Annex B. Dosimetry

B.1. Ultrafine Disposition

Table B-1. Ultrafine disposition in humans.

Reference	Study Group	Aerosol	Study Protocol	Observations
Mills et al. (2006)	Healthy nonsmokers (5 M, 5 F; 21-24 yrs)	Carbon - ^{99m}Tc 108 nm CMD (σ_g = 2.2) Technegas Generator	Lung activity in the lung was measured at 0, 1, and 6 h post aerosol inhalation.	On avg, lung activity decreased 3.2 ± 0.7% during the first h and 1.2 ± 1.7% over the next 5 h. With 95.6% of the particles in the lungs at 6 h post inhalation and no accumulation of radioactivity detected over the liver or spleen, findings did not support rapid translocation from the lungs into systemic circulation.
Möller et al. (2008)	Healthy nonsmokers (n = 9; 50 ± 11 yrs) Smokers (n = 10; 51 ± 10 yrs) COPD patients (n = 7; 69 ± 10 yrs)	Carbon - ^{99m}Tc ~100 nm CMD Technegas Generator	On two separate occasions, subjects inhaled 100 mL aerosol boli to target front depths of 150 and 800 mL into the lungs to target the airways and alveoli, respectively. Retention measured at 10 mins, 1.5, 5.5, 24 and 48 h post inhalation. Isotope (^{99m}Tc) leaching from particles assessed via filters in saline, blood, and urine. ^{81m}Kr utilized to assess ventilation.	Shallow airways boli – Total deposition in airways (shallow boli) similar between groups. Pattern of deposition was significantly more central in the healthy subjects which was thought due to non-uniform ventilation distribution in smokers and COPD patients as visualized by gamma-camera scans. Airway retention after 1.5 h was significantly lower in healthy subjects (89 ± 6%) than smokers (97 ± 3%) or COPD patients (96 ± 6%). At 24 and 48 h, retention significantly remained higher in COPD patients (86 ± 6% and 82 ± 6%) than healthy subjects (75 ± 10% and 70 ± 9%). Deep alveolar boli – Total deposition in alveoli (deep boli) significantly greater in smokers (64 ± 11%) and COPD patients (62 ± 5%) than healthy subjects (50 ± 8%). Alveolar retention of particles similar at all times between groups. For example, at 48 h, 97 ± 3% in healthy subject, 96 ± 3% in smokers, and 96 ± 2% in COPD patients. Retention at 24 and 48 correlated with isotope leaching, suggesting that the small amount of clearance primarily reflected the disassociation of ^{99m}Tc from the particles with little transport of particles from the lungs.
Wiebert et al. (2006b)	Subjects having varied health status (9M, 6F; 46-74yrs) 6 healthy 5 asthmatic 4 smokers	Carbon - ^{99m}Tc 87 nm CMD (σ_g = 1.7) Technegas Generator	Technegas system was modified to reduce leaching of ^{99m}Tc radiolabel from particles. The avg tidal volume during aerosol inhalation was 1.8 L (range 0.8 – 3.3). Activity in chest region measured at 0, 2, 24, 46, and 70 h after inhalation. Leaching assessed in vitro and via urine collection.	Lung function not significantly different between healthy and affected lungs. The aerosol deposition fraction was 41 ± 10%. Lung retention was 99 ± 3%, 99 ± 5%, and 99 ± 10% at 24, 46, and 70 h post inhalation. Cumulative in vitro leaching by 70 h was 2.6 ± 0.96%. Except for radiotracer leaching from particles (1.0 ± 0.6% of initially deposited activity in urine by 24 h), there was not significant clearance from the lungs by 70 h. Individual leaching was not correlated with individual retention.
Wiebert et al. (2006a)	Healthy subjects (4M, 5F; 56 ± 9 yrs) Asthmatics (2M, 3F; 59 ± 6 yrs) Control (1M; 50 yrs)	Carbon - ^{99m}Tc 34 nm CMD (σ_g = 1.5) Technegas Generator	Slow deep aerosol inhalations with 10s breath hold. Mean inhalation time of 6 min. Control subject inhaled aerosol with loosely bound radiolabel. Retention scans at 10 min, 60 min, 100 min, and 24 h post inhalation. Leaching assessed in vitro and via collection of blood and urine.	Avg deposition fraction of 60 ± 17% which was correlated with tidal volume during aerosol inhalation (p = 0.01). Activity excreted in urine over 24-h post inhalation was 51% in the control subject (high ^{99m}Tc disassociation) and 3.6 ± 0.9% of deposited activity. In the blood of the control subject, activity was 30%, 31%, and 5% of the deposited activity at 20 min, 80 min, and 24-h (respectively), whereas it was only 0.9 ± 0.6%, 1.1 ± 0.4%, and 1.5 ± 0.5% the other 13 subjects at these times. Lung retention in the control subject was 30% at 1-h and 18% at 24 h. In the remainder of subjects, lung retention was approximately 100% through 24 h.

Table B-2. Ultrafine disposition in animals.

Reference	Study Group	Aerosol	Study Protocol	Observations
Bermudez et al. (2004)	Fischer 344 rats, females (6 wks) B3C3F1 mice, females (6 wks) Hamsters, females (6 wks)	TiO_2: 1.29–1.44 µm MMAD (σg = 2.46-3.65), 21 nm primary particles	Animals exposed 6 h/d, 5 d/wk, for 13 weeks to 0.5, 2 and 10 mg/m^3. Control animals exposed to filtered air. Animals sacrificed at 0, 4, 13, 26, and 56 (49 for hamsters) post-exposure. Groups of 25 animals per species and time point.	TiO_2 pulmonary retention half-times for the low-, mid-, and high-exposure groups, respectively: 63, 132, and 365 days in rats; 48, 40, and 319 days in mice; and 33, 37, and 39 days in hamsters. Burden of TiO_2 in lymph nodes increase with time postexposure in mid- and high-dosed rats; in high-dosed mice; but was unaffected in hamsters at any time or dosage group. In high-exposure groups of mice, epithelial permeability remained elevated (~2× control groups) out to 52 weeks without signs of recovery. Epithelial permeability was 3-4× control in high exposed rats through 4 weeks post exposure, but approached control by 13 weeks. Epithelial permeability was unaffected in all groups of hamsters.
Chen et al. (2006)	Sprague-Dawley male rats (220 ± 20 g)	Polystyrene 125I radiolabel Ultrafine: 56.4 nm Fine: 202 nm	Intratracheal instillation of particles in healthy rats or those pretreated with LPS (12 h before particle instillation). Healthy rats sacrificed between 0.5-2 h and at 24 or 48 h post-instillation. LPS treated rats were sacrificed 0.5-2 h post-instillation.	In healthy rats, there were no marked differences in lung retention or systemic distribution between the ultrafine and fine particles. Results for healthy animals focused on ultrafine particles which were primarily retained in lungs (72 ± 10% at 0.5-2 h; 65 ± 1% at 1 d; 62 ± 5% at 5 d). Initially, there was rapid particle movement into the blood (2 ± 1% at 0.5-2 h; 0.1 ± 0.1% at 5 d) and liver (3 ± 2% at 0.5-2 h; 1 ± 0.1% at 5 d). At 1 d post-instillation, about 13% of the particles where in the urine or feces. Following LPS treatment, ultrafine accessed the blood (5 vs. 2%) and liver (11 vs. 4%) to a significantly greater extent than fine particles.
Geiser et al. (2005) Also included in vitro study	Wistar rats 20 adult males (250 ± 10 g)	TiO_2 (22 nm CMD, 1.7 σg) Spark generated 0.11 mg/m^3 7.3×10^6 particles/cm^3	Rats exposed 1-h via endotracheal tube while anesthetized and ventilated at constant rate. Lungs fixed at 1 or 24-h postexposure.	Distributions of particles among lung compartments followed the volume distribution of compartments and did not differ significantly between 1 and 24-h post-inhalation. On avg, 79.3 ± 7.6% of particles were on the luminal side of the airway surfaces, 4.6 ± 2.6% in epithelial or endothelial cells, 4.8 ± 4.5% in connective tissues, and 11.3 ± 3.9% within capillaries. Particles within cells were not membrane-bound.
Kapp et al. (2004)	Charles River rats 5 young adult male (250 ± 10 g)	TiO_2 (22 nm CMD, 1.7 σg) Spark generated	Rats exposed 1-h via endotracheal tube while anesthetized and ventilated at constant rate. Lungs fixed immediately postexposure.	Of particles in tissues, 72% were aggregates of 2 or more particles; 93% of aggregates were in round or oval shape aggregates, 7% were needle-like. The size distribution of particles in lung tissues (29 nm CMD, 1.7 σg) was remarkably similar to the aerosol; the small discrepancy may have been due to differences sizing techniques. A large 350 nm aggregate was found in a type II pneumocyte, a 37 nm particle in a capillary close to the endothelial cells, and a 10^6 nm particle within the surface-lining layer close to the alveolar epithelium.

Table B-3. In vitro studies of ultrafine disposition.

Reference	Animal	Particles	Study Protocol	Observations
Edetsberger et al. (2005)	Human cervix carcinoma cells (HeLa cells)	Polystyrene spheres (0.020 µm)	Cells incubated with polystyrene particles having negative surface charges. Cell cultures were naïve or treated with Genistein or Cytochalasin B (CytB) prior to particle application. Genistein inhibits endocytotic processes, expecially caveolae internalization. CytB inhibits actin polymerization and phagocytosis.	Particles translocated into cells by first measurement (~1 min after particle application) independent of treatment group. In naïve cells, agglomerates of 88-117 nm were seen by 15-20 minutes and of 253-675 nm by 50-60 minutes after particle application. Intracellular aggregates thought to be result from particle incorporation into endosomes or similar structures. In treated cells, only a small number of agglomerates (161-308 nm) were found and only by 50-60 minutes. At 50-60 minutes, 90% and 98% of particles were in the 20-40 nm range in naïve and treated cells, respectively. Particles did not translocate into dead cells, rather they attached to outside of the cell membrane.
Geiser et al. (2005) Also included inhalation study	Porcine lung macrophages (10^6 cell/mL)Human red blood cells (RBC; 8 × 10^6 cells/mL)	Fluorescent polystyrene spheres (0.078, 0.2, and 1 µm) Gold shheres (0.025 µm)	Cells cultured for 4 h with each sized polystyrene spheres. RBC were employed as a model of nonphagocytic cells. Some macrophages cultures were treated with cytochalasin D (cytD) to inhibit phagocytosis. In addition, RBC were also cultured with gold particles.	Of the non-cytD treated macrophages, 77 ± 15%, 21 ± 11%, and 56 ± 30% contained 0.078, 0.2, and 1 µm particles, respectively. CytD treatment of macrophages effectively blocked the phagocytosis of 1 µm particles, but did not alter the uptake of the 0.078 and 0.2 µm particles. Human RBC were found to contain 0.078 and 0.2 µm polystyrene spheres as well as the 0.025 µm gold particles, which were not membrane bound. In contrast, the RBC did not contain the larger 1 µm polystyrene spheres. Results suggest that ultrafine and fine (0.078 and 0.2 µm diameter) particles cross cellular membranes by a non-endocytic (i.e. not involving vesicle formation) mechanisms such as adhesive interactions and diffusion.
Geys et al. (2006)	Human alveolar (A549) and bronchial (Calu-3) epithelial cellsRat primary type II pneumocytes	Amine- and carboxyl-modified fluorescent polystyrene (46 nm)	Cells cultured in clear polyester transwells with 0.4 or 3 µm pores. Monolayer considered "tight" when <1% sodium fluorescein moved from apical to basolateral compartment. Particle translocation assessed in transwells with and without cells. Cells incubated with particles for 14-16 h to assess translocation from apical to basolateral compartment.	Without cells, 13.5% of carboxyl-modified particles passed through the 0.4 µm pores (n = 7) and 67.5% through 3 µm pores (n = 3). Movement of the amine-modified particles was 4.2% through 0.4 µm pores (n = 7) and 52.7% through 3 µm pores (n = 3). The integrity of the monolayer was insufficient for translocation studies using the A549 cells (0.4 and 4 µm pore size) and rat pneumocytes (0.3 µm pore). Using 0.4 µm pores, there was no detectable translocation through either Calu-3 or rat pneumocyte monolayers. Using 3 µm pores, ~6% of both particle types passed through the Calu-3 monolayer; however, results were highly variable with no translocation in 2 (of 5) and 3 (of 6) trials with carboxyl- or amine-modified particles, respectively.

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B.2. Olfactory Translocation

Table B-4. Olfactory particle translocation.

Reference	Study Group	Aerosol	Study Protocol	Observations
DeLorenzo (1970)	Squirrel monkeys young males (1 kg)	Silver-coated colloidal gold (50 nm)	Intranasal instillation of 1 mL particle suspension. Animals sacrificed at 0.25, 0.5, 1, and 24-h after instillation.	Rapid movement (30-60 min) into olfactory bulbs. Within 30 min of being placed on nasal mucosa, particle aggregates were seen in axoplasm of the fila olfactoria Within 1 h, particles were in olfactory glomerulus. Particles in the olfactory bulb were located preferentially in mitochondria and not free in the cytoplasm.
Dorman et al. (2001)	Crl: CD rats Males (6-wk-old)	Soluble and insoluble Mn particle types; MMAD = 1.3-2.1 µm; GSD<2	Whole body exposure (6 h/day, 14 consecutive days) to 0, 0.03, 0.3, and 3 mg Mn/m^3. Tissues analyzed in six animals per concentration exposed to soluble ($MnSO_4$) or insoluble (Mn_3O_4) aerosols.	Increased Mn levels in olfactory bulb observed following $MnSO_4$ of ≥ 0.3 mg Mn/m^3 and following Mn_3O_4 of 3 mg Mn/m^3. At 3 mg Mn/m^3, Mn levels were significantly greater in olfactory bulb (1.4-fold) and striatum (2.7-fold) following soluble MnO_4 than insoluble Mn_3O_4. Mn levels in the cerebellum were unaffected following all exposures.
Dorman et al. (2004)	Crl: CD rats Males (6-wk-old)	Soluble and insoluble Mn particle types; MMAD = 1.5-2 µm; GSD = 1.4-1.6	Whole body exposure (6 h/day, 5 d/wk, 13 wks) to $MnSO_4$ at 0, 0.01, 0.1, and 0.5 mg Mn/m^3. Compared to Mn phosphate (as hureaulite) exposure of 0.1 mg Mn/m^3. Brain Mn levels assessed immediately following 90 days of exposure or 45 days postexposure.	Relative to air, the insoluble hureaulite was significantly increased at 90 days of exposure in the olfactory bulb, but not striatum or cerebellum. The soluble Mn phosphate showed a dose dependent increase in olfactory bulb Mn levels at 90 days. At 0.1 mg Mn/m^3, Mn levels following Mn phosphate were significantly increased in the olfactory bulb and striatum relative to hureaulite and air exposures. At 45 days postexposure, relative to air, olfactory bulb Mn levels only remained increased Mn phosphate group at 0.5 mg Mn/m^3.
Elder et al. (2006)	Fisher 344 rats Males (200-250 g)	Mn oxide (~30 nm equivalent sphere with 3-8 nm primary particles) Spark generated 0.5 mg/m^3 18×10^6 particles/cm^3	Whole body inhalation exposure to either filtered air or Mn oxide for 12 d (6 h/d, 5 d/wk) with both nares open or Mn oxide for 2 d (6 h/d) with right nostril blocked. Intranasal instillation in left nostril of Mn oxide particles or soluble $MnCl_2$ suspended in 30 µL saline. Analyzed Mn in the lung, liver, olfactory bulb, and other brain regions.	After 12 d exposure via both nostrils, Mn in the olfactory bulb increased 3.5-fold, whereas in the lung Mn concentrations doubled; there were also increases in the striatum, frontal cortex, and cerebellum. After the 2 d exposure with the right nostril blocked, Mn accumulated in the mainly in the left olfactory bulb (~2.4-fold increase) in to a lesser extent in the right olfactory bulb (1.2-fold increase). At 24-h post instillation, the left olfactory bulb contained similar amounts of the poorly soluble Mn oxide (8.2 ± 0.7%) and soluble $MnCl_2$ (8.2 ± 3.6%) as a percent of the amount instilled.
Oberdörster et al. (2004)	Fisher 344 rats Males (14 wks; 284 ± 9 g)	^{13}C (36 nm CMD, 1.7 σ_g) Spark generated	Rats (n = 12, 3 per time point) exposed to 160 µg/m^3 for 6 h in whole-body chamber and sacrificed at 1, 3, 5, and 7 d postexposure. Lung, olfactory bulb, cerebrum, and cerebellum removed for ^{13}C analysis. Tissue ^{13}C-levels were determined by isotope ratio mass spectroscopy and background corrected for ^{13}C levels in unexposed controls (n = 3).	At 1 day postexposure, the lungs of rats exposed to ultrafine ^{13}C particles contained 1.34 ± 0.22 µg of ^{13}C (1.39 µg/g-lung) following background corrected. By 7 days postexposure, the ^{13}C concentration had decreased to 0.59 µg/g-lung. There was a significant and persistent increase in ^{13}C in the olfactory bulb of 0.35 µg/g on day 1, which increased to 0.43 µg/g by day 7. Day 1 concentrations of ^{13}C in the cerebrum and cerebellum were also significantly increased but the increase was inconsistent, possibly reflecting translocation of particles from the blood across the blood–brain barrier into brain regions.
Persson et al. (2003)	Sprague-Dawley male rats (150 g) Freshwater Pike female (3 kg)	$^{65}ZnCl_2$ dissolved in 0.1 M HCl	Rats: intransal (0.03 µg Zn in 10 µL) or intraperitoneally (0.03 µg Zn in 100 µL); autoradiography and γ spec at 1 day or 1, 3, or 6 weeks postexposure. Pike: instilled (0.12 µg Zn in 10 µL) in right or both olfactory chambers, assayed 2 weeks postexposure	Zn uptake in olfactory epithelium and transport along olfactory neurons to olfactory bulb. Zn continued into interior of olfactory bulb and in rat went into anterior olfactory cortex. Zn found bound to both cellular constituents and cytosolic components. Some Zn bound to metallothionein in olfactory mucosa and olfactory bulb.
Wang et al. (2007)	CD-1 (ICR) mice	Rutile TiO_2 21 and 80 nm Anatase TiO_2 155 nm	Twenty mice (n = 5 per group) exposed 0 or 0.01 g-TiO_2 per mL DI. Instilled 25 µL each day for 5 d, then inhaled 10 µL every other day. Mice sacrificed after one month.	Rutile particles were observed to be column/fiber shaped, whereas anatase was octahedral. TiO_2 particles taken up by olfactory bulb via the olfactory nerve layer, olfactory ventricle, and granular cell layer of the olfactory bulb. Fine TiO_2 showed greater entry into the olfactory bulb presumably due to aggregation of smaller rutile particles that was not seen for the fine anatase particles.

Reference	Study Group	Aerosol	Study Protocol	Observations
Yu et al. (2003)	Sprague-Dawley male rats, 6 wk old (218 ± 10 g)	Stainless steel welding-fume <0.5 µm	Whole body exposure 2 h/day for 1, 15, 30, or 60 days Low: 64 ± 4 mg/m^3 (1.6 mg/m^3 Mn) High: 107 ± 6 mg/m^3 (3.5 mg/m^3 Mn)	Significant increases in cerebellum Mn at 15 – 30 days of exposure. Slight increases in Mn in substantia nigra, basal ganglia, temporal cortex, and frontal cortex after 60 days. Significant increase at 30 days in basal ganglia at low dose. Authors suggested that pharmacokinetics and distribution of welding fume Mn differs from pure Mn.

B.3. Clearance and Age

Table B-5. Studies of respiratory tract mucosal and macrophage clearance as a function.

Reference	Animal	Particles	Study Protocol	Observed Effect(s)
NASAL AND TRACHEAL CLEARANCE				
Ho et al. (2001)	Human, males and females	Not applicable	Ninety subjects (47 M, 43 F; 52 ± 23 yrs) between 11 and 90 years of age were recruited to measure nasal saccharine clearance and ciliary beat frequency.	Ciliary beat frequency (n = 90; r = -0.48, p <0.0001) and nasal mucociliary clearance time (n = 43; r = 0.64, p <0.001) were correlated with subject age. Nasal clearance times were significantly (p<0.001) faster in individuals under 40 years of age (9.3 ± 5.2 min) versus older subjects (15.4 ± 5.0 minutes). Results similar between males and females.
Goodman et al. (1978)	Humans, males and females	Radiolabed Teflon disks (1 mm diameter, 0.8 mm thick)	Tracheal mucus velocity following delivery via bronchoscope to the tracheal mucosa. Ten young (2 M, 8 F; 23 ± 3 yrs) and ten elderly (2 M, 5 F; 63 ± 5 yrs) nonsmokers served as control subjects. Measurements were also made in young smokers, ex-smokers, and individuals with chronic bronchitis.	Young nonsmokers had a tracheal mucus velocity of 10.1 ± 3.5 mm/min which was significantly faster than the velocity of 5.8 ± 2.6 observed in the elderly nonsmokers.
Whaley et al. (1987)	Beagle dogs, males and females	Macroaggregated albumin^{99m}Tc labelled	Intratracheal instillation of 10- µl droplet of labelled albumin in saline. Tracheal clearance followed 25 minutes. Longitudinal measure measurements in 5 males and 3 females when young adults (2.8-3 yr), middle-aged (6.7-6.9 yr), and mature (9.6-9.8 yr). Additional 5 females and 3 males comprised immature group (9-10 mo) and 4 males and 4 females used as aged group (13-16 yr).	Tracheal mucus velocity significantly (p<0.05) greater in young (9.7 ± 0.6 [SE] mm/min) and middle-aged (6.9 ± 0.5) groups than in immature (3.6 ± 0.4), mature (3.5 ± 0.8), and aged (2.9 ± 0.5) dogs.
Yeates et al. (1981)	Humans, males and females	Radioaerosols ^{99m}Tc labelled	Tracheal mucus velocities compiled for 74 healthy non-smoking subjects (60 M, 14 F; 10-65 yrs, mean 30 yrs) from prior studies. Forty-two (32 M, 10 F) inhaled albumin in saline droplets (6.2-6.5 µm MMAD), Yeates et al. (1975); twenty-two (21 M, 1 F) inhaled iron oxide (4.2 µm MMAD), Yeates et al. (1981b); and ten (7 M, 3 F) inhaled monodisperse iron oxide aerosol (7.5 µm MMAD), Leikauf et al. (1981). Inhalations were via a mouthpiece with an inspiratory flow of ~1 liter/sec.	A lognormal distribution of tracheal mucus velocities was reported. Age did not appear to affect velocities, e.g., 4.7 ± 2.5 mm/min in 18-24 yr olds vs. 4.6 ± 3.2 mm/min in individuals >30 yrs of age. However, it should be noted that only 2 subjects were greater than 45 yrs of age and that the data was complied from three studies using differing experimental techniques. Rather similar tracheal mucus velocities in males (4.7 ± 3.0 mm/min) and females (4.9 ± 2.4 mm/min).

Reference	Animal	Particles	Study Protocol	Observed Effect(s)
BRONCHI AND BRONCHIOLES CLEARANCE				
Puchelle et al. (1979)	Human, males	7.4 µm MMAD^{99m}Tc labelled resin	Mucociliary clearance measured for 1-h post aerosol inhalation in 19 healthy non-smoking males (21-69 yrs of age). Clearance measure on two occasions in 16 individuals.	Negative correlation ($r = -0.472$, $p<0.05$) between mucociliary clearance and age. Younger subjects (n = 9; 21-37 yrs) had 1-h clearance of 34 ± 14% which was significantly greater than the 22 ± 8% found in the older subjects (n = 5; >54 yrs). Separated by 5.4 wks (on avg), there was a good correlation between repeated clearance measurements ($r = 0.65$, $p<0.001$)
Svartengren et al. (2005)	Humans, males and females	6 µm MMAD111In labelled Teflon	Small airway clearance measured in five age groups (≤ 24 yrs, n = 13; 25-29 yrs, n = 8; 30-49 yrs, n = 7; 50-64, n = 9; >65 yrs, n = 9) of healthy subjects. Aerosol inhaled via mouthpiece at extremely slow rate of 0.05 L/s. Activity in lungs measured at 1 d, 2 d, and 1, 2, and 3 wks post-exposure. Under the presumption that most large airway clearance was complete by 24 h, retention at 24 h was normalized to 100%.	Large and small airway clearance slowed with increasing age. Clearance correlated with age at all times ($r = -0.46$ to -0.50, -0.55, -0.66, and -0.70 at 1 d, 2 d, 1 wk, 2 wk, and 3 wks, respectively). Based on linear regression, the clearance from 1 to 21 days post-exposure was 47% in a 20 yr-old versus 23% in an 80 yr-old. Lung function was not a significant predictor of clearance when age considered.
Vastag et al. (1985)	Humans, males and females	Monodisperseerythrocytes^{99m}Tc labelled	Clearance measured for 1-h post-inhalation in eighty healthy (59 M, 21 F; 43 ± 17 yrs) subjects who had never smoked. Smokers and ex-smokers also studied. Aerosol inhalation not described.	Clearance significantly associated with age. Based on linear regression, total mucociliary clearance at 1-h post-exposure was 46% in a 20 yr-old versus 23% in an 80 yr-old. Similar results for males and females.
ALVEOLAR CLEARANCE				
Muhle et al. (1990)	Fischer 344 rats	3.5 µm MMAD 85Sr labelled polystyrene latex	Control animals compared across several studies. Aerosol inhaled by short-term nose only exposure. Alveolar clearance determined by exponential fit to thoracic activity measured over 75-100 days excluding the first 15 days post-exposure.	Typical alveolar clearance half-time of 45 days in 5-month old rats compared to 74 days in 23-month old rats. Statistical significance of findings not proved.

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