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Exposure to Nano-Sized Particles and the Emergence of Contemporary Diseases with a Focus on Epigenetics

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1. Introduction

Mankind has been exposed to airborne nano-sized particles for eons, yet mechanization and industrialization of societies has increased the overall aerosol pollution load to which humans are exposed to. Nano-aerosols with a diameter below 1 µm, can be incorporated via any biological surface structure and in particular when the area available is large enough as is the case with the skin (approx. $1.5-2 \text{ m}^2$), the digestive tract (intestinal villi, approx. 200 m²) or the respiratory tract (alveolar surface area reaching approx. 140 m²).^(Raab et al, 2010) Since aerosolised particles are readily inhaled rather than ingested, the lungs represent an ideal gateway with high penetration efficiency rates. From a toxicological rather than from a therapeutic point of view, a deposited xenobiotic particle first interacts with biological tissues on a cellular level. From there it is readily translocated into the cell to interfere with metabolic pathways, eventually inducing inflammatory cellular responses. At an organismic level - along with long-term exposure - these particles become redistributed via the lymphatic or the blood circulatory system to reach sensitive organs or tissues, such as the central nervous system, bone marrow, lymph nodes, spleen, heart, etc.^(Oberdörster et al. 2005a) At this level, persistent particle exposure may trigger chronic diseases or when already present, modulate the severity of its course.

1.1 Classification of nano-aerosols

With every breath, with every bite, with every sip, we introduce countless nano-sized particles, viruses and bacteria into our organism. Since the onset of the industrial revolution, some 150 years ago, people are progressively exposed to elevated concentration of arbitrarily shaped nano-aerosols in combination with chemical by-products such as carbon monoxide (CO), nitric oxide (NO), semi-volatile (SVC) and volatile organic compounds (VOCs) of anthropogenic origin – mostly in the form of incompletely combusted by-products that leave stacks or tailpipes as macromolecular clusters (Figure 1). Their minute size grants them easy access even to indoor environments.^(Costa & Dreher, 1997)

The terms nano- or ultrafine particles (UFP) comprise particles of less than 100 nm diameter.^(Chang, 2010; Alessandrini et al., 2009) Depending on their origin, particles of this size have

been categorized as (i) naturally occurring ultrafine particles (UFPs), e.g. volcanic ash, mineral compounds, ocean spray and plant debris, (ii) anthropogenic UFPs, such as diesel exhaust particles (DEPs) as well as environmental tobacco smoke (ETS) and (iii) deliberately tailored nano-particles with designed functions; e.g. DNA- and carbon nano-tubes, fullerenes, nano-wires and nano-coatings, carbon black, synthetic agents contained in whiteners and additives supplemented to food for modification of texture.^(Chang, 2010) With recent advances in nanotechnology, these designed and engineered nano-particles are being introduced in ever greater varieties, such as scratch-proof paints, lotus-effect stained glass, suntan lotion, toothpaste, etc.^(Raab et al., 2010) Although their release into the environment is not intended in the first place, it will occur sooner rather than later - especially once wear and tear along with product degradation releases contained nano-particles into the environment where they easily can enter the food chain either via aerosolization or washing-out from dumping sites.

Regardless of the particle's origin, the young research field of nano-toxicology deals with effects and potential risks of particle structures <1 µm in size. Indeed, the adverse functions of these aerosol pollutants have been recognized based on their interaction with biological systems on macro-molecular, sub-cellular, cellular, tissue and organism levels. The passage of nano-aerosols from the environment into humans occur via interfacing tissues, e.g. skin, gut and mainly the respiratory system. (Chang, 2010; Traidl-Hoffmann et al., 2009) Due to their small size, these particles possess completely different biological potentials when interacting with living organisms in comparison to particulate matter of increased dimensions. The unique properties are related to their enlarged surface-to-mass ratio in combination with their higher propensity for penetration of biological barriers, for deposition, e.g. in the peripheral lung, and the increased overall retention in biological systems.(Chang, 2010; Alessandrini et al., 2006; Alessandrini et al., 2009) This is particularly true for nano-sized particles as the larger surface area per unit volume compared with their larger-sized siblings renders them biologically more active.(Geiser & Kreyling, 2010) Thus, within these dimensions, the well-known quote of Paracelsus "the dose makes the poison", needs to be revised in that "the dose determines the mechanism".(Oberdörster et al. 2005a)

The minute dimensions of UFPs enable their direct passage by crossing cell barriers to enter blood and lymphatic streams and promote further distribution to various target organs, tissues and interstitial of cells.^(Chang, 2010; Alessandrini et al., 2009) At the same time, they also penetrate cells and interact with intracellular structures leading to oxidative stress. Here in particular, insoluble nano-aerosols can extend their multiple adverse effects even further when redistributed from one line of defence to the next as metabolites or cellular debris are released back into the interstitial after cell death.^(Casal et al., 2008)

This review aims to provide an overview regarding hazardous effects relevant to humans and at the same time to promote a better understanding of how most contemporary diseases relate to UFPs. Although the review deals with aspects mostly outside the immunological field, and therefore does not take into account virulence of viral agents or immune system conditioning, the absorption of nano-aerosols via various pathways affects essential functions of the immune defense system that include even allergens.^(Chang, 2010; Traidl-Hoffmann et al., 2009)

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Fig. 1. Schematic representation revealing the formation process and the fractal nature of a nano-sized DEP/MEP cluster and its adsorbed vapour-phase compounds. Model of the carbon core of a DEP that is covered with a layer of inorganic components as well as (bio)organic compounds and pollutants. Solubilisation of the adsorbed fraction is an issue when the semi-/volatile fractions come into contact with the surfactant of the lung.^(modified after Madl, 2003)

1.2 Composition of diesel- and ultrafine nano-particles

In the context of health effects of nano-aerosols, diesel exhaust particles (DEPs) as shown in Figure 1, represent a primary source and have extensively been used as a model to investigate the induction of oxidative stress as well as modulation of the immune system.(Chang, 2010) This is also related to the fact, that diesel engines expel about 100 times more particles than gasoline engines.(Riedl & Diaz-Sanchez, 2005) Exhaust particles produced by motorcycles (MEPs) differ from DEPs in their composition, since fuel of two-stroke engines contains a lubricant additive entailing incomplete combustion. Generally, MEPs contain higher amounts of benzene, toluene and xylene than DEPs. Likewise, their polyaromatic hydrocarbon (PAH) spectra differ.(Cheng et al., 2004) DEPs are rather heterogeneous in their composition but share a consensus structure with a carbonaceous core, whereon a multitude of hydrocarbon compounds (10-20,000) can be attached onto, (Riedl & Diaz-Sanchez, 2005; Costa & Dreher, ¹⁹⁹⁷⁾ with the latter encompassing about 20-40% (mass per mass) of DEPs.^(Lubitz et al., 2009) Within this attached layer, PAHs (Chang, 2010; Nel, 1998; Takenaka et al., 1995), nitro-PAHs, (Kocbach, 2008) but also bioavailable (transition) metals, such as Fe, Cu, Ni, V, Zn, nitrates, sulfates, (Chang, 2010; Costa & Dreher, 1997) allergens, (Ormstad et al., 1995; Riedl & Diaz-Sanchez, 2005) plant debris, (Solomon, 2002); Taylor et al., ²⁰⁰²) mineral constituents, endotoxins, e.g. lipopolysaccharide (LPS), hopanes, and steranes have been identified.(Kocbach et al., 2008) In the case of wood smoke particles (WSPs), the PAH content is ~150-fold higher (9750 ng/mg) in comparison to DEPs. WEPs slso contained sugars, methoxy-phenols, PAHs, benzene and alkali salts. However, with 31 nm (at the site of formation), the diameter of WSPs is significantly larger than for traffic related UFPs (24-25 nm). For WSPs, the spectrum of core-attached compounds is also influenced by the combustion temperature.(Kocbach et al., 2008) In case of organic dust, as produced by modern

farming operations, the nano-aerosol fraction is composed of particulate matter and microbial compounds, including endotoxins, such as LPS, and peptidoglycans (PGNs). The latter compound class represents cell wall constituents particularly of gram-positive bacteria.(Poole et al., 2008)

1.3 Particle deposition and clearance within the human respiratory tract

Deposition of inhaled particles in the human respiratory tract is determined by several biological factors, such as lung morphology and breathing patterns, as well as by physical factors, such as fluid dynamics, particle properties, and deposition mechanisms. Since particle deposition in individual airways cannot be thoroughly analyzed *in-vivo*, particle inhalation and the corresponding deposition patterns are simulated by analytical computer models, which require regular comparison with experiments obtained from human subjects.^(Hofmann, 2011) In principle, particle deposition within the respiratory tract is bound to physical principles such as impaction, gravitational settling, diffusion, and electrical attraction (Figure 2).

With the introduction of particle filters and catalytic converters in the exhaust stream, most coarse particles are efficiently removed. Filtering out the coarse fraction usually leaves the smaller without the coarser sibling where the former tend to agglomerate on. Due to their minute dimensions, nano-sized particles largely escape filtering devices and are emitted into the environment where they interact photochemically to form secondary by-products. Upon inhalation, nano-aerosols, along with the adsorbed semi-volatile / volatile chemical cocktail predominantly deposit via Brownian diffusion and electrostatic mechanisms in the nose and the alveolar region where they can unfold their toxicological potential.^(Donaldson et al., 1998)



Fig. 2. Total deposition function versus particle diameter for an adult individual with a tidal lung volume of 660 mL at 30 breaths per minute (left). Particle regime <300 nm is dominated by diffusional deposition patterns, those >300 nm by sedimentation and impaction.^(modified after Hussain et al., 2011) On the right a schematic view of the pulmonary domains is shown, with the naso-pharyngeal and tracheo-bronchial pathway at the top and the bronchiole and alveolar regime at the bottom, alongside the flow velocities of the in-/exhaled air. ^(modified after Yip., 2003)

1.4 Potential health effects of nano-aerosol exposure

To a certain degree, macrophages possess the ability to process and detoxify organic constituents adhered to DEP surfaces. Once DEPs are endocytosed (Figure 3a), their clearance can occur by the so-called "mucociliary escalator" whereby mucus along with DEPloaded alveolar macrophages are transferred to the oropharyngeal region by movements of cilia. Their clearing transport might be assisted by an increase in pneumocytes of type-II, which are responsible for the secretion of the alveolar surfactant (see Figure 3b). Finally, the mucus containing macrophages, which are loaded with endocytosed DEPs is either expelled as sputum or swallowed and rerouted over the gastrointestinal tract where DEPs can be reabsorbed over the interstitial lining.(Vostal, 1980) However, cilia-mediated clearance does neither cover terminal bronchioles nor alveoli. Here, nano-particle loaded macrophages readily enter the lymphatic as well as the blood circulatory system. Studies have shown that size and associated surface area do make a difference in terms of penetration efficiency, thereby significantly extending the retention time of inhaled nano-sized particles in comparison with the larger counterparts in alveolar macrophages. (Geiser & Kreyling, 2010; Oberdörster et al. 2005a) Although macrophages represent the most important defense mechanism in the alveolar region against fine and coarse particles, this mechanism is impaired in the case nano-aerosols, which - when inhaled in high abundances - renders phagocytosis inefficient. Subsequent to aerosol exposure, animal studies have shown that only about 20% of the nano-sized fraction (15-20-nm sized particles) can be flushed out by tracheo-bronchial lavage together with the macrophages, whereas lavage efficiency increased to approximately 80% in the case of coarser particles (>0.5 µm in size). (Geiser & Kreyling, 2010; Oberdörster et al., 2005a) As demonstrated in Figure 3a, removal of these particles can only occur via redistribution into the lymphatic or blood stream. With regards to the coarser particle fraction, the larger number of ultrafine siblings leads to particle dispersion into other tissues and organs representing a further burden for the entire organism.



Fig. 3. (a) Schematic drawing of the alveolar tissue showing different clearance mechanism of deposited particles. Pulmonary alveolar macrophage (PAM) mediated removal from the lungs away towards other excretory organs. Colored insert: PAM loaded with 80 nm particles. Approx. 40 nm-sized caveolar openings dis- and re-appear, forming vesicles that constitute pathways through the cells for encapsulated macromolecules.^(Madl, 2009, Oberdörster, Donaldson et al., 1998) (b) Schematic and microscopic image of mucociliary escalator transporting macrophages containing DEPs through bronchial tubings.^(Vostal, 1980)

Due to their minute size, these particles are also routed through the interstitial compartment between cells or straight through the cells via caveolae; these are openings of around 40 nm in diameter that engulf these nano-sized particles, forming vesicles that are thought to function as transport vehicles for macromolecules across the cells. A similar observation has been described for nano-particle translocation across the olfactoric bulb into the brain, thereby short-cutting the blood-brain-barrier (Figure 4). Studies performed in the 1940s dealt already with this challenge as it was possible to document how 30 nm polio viruses use these nerves as portals of entry into the CNS.^(Howe & Bodian, 1940) It is estimated that ~20% of the nano-sized particles deposited onto the olfactoric epithelium translocate to the olfactory bulb within seven days after exposure.^(Oberdörster et al., 2004)



Fig. 4. Nano-particle translocation across the olfactoric bulb into the brain. While approx. 80 % of the nano-particle matter remain attached at the epithelial mucosa, around 20 % of it is capable of transmigration.^(modified after Oberdörster et al., 2004, Tortora & Grabowski, 1996)

In the context of nano-sized particle exposure, health consequences become even more challenging when considering that most nano-particles originating from incomplete combustion are of hydrophobic nature. Thus, hygroscopicity and growth via condensation of water vapour is almost inexistent, thereby increasing penetration efficiencies even further - particularly into the alveolar regime of the lungs. In addition, the fractal nature of these incompletely combusted agglomerates are ideal substrates for volatile chemicals or radionuclides to adsorb onto.(Donaldson et al., 1998) In combination, both their low solubility and their role as a "Trojan horse" act threefold: (i) as known with asbestos, insoluble or low soluble matter exerts chronic irritation onto the target cells, (Donaldson et al., 1998) (ii) adsorbed substances on the nano-particle surface unfold their bioreactive properties once in contact with tissues,(Baron & Willeke, 2001) and finally, (iii) UFPs are known to be far more toxic than their coarser siblings (Geiser & Kreyling, 2010; Oberdörster et al. 2005b) - compare with Figure 5. Studies confirmed that nano-particles measuring 20 nm, which were administered directly into the lungs trigger stronger inflammatory reactions than 250 nm particles that are chemically identical. This implies that the toxicological property of the particle is determined by the surface area per unit volume rather than by mass.(Oberdörster et al. 2005a)



Fig. 5. Exposure of human lung fibroblast to ceria nano-particles (arrows) of 20-50 nm in diameter. (a) Vesicles inside a fibroblast cell with ceria agglomerates. (b) A cluster of nano-particle agglomerates close to the cell membrane. (c) Nano-particles both inside the cell (vesicle) and outside are exclusively found in the form of agglomerates.^(adopted from Limbach et al., 2005)

1.5 Toxicity at the cellular level

Adverse effects of nano-aerosols at the cellular level regard (i) inflammation, (ii) oxidative stress, (iii) modulation, enhancement and induction of immune- as well as allergic reactions, e.g. (pulmonary) allergic reactions.^(Chan et al., 2008: Alessandrini et al., 2009) Particle interaction with epithelial cells and macrophages are known to trigger inflammatory signalling pathways.^(Kocbach et al., 2008)

Figure 6 reveals the cyto-toxicological potential of nano-particles by emphasizing oxidative stress induced by these xenobiotic substances.^(Oberdörster et al., 2007) Due to their oxidative properties (step "a" in Figure 6), nano-particles are capable to induce lipid peroxidation. Upon endocytosis (step "b"), these particles exert intracellular oxidative stress and increase cytosolic calcium ion concentration, besides triggering the activation of NADPH oxidase and generation of reactive oxygen species (ROS). Although the latter is essential for normal vital activity,^(Voiekov, 2001) improper timing of ROS formation at inappropriate intracellular sites is known to play a crucial role in the initial stage of carcinogenesis.^(DeNicola et al., 2011) Depending on ROS concentrations, the effect can be adverse, inducing oxidative stress, damage of DNA, cancer, cardiovascular or neurodegenerative diseases or at appropriate concentrations also protective by beneficial modulation of gene expression.^(Chang, 2010)



Fig. 6. Hypothetical cyto-toxicological effects of nano-particles range from membrane peroxidation (a), once incorporated formation of reactive oxygen species (ROS) (b), activation of cell-receptors (c), triggering unnecessary cell-metabolic functions, activate expression of inflammatory responses (d), interaction with organelles, such a mitochondria (e), disruption of the electron transport chain (f), interaction with the DNA itself (g) and unfolding genotoxic potential by formation of DNA adducts (h).^(modified after Oberdörster et al., 2007)

Both the particles together with the adhered organic fraction and the consecutively induced oxidative stress can activate cell receptors (step "c") - thereby exploiting the energy reservoir of cells for the induction of appropriate compensatory pathways, which trigger several intracellular signalling cascades. These cascades, along with transcription factors activate the expression of pro-inflammatory genes (steps "d"). Apart from interfering with intracellular communication pathways, nano-particles may also enter the cytosol from where they can access mitochondria (steps "e, f") and disrupt normal electron transport, leading to additional oxidative stress (step "f"). Translocation of nano-aerosols into the nucleus may also occur where they interact with the genetic material (step "g"). Eventually, lipid peroxide-derived products can form DNA adducts, which may lead to genotoxicity and mutagenesis (step "h"). In less severe cases, the cell may enter the apoptotic pathway, thereby inducing premature cell death.^(Elder et al., 2000) However, apoptosis leaves behind cellular debris together with a toxic particle load that requires clean-up by other cells.

As outlined in Figure 6 (step "g"), genotoxic effects are known to occur also upon MEP exposure as this kind of aerosol induces structural aberrations of chromosomes, formation of micronuclei and DNA adducts. The described mutagenicity seems to be related to PAHs adhered to the surface of DEPs/MEPs.^(Cheng et al., 2004) Apart from ROS-mediated activity (step "b"), oxidative DNA damages, such as strand breaks, are associated with the cocktail of UFPs and organic pollutants, e.g. benzene, in ambient air.^(Cheng et al., 2004; Avogbe et al., 2005) These

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DNA damages have been observed for respiratory as well as for gastrointestinal uptake of UFPs.(Avogbe et al., 2005; Dybdahl et al., 2003) The encountered genotoxity is apparently induced by intracellular ROS, since observed adverse effects were reduced by pre-treatment of cells with anti-oxidants. However, the extent of attenuation depends on the applied anti-oxidant and the protective effects were not complete. Organic fractions of DEPs and MEPs induced ROS are involved in the formation of DNA adducts, e.g. 8-hydroxy-deoxy-guanosine (8-OHdG), at least in the mouse model. This modification is considered a pro/e?-mutagenic lesion.(Cheng et al., 2004; Nagashima et al., 1995) Beside superoxide, also hydroxyl-radicals were formed when challenging mice with DEPs.(Nagashima et al., 1995) Nevertheless, PAHs have to be metabolized into their active forms via the P450-1A1 pathway. Additionally, MEPs contain constituents, which possess direct mutagenic potential and circumvent ROS formation.(Cheng et al., 2004) Furthermore, a genetic pre-disposition has to be considered, since genetic polymorphism in protective protein systems, e.g. glutathione S-transferase, glutathione peroxidase and NAD(P)H:quinone oxireductase-1 seem to be involved as well.(Avogbe et al., 2005)

As mentioned before, organic chemicals adhered to DEPs are apparently directly involved in the formation of reactive nitrogen oxygen species (RNOS) and thus the induction of oxidative stress. Halogenated hydrocarbons and PAHs can induce phase-I drug metabolizing enzymes in alveolar macrophages and epithelial cells, such as cytochrome P450-1A1, which in turn degrade PAHs to redox active metabolites, e.g. quinones and phenols.(Nel et al., 1998; Devouassoux et al., 2002) Production of ROS has been related to the interaction between quinones and DEPs with P450 reductase.(Kumagai et al., 1997) Quinones will then contribute to ROS formation and macrophage activation.(Nel et al., 1998; Devouassoux et al., 2002) Benzo-[a]-pyrene (B[a]P) attached to black carbon enhanced the tumor necrosis factor- α (TNF- α) release of macrophages. Evidently, carbon particles with adhered organic compounds are endocytosed and PAHs get activated by intracellular ROS.(Kocbach et al., 2008) The increase in transcription induced by PAHs has been postulated to be promoted by a cytoplasmatic aryl hydrocarbon receptor (AhR), acting as a nuclear transporter/DNA binding protein PAH complex. Once released from DEPs, PAHs enter adjacent cells due to their hydrophobicity and adhere to the PAH ligand binding part of AhR which is then translocated to the nucleus. There, a heterodimer is created between the AhR and a nuclear translocator. This heterodimer binds to response sequences situated upstream of the target genes promoting e.g. the expression of plasminogen activator inhibitor and interleukin-1 β (IL-1 β), which would explain the modulating effects of PAHs upon expression. Beside, signalling via AhR also Ca++ depending pathways have been discussed as intracellular transmittance channels.(Takenaka et al., 1995; Fahy et al., 1999) Since NO-pathways induce Ca++ release to regulate neuronal function, interference via nano-particles adversely affect Ca⁺⁺ release, and ultimately synaptic plasticity.^(Kakizawa et al., 2011) As mentioned before, the expression of several enzymatic systems, e.g. the P450-1A1 cytochrome system, are induced. The latter metabolizes PAHs to electrophilic epoxides, which are mutagenic and can interact with DNA. Since 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is not metabolized by this system, alternative pathways are likely to co-exist.(Takenaka et al., 1995)

1.6 Short term exposure to airborne pollutants

Studies have shown a decrease in pulmonary function associated with short-term exposure to UFPs. These decrements in lung function appear to persist for several weeks

after exposure even when the distressing particle load is no longer present. Apart from lung-related pathologies, such as respiratory problems, nocturnal and chronic cough as well as bronchitis and asthma, adverse health effects of UFPs/DEPs at the organismic level that also include cardiovascular disorders.^(Chang, 2010; Riedl & Diaz-Sanchez, 2005; Ware et al., 1986) As shown in Table 1, acute exposure to UFPs is associated with increased alveolar inflammation, morbidity, platelet aggregation, accompanied by altered blood coagulation altered heart frequency, myocardial infarction, and including mortality.^{(Costa & Dreher 1997; Dockery et al. 1982; Brook et al., 2004; Rückerl et al., 2006) However, most noteworthy are thrombogenesis, ischemia (reduction of oxygen supply to target organs due to plaque destabilization and blood clothing) and arrhythmia (disturbance of the electrical activity of the heart muscle).^(Bacarelli et al., 2008; Kreyling, 2003)}

	Case	Date o. death	Age [yrs]	Sex	Diagnosis 1	Diagnosis 2
-	1	07 Dec	76	Ŷ	Heart failure	Bronchitis
	2	23 Jan	61	3	Bronchitis*	Emphysema
	3	03 Dec	65	3	Pulmon. embolism	Lung cancer
	4	06 Dec	53	3	Heart failure	Bronchitis
	5	10 Dec	20 hrs	3	Prematurity	
	6	12 Dec	54	Ŷ	Emphysema	Hodgkin's disease
	7	17 Dec	51	Ŷ	Sarcoidosis	
	8	19 Dec	53	3	Heart failure	Bronchitis
	9	25 Dec	51	3	Pneumonia	Tuberc. meningitis*
	10	04 Jan	60	3	Heart failure	Syphilitic aortitis
	11	06 Jan	62	Ŷ	Heart failure	Emphysema
	12	12 Jan	0.5	Ŷ	Pneumonia	prob. Cystic fibrosis
	13	14 Jan	55	3	Bronchitis*	Gastric ulcer
London during the smog	14	17 Jan	64	Ŷ	Esophageal cancer	Aspiration
event in 1952. ^(Stobbs, 1952)	15	23 Jan	44	Ŷ	Bronchitis*	Pneumonia
	16	28 Jan	62	Ŷ	Lung abscess*	
	17	12 Feb	61	3	Heart failure	Bronchitis
	18	05 Mar	66	3	Emphysema*	Myocard. infarction

Table 1. Confirmed deaths of the short-term London smog event (5th - 9th Dec. 1952) with analysis of autopsy, demographics and cause of death. (*) Autopsy note: condition worsened during smog event.^(Hunt et al., 2003) London insert: Reduced visibility due to smog-related light scattering and absorption at Nelson's Column in that period.

Following the events of the great London smog, several investigations tried to highlight the adverse health effects of airborne pollutants. The "six cities study" could positively correlate death from cardio-pulmonary diseases and lung cancers with air pollution of PM_{2.5} - that is particle mass with diameters smaller than 2.5 μ m.^(Dockery et al. 1993) Stimulated by the outcome of this study, and due to the occurrence of several severe air pollution events following thereafter, it was attempted to relate cardiopulmonary mortality as well as lung cancer with long-term exposure to particle-related air pollution. Indeed, exposure to fine particle in combination with sulfur oxide (SO₂) could be associated with the formation of lung cancer and cardiopulmonary mortality. Moreover, each stepwise increment by 10 μ g/m³ of fine particle mass exposure was correlated with an approximate 4% increase in overall mortality, 6% for cardiopulmonary and 8% for lung cancer mortality.^(Pope et al., 2002) This relationship was found to be less pronounced for coarse particle fractions than it was for smaller ones.^(Perez et al., 2008). This correlation is most obviously related to the cubic relationship between particle mass [μ g/cm³] and number concentration [cm⁻³] on one side as well as the higher

penetrability of the smaller, fine and ultrafine particle fractions for the deeper lung on the other side. While the former (μ m-sized class) is efficiently filtered out by the upper respiratory system, the latter (nm-sized class) passes the tracheo-bronchial airway down to the alveolar, gas-exchange regime.(Hussain et al., 2011) Despite their low overall mass concentration, the fractions of nano-particles can reach high concentrations in terms of particle numbers – a tribute that is related to the improved combustion efficiencies and the applied filtering technologies. This is in accordance with the findings of a Dutch research group, which correlated a shortened life expectancy with exposure to nano-sized particles originating from vehicle exhaust.(Hoek et al., 2002). When exposed to long-term elevated doses of nano-sized particles, such as diesel fumes and the corresponding by-products of nitrogen dioxide (NO₂), the authors documented organismic-wide effects, such as cardio-pulmonary mortality, which was significantly increased by at least a factor of two. This disturbing observation is not correlated to intense short-term air pollution events that last for a few days, but more related to chronic and long-term exposure of significantly lower dosages that cover several weeks or even months.

1.7 Long-term exposure to airborne pollutants

As outlined previously, the olfactoric system offers a more straightforward option for nanoparticle uptake. Apart from deteriorating effects on the olfactory bulb and alterations of the blood-brain barrier in response to chronic exposure to these aerosols, some neuropathologic effects have been observed and include (i) degeneration of cortical neurons, (ii) apoptotic glial white matter cells, as well as formation of (iii) non-neuritic plaques, and (iv) neurofibrillary tangles.^(Calderón-Garcidueñas et al., 2004) There is mounting evidence that neurodegenerative disorders, such as Multiple Sclerosis,^(Bizzozero et al., 2005) Alzheimer's-,^(Hautot et al., 2003, Sayre et al., 1997) Parkinson's-disease,^(Zhang et al., 1999) Amyotrophic Lateral Sclerosis (Shibata et al., ²⁰⁰¹⁾, and even Creutzfeldt-Jakob disease (Oberdörster & Utell, 2008)</sup> are favoured or at least promoted by chronic exposure to a cocktail of nano-sized particles and their associated chemical by-products.

The combination of UFPs, which are wrapped with a soluble organic fraction (e.g. SVCs/VOCs), with gaseous irritants (usually O₃ and NO_x) is known to increase the susceptibility, sensitization and chronic allergic inflammation that are associated with changes in the epithelial structure.^(Traidl-Hoffmann et al., 2009; Galli et al., 2008) Over the past decades, a pronounced increase in allergic disorders has been witnessed particularly in western industrialized countries.^(Ring et al., 2001) This prompted allergists to coin the so-called *hygiene hypothesis*, which assumed that frequent contact to pathogenic agents, particularly in early infancy, reduces the likelihood of the immune-system for a polarization towards immunoglobulin (IgE)-based responses (i.e. allergies). Such triggers include bacteria, molds, microbial agents (such as LPS), viruses, and potential antigens. With improved domestic hygiene standards in affected populations, contact with these agents is progressively prevented in favor of the propensity for allergies.^(Galli et al., 2008; Ring et al., 2001; Yazdanbakhsh et al., 2001)

To shed some light on this intrinsically interwoven network, synergism between two types of aerosols shall be demonstrated – the combined effect of carbonaceous nano-particles, such as UFPs, and pollen allergens. Allergens, e.g. from grass pollen, attach to the surface of starch granules (amyloplasts) of plants or other plant fragments as so-called pollen-related

micro-aerosols.(Solomon, 2002) Although such starchy granules are considerable larger (600 nm -2.5 µm) than UFPs, they still are inhalable aerosol particles.(Taylor et al., 2002) Remarkably, allergen-carrying micro-aerosols have been shown to interact with DEPs resulting in stable aggregates.^(Solomon, 2002) The release of allergens, amyloplasts and cytoplasmic debris occur by a rupture of pollen grains triggered by a cycle of wetting - e.g. dew, fog, gentle rain - and drying events.(Taylor et al., 2002) Additionally, airborne house dust is present as suspended particulate matter (5-10 µm), and can also act as a carrier of allergens; e.g. of the cat allergen Fel-d1, which becomes airborne from saliva and sebaceous glands of cats. (Chang, 2010; Ormstad et al., 1995) Similar carrier functions for Fel-d1 might also be assigned for DEPs. Fel-d1 was visualized on dust particles by scanning electron microscope (SEM) inspection of particles which have been labelled by monoclonal antibodies.(Ormstad et al., 1995) Furthermore, mite allergens, e.g. Der-p1, have been encountered up to 22.8 µg/g in carpet dust.^(Warner, 2000) Although these data are not referring to UFPs, (Warner, 2000) release as airborne particulate matter cannot be ruled out. This is of relevance as DEPs readily sneak through the ventilation system thereby entering indoor environments, whereby they readily interact with suspended dust particles.^(Guo, 2010) Since about 30% of inhaled 80-90 nm DEP-cluster can deposit in the alveolar region (Ormstad et al., 1995; Vostal, 1980) - see Figure 2 - UFPs that adsorb onto micro-aerosols are deposited in the upper respiratory system (typically in the naso-pharynx and tracheo-bronchial region with deposition efficiencies topping at least 80%),(Hofmann, 2011) where they unfold adverse synergistic or even novel effects. (Donaldson, 2009; Oberdörster & Utell, 2008)

In such cases, an exposure to carbonaceous nano-aerosols prior to challenge with allergens exerts strong adjuvant effects on the manifestation of allergic airway inflammation.^{(Alessandrini} et al., 2006)</sup> Hence, allergen-sensitized individuals are more susceptible to the detrimental health effects of nano-particle exposure. Similar studies investigating the conditioning effects of DEPs with adsorbed volatile organics on the immune system confirmed the pro-allergenic potential. Thereby, a crucial role for these pollutants mediating the allergic breakthrough in atopic individuals, who have not yet developed an allergic disease, was suggested.^(Lubitz et al., 2009) In this context it has to be stressed, that the conditioning effects of the immune system can occur within relatively short periods of time.^(Alessandrini et al., 2006)

Furthermore, there is evidence that UFPs induce autoimmune diseases. Mice exposed to ambient PM on a weekly basis showed an accelerated onset of diabetes type-1. Adequately, similar risks were shown for lupus and collagen induced arthritis in murine models. Crohn's disease was found to be related to micro-particle contamination of food. However, one has to be aware that the apparent UFP-related autoimmune effects are multi-factorial. In case of diabetes type 1, correlated influences of O₃ co-exposure with cigarette smoke or particulate pollutants are known.^(Chang, 2010)

Beside PAHs, bioavailable, ionizable metals might induce inflammation. Fly ash from domestic oil-burning furnaces was found to contain up to 166 μ g total metal content per mg particulate matter. Metals increase recruitment of macrophages and neutrophils but also eosinophils - the latter are also involved in parasitic and allergic inflammation. An induced cell influx of UFPs was found to be correlated with an elevated intracellular metal content. O₂⁻ and H₂O₂ release during inflammation can occur via the Fenton reaction with transition metals boosting the oxidative burden by the creation of ROS.(Chang, 2010; Costa & Dreher, 1997)

As will be demonstrated in the following section, long-term exposure to elevated levels of PM mixed with inhalable nickel and arsenic vapors induces also epigenetic changes in human subjects.^(Cantone et al., 2011) Thus, the information due to conditioning of the immune system leads to memorization of long-term exposure events at cellular level and is somatically passed on to progeny cells via epigenetic means. As will be exemplified, this also enables cells to leave marks on reproductive cells so that these events can be passed on the filial generation. This rather new field in genomic research is about to unravel - apart from the more rigid lower genome level (nucleotide sequence) - a second, very plastic level of information processing, which employs the epigenome and follows a kind of Lamarckian rule of inheritance.^(Bird, 2007)

Passing from milder to more severe, chronic disease pattern, it can easily be deduced that (epi-)genotoxic properties of long-term nano-aerosol exposure replaces acute symptoms by unfolding the full spectrum that obviously includes even cancer cases. Table 2 summarizes some of the major findings of the epidemiological investigation made in Mexico City, known for its notorious pollutant laden air.^(Calderón-Garcidueñas et al., 2004) Although the list is not extensive, the high occurrence of various types of cancers is striking. Just by considering the fact that only about 5-10% of cancer and cardiovascular cases can be attributed to heredity, it becomes obvious that 90-95% might be controlled by our lifestyle.^(Willet, 2002) Hence, malignancies are derived from environmentally induced epigenetic alterations and not defective genes.^(Jones, 2001; Seppa, 2000; Baylin, 1997) While (epi-)genetic factors determine the tendency towards malignancy, environmental factors largely contribute to heart-rate-variabilities, cardiovascular diseases, cancers, and other major causes of mortality.^(Bacarelli et al., 2008, Baccarelli et al., 2010b, Willet, 2002)



Mexico City, the world's third largest urban area, has some of the worst air quality in the world.^(Marley, 2006)

Pollution	on Age Cau Occuration		Ormertien	Schooling	Clinical dia amagia
level	[yrs]	Sex	Occupation	[yrs]	Clinical diagnosis
Low	34	Ŷ	Housewife	14	Undiff. carcinoma
Low	46	Ŷ	Housewife	10	Lung embolism
Low	49	Ŷ	Housewife	10	Cervic. carcinoma
Low	53	3	Carpenter	12	Myocard. infarction
Low	58	3	Farmer	6	Renal carcinoma
Low	66	3	Farmer	7	Gastric carcinoma
Low	68	3	Laborer	6	Myocard. infarction
Low	73	9	Housewife	6	Myocard. infarction
Low	76	9	Fruit seller	9	Cervical carcinoma
High	32	3	Policeman	13	DOA accident
High	38	9	Secretary	15	DO A accident
High	39	3	Office worker	12	DOA accident
High	42	3	Electrician	12	Lung carcinoma
High	43	3	Policeman	13	Myocard. infarction
High	52	Ŷ	Housewife	6	Breast carcinoma
High	55	3	Outdoor vendor	6	DOA accident
High	61	3	Laborer	6	Colon Carcinoma
High	67	Ŷ	Housewife	7	Cervical Carcinoma
High	83	9	Housewife	7	Arrhythmia

Table 2. Clinical data for subjects experiencing long-term UFP-pollution exposure. The primary causes of death included accidents resulting in immediate death (death on arrival, DOA), arrhythmias, myocardial infarctions, and carcinomas like: gastric, lung, colon, breast, and cervical cancers.^(modified after Calderón-Garcidueñas et al., 2004) Insert: Aerial view of Mexico City revealing reduced visibility due to nano-particles from combustion sources.

2. Epigenetics

Since the onset of the initial reports addressing modification and associated inheritable changes of the DNA due to air pollution in animal studies, (Somers et al., 2004; Samet et al., 2004), research activities tried to tackle detrimental health effects related to nano-particle aerosol exposure. (Bacarelli 2009; Nawrot & Adcock, 2009) It soon became evident that the persistent effects of air pollution have a more pronounced effect on the phenotype rather than on the genotype. (Yauk et al., 2007; Vineis & Husgafvel-Pursiainen, 2005; Mahadevan et al., 2005) These findings support the already pursued hypothesis that mutagenic volatile chemicals adsorbed onto airborne particle pollutants induce somatic and germ-line mutations. While it was not always apparent why and how these mutations do occur, recent evidence suggests that a sensitive, easy to modulate layer (via methylation, acetylation, phosphorylation, etc.) is characterized by the so-called epigenome. (Mathers et al., 2010)

The epigenome, in its literal sense, can be regarded as a molecular sleeve sitting on top (*epi*-) of the genome. Without altering the DNA sequence itself, it enables or blocks the readout of the underlying genetic information.(Nadeau et al., 2010; Blum et al., 2010) In fact, many disorders, related either to epi- or genetic mutations can lead to similar or even congruent phenotypes, with the only difference that mutations of the genome are irreversible, whereas epigenomic changes in theory are plastic, thus of non-permanent nature. So far, the relationships between the genome and the epigenome have broadened the spectrum of molecular events, which are related to human diseases. These can be induced *de novo* or inherited, genetic or epigenetic, and most interestingly, some events are influenced by environmental factors. The findings that environmental factors, such as exposure to environmental stimuli (diet, toxins, and even stress) alter the epigenome provide insight to a broad spectrum of disorders. In a bee-hive for example, worker-bees and queens share the same genetic material, yet the differences among them does not consist in altered genetic information, but in the phenotype, fertility, size and life expectancy. The key ingredient that makes a larvae to develop into a worker-bee or a queen is purely based on its nutrition - that is workers receive mainly pollen and honey while queens are fed with royal jelly.(Haydak, 1970) This nutritional difference induces epigenetic modifications that determine the accessibility of genes for their expression (see schematic Figure 7). Similarly, it was possible to show that nutrition during embryonic development affects adult metabolism in humans and other mammals, via persistent alterations in DNA methylation. In particular, dietary supplementations have unintended deleterious influences on the establishment of epigenetic gene regulation.(Waterland & Jirtle, 2003) Even pure physico-environmental stimuli unveiled their epigenetic effects on stem cells that have been exposed to THz radiation. The non-destructive mode revealed athermal effects, like changes in cellular function in which some genes were activated, while others were suppressed.(Alexandrov et al., 2011) These are just some of many investigations that identified environmental factors as modulators of the epigenome and provide perspectives for developing interventions that might decrease the risk of developmental abnormalities, chronic inflammation, cancer, and neuropsychiatric disorders.(Zoghbi & Beaudet, 2007)

The basics of epigenetics are rooted in bio-physico-chemical processes, which can be considered as bookmarks placed into the book of life. Indeed, faulty epigenetic regulations are regularly behind chronic diseases. This can even extend towards a deactivation of specific, fully competent tumor suppression genes.^(Rodríguez-Paredes & Esteller, 2011)

Exposure to Nano-Sized Particles and the Emergence of Contemporary Diseases with a Focus on Epigenetics



Fig. 7. The epigenome plays an essential role together with the genotype and environmental factors in determining phenotypes. Biochemical reactions affecting gene expression and genome stability include DNA methylation (Me), chromatin-remodelling complexes, covalent histone modifications (mod), the presence of histone variants, or non-coding regulatory RNAs (ncRNAs). The greyish arrows indicate the line and strength of progression.

2.1 Modulating the epigenome

As shown in Figure 8, enabling or inhibiting ribosomal activity to access genetic information is regulated by three major pathways. The first involves direct chemical modifications at DNA-level, the second regards the modification of histone proteins that are closely related with associated gene loci, whereas the third is mediated via various activities of non-coding RNAs.^(Zoghbi et al, 2007) A central epigenetic regulatory mechanism comprises methylation of cytosine – whereby DNA-methyl-transferases attaches a methyl-group from the cofactor S-adenosyl-methionin (SAM) onto the cytosine atom C5. DNA methylation mostly takes place at cytosine-guanine-nucleotide. Numerous copies of these dinucleotide sequences are



Fig. 8. Supercoiling of DNA via histone mediated proteins triggers a cascade of condensation steps that yield the highly packed mitotic chromosome. Highlighted are the various levels of epigenetic modulation. Methylation at base-level (5-Met-Cytosine) represses gene activity and boosts chromatin condensation, histone-tail modification (e.g. dimethylation, acetylation, etc.) and alters DNA-wrapping thereby inducing de-/activation. Small nuclear RNA (snRNA).^{(modified after Walker & Gore, 2011 & Qiu, 2006).}

located within CpG-islands that constitute the promoter region of genes. If methylation takes place at these sites, it mostly shuts down the corresponding genes.^(Esteller 2002) In case of hyper-methylation of promoter regions – as often encountered in tumor suppressor genes – a permanent shut down of these regions is the obvious result, which causes the affected cell to degenerate or mutate into pre-cancerogenous conditions.^(Yang et al., 2005)

Another crucial epigenetic mechanism concerns histone-modification and addresses the dense packing of the DNA-filament. If stretched out, the DNA of a cell would cover at least two meters in total length. Supercoiling of the filament enables its packing into a cell nucleus of 10 to 100 µm in diameter. Such packing is achieved via small basic proteins, termed histone cores. Some 147 base-pairs wrap around a histone-octamer, which consists of two H2A/H2B-dimers as well as a H3/H4-tetramer.^(Luger et al., 1997) This protein-DNA-unit is known as a nucleosome. Upon DNA-attachment of the linking histone H1, supercoiling occurs in a cascading manner until chromatin is present in its most condensed form: the chromosome (Figure 8). Epigenetics on the histone-level affects the N-terminal tails that protrude from the histone-octamer (see Figure 8). In particular, this regards the basic amino acids lysine and arginine but also serine and threonine. Histone-modifying enzymes append or dislodge specific amino acids. These modifications include methyl-, acetyl- and phosphoryl-groups as well as larger molecules, such as ubiquitin or ADP-ribose.^(Biel et al., 2005) In analogy to the genetic code, one refers here to the histone code, as modifications of the basic histone proteins convey specific information.(Strahl & Allis, 2004) Modification of the Nterminal tails loosen the chromatin's density that enables genes to be readily accessible and transcribed. The opposite effect regards densification of the chromatin and concomitant inhibition of gene readability. In addition to the aforementioned modifications, there are also numerous non-histone proteins that can be biochemically modified, likewise yielding de- or activation of corresponding genes. This regards in particular the tumor-suppressor protein p53, which can be deactivated through deacetylation of histone deacetylase-1 (HDAC1).(Luo et al., 2000) Furthermore, a surprisingly large number of RNAs neither functions as messenger, transfer or ribosomal RNAs, and are thus called non-coding RNAs (ncRNAs). Such RNAs regulate gene expression on various levels, including chromatin modification, transcription, RNA modification, RNA splicing, RNA stability and translation. Among them, small interfering RNAs (siRNAs) and microRNAs (miRNAs) are most prominent. Both regulate gene expression through the RNA interference (RNAi) pathway. More than 1% of predicted genes in higher eukaryotic genomes and up to 30% of protein-encoding genes are assumed to be subjected to miRNA regulation. In addition, miRNAs cooperate with transcription factors (TFs) to control gene expression.(Yu, 2007)

Although all cell types within an organism share identical genetic material, they perform different tasks. Task sharing requires a cell-specific readout of genes, which is realized by biochemical markers. Here, epigenetics controls the fate of progeny cells after mitotic division. i.e. lung specific stem cells yield differentiated lung cells although their genome would potentially enable differentiation into any kind of cell. This kind of cellular memory requires to be passed on to the progeny cells. Thus, cellular "learning" predominantly occurs in two ways: either via "bookmarking" or via "paramutation".^(Hollick et al., 1997, Sarge & Park-Sarge, 2005) While the former regards cellular regeneration during the fetal stage all the way through the adulthood, the latter is a characteristic feature for the embryonic phase.

2.2 Adult epigenome

Bookmarking transmits cellular memory (i.e. patterns of cellular gene expression) via mitosis to somatic progeny cells of the same type. Throughout one's lifespan, tissue-specific stem cells are responsible for the development and regeneration of entire organs, such as skin, lung, gut, blood system, etc. In order to meet this task, these stem cells, besides revealing an extensive self-renewal potential, encompass also pluripotency. These properties give rise to all cell types of an organ that differentiate to multipotent progenitors with gradually restricted developmental potential. These progenitors subsequently undergo commitment to one of several lineages and then differentiate along the selected pathway into a functionally specialized cell type of that organ.(Fisher, 2002) In other words, stem cells and resulting progenitors as well as specialized tissue cells share the same genome. Yet, the lower the ranking within cellular ontogenesis, the more genes have to be silenced in order to fulfil the requirements that match organ function. Practically, a healthy somatic epithelial lung stem-cell divides to yield a progeny cell that becomes epigenetically tagged in such a way as to provide a specialized cell. This differentiated cell becomes part of the cellular consortium that constitutes an ensemble yielding the lung with all its physiological functions. Under normal physiological conditions, it would be senseless to differentiate into a cell linage other than e.g. specialized epithelial lung cells. This kind of epigenetic tagging (e.g. epithelial lung cell-linage) is stable and heritable such that a mitotically dividing cellular system gives rise to more cells that correspond to the overall phenotype.(Tost, 2008) Studies based on monozygotic twins with similar epigenomes during early years of life revealed remarkable differences in methylated DNA and acetylated histones during later stages of life. This underlines the temporal metastability of the epigenome. (Fraga et al., 2005)

Now, how is epigenetics related to nano-aerosol exposure? As highlighted in Figure 9, environmental exposure of any kind acts as a modulator to the metastable epigenome.^{(Anway} et al., 2005)</sup> Metastability affects responsiveness to oxidative stress (Figure 6) and as such



Fig. 9. Potential mechanism linking environmental exposures to epigenetic effects. These effects include DNA methylation, histone codes and miRNA expression. The associated changes modify chromatin organization and condensation, gene expression and ultimately disease risks.^(modified after Baccarelli & Bollati, 2009)

renders the organism more susceptible to cardio-vascular as well as respiratory effects of air pollution. The resulting adverse health effects include generation of oxidative stress, inflammation as well as morbidity.^(Bollati & Baccarelli, 2010) It was possible to demonstrate that the underlying mechanism regards methylation of the promoter region of the iNOS (inducible nitric-oxide synthase) – found to be suppressed in foundery workers who were exposed to UFPs.^(Tarantini et al., 2009) The same authors also reported demethylation effects induced by long-term exposure to particle mass (PM₁₀) exposure in younger individuals individuals. These effects resemble demethylation patterns that are typically observed in old age. Histone modifications have been observed in workers who experienced long-term exposure to nano-sized aerosols at smelters. Both acetylation of the histone H3K9 and demethylation of H3K4 increased by about 15% after a >21 year exposure near the smelter.^(Cantone et al., 2011)

Another key concept for the developmental origin of diseases comprises a transfer of the acquired predisposition onto subsequent generations without further environmental impacts (see Figure 10). Such trans-generational epigenetic inheritance is responsible for wider effects, such as a fast-track pathway of adaptation to environmental stress. This improves survival until either more stable genetic changes can provide better adaptations or the environment reverts to the previous status.^(Finnegan, 2002)



Fig. 10. Epigenotype model of developmental origins of disease. Environmental factors acting in early life (from conception to early infancy) have consequences, which become manifest as an altered risk for diseases in later life. The mother conveys a forecast of the post-natal environment to the genome of the unborn. This includes modifications to its metabolism, whole body physiology and growth trajectory to maximize its chances of post-natal survival. These adaptations become detrimental if the environmental conditions after birth differ from those of the fetal stage. Ac - Histone acetylation/active genes; CH₃ - DNA methylation/silent genes.^(modified after Sandovici et al., 2008)

2.3 Embryonic epigenome

Paramutation in comparison to bookmarking, regards the quasi "inheritance" of genecharacteristics (allelic interactions) that are "remembered" and expressed in later generations (e.g. via the germ cell linage). Paramutation occurs when certain control alleles impose an epigenetic imprint on susceptible (paramutable) inferior alleles. The epigenetic imprint is inherited through meiosis and persists even after the interacting alleles have segregated. The observation of heritable but reversible changes in gene expression, is evidence for non-Mendelian genetics, and apparently also in mammalian systems.^(Chanlder & Stam, 2004) Paramutation fulfils the criteria for a parental identity mark or "imprint" because it can be established either in the sperm or the oocyte by *de novo* methyl-transferases that act only in one gamete. Once established, it can be stably propagated at each embryonic cell division by a maintenance methyl-transferase, and it can also be erased in the germ line to reset the imprint in the next generation, either by passive demethylation or possibly through the action of a demethylase.^(Barlow & Bartolomei, 2008).

The newly fertilized egg or zygote is unique since no other cell has the potential to develop into an entire organism. In order to achieve that, epigenetic marks of both oocyte (female) and sperm (male) are usually efficiently reprogrammed at fertilization, so that upon fertilization the embryonic genome becomes totipotent - an essential property of the zygote.(Surani & Reik, 2007) At the first mitosis after fertilization, most histone marks are quite similar on the maternal and paternal chromosomes.(Santos et al, 2005) To yield the totipotent zygote, dramatic DNA demethylation of the parental genome must be induced by "active demethylation".(Morgan et al., 2005) Hence, gene expression depends on the origin of inheritance. This implies that at an imprinted diploid locus, there is unequal expression of the maternal and paternal alleles. So much so, that in each generation, the parent-specific imprinting marks have to be erased, reset, and maintained. It is obvious that imprinted loci are somewhat prone to errors that may occur during these processes. Indeed, at such an early stage of development, erroneous imprinting in genes, which encode proteins involved in DNA methylation, binding to methylated DNA, and histone modifications may contribute to the fast-growing class of human disorders affecting the epigenome. (Zoghbi & Beaudet, 2007) After further cell divisions, the embryonic stem cells differentiate into roughly 200 different cell lineages, whereby totipotency is gradually downregulated to pluripotency.(Tada et al., 1997; Tada et al., 2001; Cowan et al., 2005) The latter give rise to adult stem cells that generate tissue specific cells.(Surani & Reik, 2007). Tissue-specific stem cells are responsible for the development and regeneration of entire organs, such as skin, gut, and blood system throughout life. To comply with this task, stem cells encompass two unique properties: (i) an extensive selfrenewal potential that enables them to propagate in their uncommitted state; (ii) pluripotency that gives rise to all cell types of an organ by differentiation to multipotent progenitors with gradually restricted developmental potential. These progenitors subsequently undergo commitment to one of several cell lineages and then differentiate along the selected pathway into a functionally specialized cell type of the organ.(Fisher, 2002) Transcription factors reprogram the expression of large sets of genes. They act indirectly by (i) affecting gene expression programs (antagonizing other transcription factors through protein-protein interaction) and directly by (ii) the control of gene transcription (recruiting coactivators or corepressors with histone-modifying or chromatin-remodeling activities to regulatory DNA elements). Hence, the activity of a gene is influenced by the local DNA

methylation pattern, the state of histone modifications, the nuclear position of the gene relative to repressive heterochromatin domains, and the architecture of the gene locus.^(Vickaryous & Hall, 2006) In any case, epigenetic imprinting associated with the in- and/or activation of genes implies that changes acquired during gametogenesis are not only passed on but also extend into embryonic development.^(Jaenisch & Gurdon, 2007) In animal studies it was possible to correlate nano-size particle exposure of a smelter to hypermethylation of sperm-DNA that persisted into the next generation even though the filial generation was no longer exposed to this aerosol.^(Yauk et al., 2008) Since epigenotypic flexibility regards plasticity during fetal and embryonic development and extends well into the post-natal phase, it is not surprising that the epigenome contributes not only to developmental human disorders, but also to post-natal and even adult diseases.^(Jaenisch & Gurdon, 2007) With reference to Table 2, it becomes evident that chronic disease processes can be readily attributed to a long-term exposure to environmental nano-aerosols.

2.4 Chronic diseases and cancer

It is well established that complex diseases, such as heart diseases, diabetes, obesity, Alzheimer's disease, schizophrenia, and bipolar disorder etc. result from the interplay between (epi-)genetic and environmental factors. The interaction with nano-aerosol exposure not only conditions the immune system, thereby inducing to allergic reactions, but also affects the epigenome, which leads to neuro-degenerative disorders or even towards malignancy. It has also been proposed that epigenetic mechanisms explain significant fluctuations of the phenotype between individuals, or even dramatic changes in the incidence of some diseases over short periods of time, such as the rapid increase of asthma incidence in the population.^(Petronis, 2001; Bjornsson et al, 2004) Examples include increased methylation levels at the estrogen receptor-alpha and the estrogen receptor-beta gene promotors in proliferating human aortic smooth muscle cells and in atherosclerotic cardiovascular tissues, respectively ^(Ying et al, 2000; Kim et al, 2007) It has also been demonstrated that



Fig. 11. Interacting pathways to cancer - a mechanism-based model of the pathogenesis of human cancer. Sporadic cancers, which comprise 90-95% of all cancers, almost uniformly exhibit both genetic and epigenetic defects. As suggested by the vertical arrows, these mechanisms show substantial interaction. That is, epigenetic events can cause genetic events, and *vice versa*. Depending on the cancer type, each mechanism can be operative early, late or continuously during the development of the tumor (horizontal arrows). CNA: copy number alteration, including gain, loss and amplification.^(modified after Costello & Brena, 2008)

workplace exposure to nano-particles and their associated volatile chemicals induce global demethylation especially of retro-transposons in LINE and SINE sequences. Lowered LINE-1 methylation in peripheral blood leukocytes is a predictor of incidence and mortality from ischemic heart disease (IHD) and stroke.(Baccarelli et al., 2010a, Baccarelli et al., 2010b) Blood samples screened for LINE-demethylation in exposed individuals (e.g. traffic wardens) can be up to 5% lower than in non-exposed subjects.(Bollati et al., 2007) This induces not only premature aging, increased risk of IHD and stroke, but also paves the way to chronic pathology, such as cancer. As stated before, numerous investigations of the epidemiology of cancer reveal that only 5 to 10% of breast, prostate or bowel cancer and 1-2% of melanoma cases are attributable to genetic mutations, while the large bulk does not involve an inherited predisposition at all.(Barlow-Stewart et al., 2007)

Several studies indicate an age-dependent decrease of global DNA methylation pattern, yet evidence suggests that there might be site-specific hyper-methylation involved in cancerogenesis.(VanHelden 1989, Cooney 1993; Rampersaud, 2000) Given the large body of data linking altered DNA methylation to cancer risk or progression, obviously epigenetic changes contribute to the age-related increase in cancer risk.(Mays-Hoopes, 1989; Issa, 1994) The role of diet as a contributing factor in controlling global methylation and its relationship to cancer development has already been illustrated in several cases.(Ingrosso et al., 2003; Waterland & Jirtle, 2003) Thereby epigenetic changes take place despite the pre-systemic metabolic effect of the liver. Since this first-pass effect of the liver is almost inexistent during inhalation, it is apparent that modifications to the epigenome in response to airborne stimuli are even more pronounced and thus directly linked to chronic exposure to airborne pollution. The synergism of nano-aerosols and VOC exposure is known to reduce epigenetic imprinting.(Bollati et al., 2007) As already outlined, suppressed LINE-1 methylation by just 10% (from 82.4% to around 72.6%) increases the associated risk of cancer by a factor of seven.(Zhu et al., 2011) Although aging is the major risk factor associated with cancer development, epigenetic modifications occurring earlier in life underline the important role of the environment in various cancer types. Epigenetic changes induced by environmental factors in the pool of progenitor stem cells of each tissue might be the earliest events during carcinogenesis. It is assumed that the epigenetic progenitor model provides a plausible explanation for both the age dependency and environmental sensitivity of associated cancer risks.(Feinberg et al., 2006). This multistep process implies that an environmental insult induces changes in the epigenome during the early environment at particularly sensitive timewindows during developmental plasticity.(Ozanne & Constincia, 2007) Once environmentally induced epigenetic changes are established, they will be maintained throughout many cell divisions by the epigenetic signalling procedure. The maintenance of such altered epigenetic states leads to stable alterations in gene expression with physiological adapted consequences. Epigenetic programming defects can become irreversible if aberrant organ growth and differentiation ensues as a consequence of an acute response to a transient environmental insult.(Costello & Brena, 2007) Nano-aerosols in combination with benzene exposure for instance are known to induce a significant reduction in LINE-1 and Alu methylation. Both are related to acute myelogenous leukemia.(Snyder, 2002) Likewise, airborne benzene was also associated with hypermethylation in protein p15 and hypomethylation of the cancerantigen gene MAGE-1.(Bollati et al., 2007)

Since the involvement of proteins in epigenetic pathways is tightly regulated, perturbations at a given level – e.g. through loss-of-function – inevitably will cause human disorders. This implies that epigenetic imprints do also affect transcription, RNA splicing, and protein modifications.^(Zoghbi et al., 2007) Evidence is given by studies employing both animals ^{(Liu et al., 1997;} Waterland & Jirtle, 2003; Weaver et al., 2004; Wolff et al. 1998) as well as humans ^{(Albert el al., 2005; Bottiglieri et al. 1994;} Reynolds et al. 1984;), emphasize the crucial role of epigenetic modulation and the onset of a chronic disease pattern.

From all stated facts, it is obvious that the organism is capable to adapt to a vast range of environmental exposures. The resulting epigenetic modifications are stable and heritable via cell divisions for a given lifespan and affect the phenotypic appearance both on the cellular as well as on the organismic level.^(Thaler, 1994) Figure 12 presents a dynamic map that highlights the feedback-cycles of involuntarily as well as deliberate environmental exposure. Thus, epigenetics makes it possible to associate a given exposure related lifestyle to the corresponding phenotype. Hence, long-term environmental exposure must be epigenetically manifest also within the germ cell linage. In this case environmentally related stress-information is passed on to progeny. However, inherited epigenetic imprints are not entirely permanent, as paramutating effects have been documented to persist for up to three generations before they are lost again without altering the sequence of the DNA itself. (Jablonka, 2001)



Fig. 12. Environmental influences, exposure to constituents in drinking water, consumed food, inhaled air along with stress and emotions, epigenetically modify genes, without altering the nucleotide sequence. The numbers above outline hierarchical interdependences of eco-systemic relationship in which the organism is embedded in: (1) The environment is the proximate agent of selection. (2) Organism perceives environment. (3) Organismic perception acts on physiology. (4) Organisms modifies genetic metabolism. (5) Environmental impact on DNA. (6) Environmental interaction with genes. (7) Organismic modification of environmental interaction.^(modified after Thaler, 1994)

3. Conclusion

Exposure to anthropogenically released nano-aerosols originating mainly from incomplete combustion processes fully unfold their toxicological potential – particularly in congested areas. These particles have multitude ways to enter the body, including adsorption via the

skin, the olfactoric nerve bundles (inducing neurodegenerative diseases), deposition within the respiratory tract (directly related to respiratory diseases), ingestion of cleared particle laden mucus (in combination with the former mode of entry, responsible of the wider organismic health problems). Redistribution of the cellularly absorbed particle load throughout the organism is achieved via the blood circulatory and the lymphatic system. Toxicity itself not only depends on the nature of the particle (solubility and hydrophobicity) but also on the surface structure, onto which volatile substances and radionuclides can adsorb. Since nano-sized particles exert more severe distressing effects on the cellular level than their coarser siblings, these aerosols significantly contribute to chronic disease patterns and epigenetic imprinting, which enables acquired lifestyle-related stress-response patterns to be passed on to subsequent generations. Due to the fact that these particles access secondary target organs along with their effects on the organismic level, they definitely will attain further toxico-medical attention in the near future. The availability of more and more products containing designed and engineered nano-particles and fibers, contributes to this dilemma as awareness of associated risks and benefits have not yet led to regulatory guidelines in order to limit side-effects of improper production methods, inadequate usage and irresponsible disposal of these materials. While the exact risk of aerosolized particles is still cumbersome to define, current scientific evidence already stresses the adverse effects of long-term exposure as it tilts the balance towards the emergence of so called "civil-societyrelated" diseases that so far were either considered harmless or not yet associated to these environmental stressors. While it is not always possible to assign a single detrimental aerosolized agent to a particular disease, the evidence given so far indicates that xenobiotic nano-aerosols along with the adsorbed cocktail of semi-/volatile organic compounds should be considered as promoters and modulators in the emergence of chronic diseases. This interrelation has scarcely been considered in the past. Since epigenotypic flexibility regards plasticity during embryonic development, the post-natal phase, and well into adulthood, it is not surprising that epigenetic imprinting due to airborne nano-aerosol exposure not only contributes to developmental disorders, but also to post-natal and even adult human diseases. This perspective will disproportionally challenges our existing medicare system. This Lamarckian-type of inheritance is achieved via various processes and involves in particular DNA-methylation, histone modifications, mRNA silencing and other regulatory interference mechanisms. Although it is well known that anthropogenic aerosols exert their effects on the cellular, tissue, organ, and organismic level, interference with the phylo-ontogenetic patterns, currently investigated in the field of epigenetics, open a new chapter to these issues. This line of argument may point towards a new understanding of health and disease, whereby the latter should just be regarded as an organismic proxy indicator in the attempt to attain a new organismic steady state. Hence, extended stress exposure (as is the case of environmental nano-aerosols) contain distressing agents that shift the constantly fluctuating homeostatic balance into new oscillating instabilities. However, the difference between these states lies in the fact that in the latter stages affected individuals increasingly feel physically less fit than in the former from which they have been kicked out of.

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Air pollution has always been a trans-boundary environmental problem and a matter of global concern for past many years. High concentrations of air pollutants due to numerous anthropogenic activities influence the air quality. There are many books on this subject, but the one in front of you will probably help in filling the gaps existing in the area of air quality monitoring, modelling, exposure, health and control, and can be of great help to graduate students professionals and researchers. The book is divided in two volumes dealing with various monitoring techniques of air pollutants, their predictions and control. It also contains case studies describing the exposure and health implications of air pollutants on living biota in different countries across the globe.

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