Supplementary Material

**Supplementary Table 1**. Toxicity studies associated with CNTs induced pathology on pleura

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| **CNT** | | **Animal** | **Dose/Max observation period** | | **Major observation** | **Ref.** | |
| **Intraperitoneal injection** | | | | | | | |
| MWCNTtangle1(D= 14.84±0.50 nm, La=1-5 µm)  MWCNTtangle2(D= 10.40±0.32 nm, La=5-20 µm)  MWCNTlong1 (D= 84.89+1.9 nm, La mean 13 µm)  MWCNTlong2 (D= 165.02+4.68 nm, La Max 56 µm) | | Wide type mice  female C57Bl/6  Age 8 weeks | One single dose of 50 µg/mouse  1 and 7 days | | MWCNTlong1 and MWCNTlong2 produce inflammation and granulomas that were similar to inflammatory response caused by long asbestos after 7 days. | (1) | |
| MWCNT-7 (D=100 nm, 27.5% particles≥5µm) | | Male p53 (+/-) mouse  Age 9-11 weeks | One single dose of 1×109 particles (3 mg)/mouse  25 weeks | | The incidence of mesothelioma after MWCNT-7 treated was 87.5% during whole periods of 25 weeks. | (2) | |
| MWCNT-7 (D=70-170 nm, mean 90 nm,  L=1-20 µm mean 2 µm, 27.5% particles ≥5 µm) | | Male p53 (+/-) mice  Age 9–11 weeks | One single dose of  300 µg (1x108 fibers)/mouse  30 µg (1x107 fibers) /mouse  3 µg (1x106 fibers)/mouse  1 year | | Cumulative incidence of peritoneal mesothelioma induced by MWCNT-7 displayed dose-dependent manner. | (3) | |
| MWCNT50a (MNCNT-7)  (D=49.95 ± 0.63 nm, L=5.29 ± 0.12 µm)  MWCNT50b  (D=52.4 ± 0.72 nm, L=4.6 ± 0.10 µm)  MWCNT115  (D= 116.2 ± 1.6 nm, L=4.88 ± 0.10 µm)  MWCNT145  (D= 143.5 ± 1.6 nm, L= 4.34 ± 0.08 µm)  MWCNTtngl (Da=15 nm, La=3 µm) | | Male and female rats  Age 6 weeks | Total dose of 1 mg or 10 mg/rat  1 year | | MWCNT-7 induced severe chronic inflammation and mesothelioma development because of its thin diameter and high crystallinity. | (4) | |
| MWCNT-M (D mean 66.8 nm, L mean 6.65 µm) (MWCNT-7)  MWCNT-N (D mean 59.2 nm, L mean 5.48 µm)  MWCNT-WL (D mean 70.9 nm, L mean 7.31 µm)  MWCNT-SD1 (D mean 177.4 nm, L mean 4.51 µm)  MWCNT-WS (D mean 44.5 nm, La=0.5-2 µm)  MWCNT-SD2 (D mean 13.5 nm, La=3 µm)  MWCNT-T (D mean 35.8 nm, La=0.732 µm) | | Male Fischer 344 rats  Age 10 weeks | a single dose of 1 mg/kg  1 year | | Four types of MWCNTs, such as M, N, WL, and SD1, which have straight, acicular in shape and few agglomerates, induced nearly 100% incidences of mesothelioma development. | (5) | |
| MWCNT Ab (D=85±1.6 nm, L=8.57±1.51µm)  MWCNT Bb (D=62±1.71 nm, L=9.3±1.63 µm)  MWCNT Cb (D=40±1.57 nm, L=10.24±1.64 µm)  MWCNT Db (D=37±1.45 nm, L=7.91±1.4 µm) | | Male Wistar Han rats | a single dose of 1×109particlesb/rat or  5×109particlesb/rat  2 years | | Highest frequencies and earliest appearances of mesothelioma development was observed after treatment with the rather straight MWCNT types A and B. | (6) | |
| Pristine MWNTs:NTlong  (L mean 10.7±1.4 µm)  alkyl functionalized MWNTs: NT-Alkyl  (L mean 8.1±0.6 µm)  tri(ethylene glycol) functionalized MWNTs: NT-TEG  (L mean 2.4±0.2 µm) | | C57BL6 mice  Age 6-8 weeks | One single dose of 50 µg/mouse  1 and 7 days | | Hydrophilic surface modification leading to shorten or untangling/debundling of aqueous dispersions of functionalized-MWNTs will help to resolve toxicological risks associated with long-fiber exposure. | (7) | |
| **Intrascrotal injection** | | | | | | | |
| MWCNT-7  (D=70-100 nm of 82% particles,  L=70-110 µm 72.5 % particles) | | Male Fischer rats  Age 12 weeks | a single dose of 0.24 mg/rat  1 year | | MWCNT-7 induced intraperitoneally disseminated mesothelioma in the incidence of 85.7% after 52 weeks. | (8) | |
| **Inhalation exposure** | | | | | | | |
| MWCNTs  (D=30-50 nm, L=0.3-50 µm) | Male C57BL6 mice  Age 6-8 weeks | | Low dose (0.2 mg/kg) or high dose (4 mg/kg) for 6h  1 day, 2 weeks, 6 weeks or 14 weeks | MWCNTs were embedded in the subpleural wall, while increasing of subpleural fibrosis was observed after 2 and 6 weeks after inhalation. | | (9) |
| MWCNT-7**c**  (D=92.9-98.2 nm, L=5.4-5.9 µm) | Male and female F344 rats  Age 6 weeks | | 0.02, 0.2, and 2 mg/m3 for 6 h/day, 5 days/week for 104 weeks  2 years | Incidence of simple mesothelial hyperplasia of the parietal pleural and focal fibrosis of the parietal pleura side of the diaphragm was observed in male rats exposed to the high dose. | | (10) |
| MWCNT-7  (Dd=1.59 µm, L ND) | Male B6C3F1 mice  Age 6 weeks | | 5 mg/m3, 5 hours/day, 5 days/week, for 15 days  17 months | Only 9% mice exposed MWCNT and methylcholanthrene developed mesothelioma, whereas mice administered MWCNT did not develop mesothelioma. | | (11) |

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| **Pharyngeal respiration** | | | | | |
| MWCNT-7  D=49±13.4 nm, L mean 3.86 µm | Male C57BL/6J mice  Age 7 weeks | One single dose of 10, 20, 40, 80 µg/mouse  1day, 1 week, 4 weeks, 8 weeks | After1 day exposure at dose of 80 µg/mouse, 0.6% MWCNT lung burden was in the subpleural regions. At day 56 approximately 1 in every 400 penetrated MWCNTs was in either the subpleural tissue or intrapleural space. | (12) |
| MWCNTshort  (D=25.7±1.6 nm, L=1-2 µm)  MWCNTtangle  (D=14.84±0.05 nm, L=1-5 µm)  MWCNTlong  (D=165.02±4.68 nm, L mean 36 µm, 84.26% fiber great than 15 µm) | Female C57BL/6 mice  Age 8-12 week | One single dose of 50 µg/mouse  1 and 6 weeks | Long MWCNT were retained at the parietal pleura and caused inflammation and lesion development. | (13) |
| **Intratracheal instillation** | | | | |
| SWCNTs  (D=1.7-2.1 nm, L=0.05-8.14 µm, mean 0.5 µm)  MWCNT-7  (D=60-100 nm, L=0.12-21.5 µm, mean 1.81 µm) | Male Wistar rat  Age 9 weeks | One single dose of 0.15 mg/kg or 1.5 mg/kg  1, 3, 7, 30, 90 days | MWCNT-7 induced greater levels of pleural inflammation than did short SWCNTs. | (14) |
| **Intratracheal intrapulmonary spraying** | | | | |
| MWCNT-N  (D ND, L=3.64 ± 2.26 µm, mean 3.02 µm)  MWCNT-7  (D ND, L= 5.11 ± 2.91 µm, mean 4.47 µm) | Male Fisher 344 rats  Age 10 weeks | 1.25 mg/rat (Five doses at 0.25 mg/rat, five times over 9 days period)  Six hours after the last exposure | MWCNTs treatment caused visceral mesothelial cell proliferation and inflammation in the pleural cavity. | (15) |
| MWCNT-L (D mean 150 nm, L mean 8 µm)  MWCNT-S (D mean 15 nm, L mean 3 µm) | Male F344 rats  Age 8 weeks | 1.625 mg⁄ rat (13 doses at 0.125 mg/rat, 13 times over 24 weeks period)  24 hours after the last exposure | MWCNT-L induced stronger inflammatory reactions in the pleural cavity and fibrosis and patchy parietal mesothelial proliferation lesions. | (16) |
| MWCNT 1  (L=7.41±3.52 µm, Da=30-200, mean 177 nm)  MWCNT 2  (L=4.27±2.88 µm, Da=70-170 nm, mean 90 nm) | Male F344 rats  Age 8 weeks | 2 mg/rat (8 doses at 0.25 mg/rat, 2 times/week for 4 weeks)  24 h and at 3 months after the last exposure | MWCNTs induced pleural inflammation, persistent pleural fibrosis, and mesothelial proliferation in both the visceral and parietal pleura. | (17) |
| MWCNT-N (Da=1-20 nm)  Unfiltered (L=4.2±2.9 µm)  Flow-through (L=2.6±1.6 µm)  Retained (>2.6 µm) | Male F344 rats  Age 10 weeks | 1 mg⁄rat (8 doses at 0.125 mg/rat, 8 times over 2 weeks period)  109 weeks after the last exposure | Both the unfiltered and flow-through fractions induced mesothelioma. | (18) |
| MWCT-7  (ND) | Male F344 rats  Age 10 weeks | 1.5 mg/rat (12 doses at 0.125 mg/rat, once a week for 12 weeks)  2 years after the last exposure | The incidence of malignant mesothelioma in the MWCNT‐7 group was significantly higher than in the vehicle control group. | (19) |
| **Intrapleural injection** | | | | |
| MWCNTStraight  SNT (D=125 nm, L <15 µm)  MWCNTLong, straight  LNT (D=165 nm, L 85% particles >15 µm) | Female C57BL/6 mice  Age 8 weeks | 1 and 12 weeks exposure:  One single dose of 5 µg/mouse of SNT and LNT  6 months and 1year exposure:  One single dose of 2.5 µg/mouse of LNT  Up to 20 months:  One single dose of 1, 0.5, 0.2 µg/mouse of LNT | CNT induced mesothelioma exhibits similar common key pro-oncogenic molecular events compared with asbestos throughout the latency period of disease progression. | (20) |
| MWCNTshort (D**a**=20-30 nm, L**a**=0.5-2 µm)  MWCNTtangle1 (D=14.84±0.05 nm, L**a**=1-5 µm)  MWCNTtangle2 (D=10.4±0.32 nm, L**a**=5-20 µm)  MWCNTlong1 (D=84.89±1.9 nm, L**a** mean 13 µm)  MWCNTlong2 (D=165.02±4.68 nm, L**a** max13 µm) | Female C57Bl/6 mice  Age 8 weeks | One single dose of 5 µg/mouse  1 day, 1 week, 4 weeks, 12 weeks and 24 weeks | Long CNT retained in pleural cavity and induced acute inflammation and progressive fibrosis on the parietal pleura. | (21) |
| MWCNT1 MWCNT-7  (D percentile 70 nm, L percentile 5.3 µm)  MWCNT2 (D percentile 31 nm, L percentile 0.843 µm) | Wide type C57BL/6 mice  IL1α/β knockout mice | One single dose of 50 µg/mouse  and 100 µg/mouse  4 weeks | MWCNT1 (MWCNT-7) induces more severe inflammatory responses than MWCNT2 and asbestos in WT mice. WT mice were more prone to development of sustained inflammation and fibrosis than IL1-KO mice. | (22) |
| Silver Nanowire  AgNW3 (D=115±3 nm, L mean 3 µm)  AgNW5 (D=118±3 nm, L mean 5 µm)  AgNW10 (D=128±2 nm, L mean 10 µm)  AgNW14 (D=121±3 nm, L mean 14 µm)  AgNW28 (D=120±4 nm, L mean 28 µm) | Female C57Bl/6 mice  Age 9 weeks | One single dose of  5 µg/mouse  1 day and 1 week | Fibers beyond 5 μm in length are pathogenic to the pleura. | (23) |
| Carbon nanofibers CNFtangle1  (D=24.79 ± 0.4 nm, L ND, Db<0.66, SBPL<0.87)  MWCNTtangle1  (L=16.37 ± 0.2 nm, L ND, Db<0.66, SBPL<0.87)  MWCNTtangle2  (D=15.64 ± 0.1 nm, L ND, Db<0.66, SBPL<0.87)  MWCNTtangle3  (D=7.75 ± 0.1 nm, L ND, Db<0.66, SBPL<0.87)  MWCNTtangle4  (D=16.7 ± 0.2 nm, L ND, Db<0.66, SBPL<0.87)  MWCNTlong1  (D=58.3 ± 1.0 nm, L=10.02 ± 0.3 µm, Db>0.97, SBPL>1.09) | Female ICR mice  Age 6 weeks | One single dose  1 day exposure: 1, 2.5, 5 µg/mouse  4 weeks exposure:  5 µg/mouse | A bending ratio of 0.97 and a static bending persistence length of 1.08 are the threshold rigidity values for asbestos-like pathogenicity. | (24) |

ND not determined, Db bending ratio, SBPL static bending persistence length

a Values obtained from the manufacturer.

b WHO fibers, a fiber length of at least 5 μm and a fiber diameter of less than 3 μm with an aspect ratio (ratio of fiber length to fiber diameter) of at least 3:1.

c Fibers collected from the inhalation chamber.

dMass median aerodynamic diameter

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