufficient evidence in experimental animals for the carcinogenicity of sidestream smoke condensates.

In addition, the Working Group noted that there are published reports on possible carcinogenic effects of secondhand tobacco smoke in household pet dogs.

Overall evaluation

Involuntary smoking (exposure to secondhand or 'environmental' tobacco smoke) is carcinogenic to humans (Group 1).

For definition of the italicized terms, see Preamble.