3658 Toxicokinetic Study following Intratracheal Instillation or Oral Gavage of Two Be-7 Tagged Carbon Black Samples

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Carbon black can be "intrinsically" labelled with a γ-tracer without evidently altering the material structure. In this study two carbon black samples, i.e. Monarch® 1000 (oxidized carbon black grade) and Printex® 90 (untreated grade) were labelled with Beryllium-7 using proton beam irradiation (half-time of Be-7: 53.3 days; γ-tracer). A triplicate of solvents (EtOH/H_2O 1/1 v/v - 0.01 N HCl - Artificial lysosomal fluid) was applied to consecutively wash and filter the carbon black samples to liberate them from soluble Be-7. Approx. 0.3 mg of the purified test items were intratracheally instilled to lungs of Wistar rats. This dose avoided a particle overload effect, thus, the toxicokinetic fate of the test item could be followed under physiological conditions of lung clearance. A total of 8 females (4 rats: feces/urine, organs; 4 rats: blood kinetics) and 4 males (lungs, liver, kidney, reproductive organs) were analysed. - In feces, Be-7 Monarch® 1000 and Be-7 Printex® 90 was detected in the first 3 days after treatment at significant levels, i.e. 17.6% and 8.2%, resp. In urine, small percentages of 6.7% and 0.4 were observed. In blood the test item was not detected at relevant levels. At day 20 post-instillation, upon necropsy, both test items were practically exclusively found in lungs (75.1% and 91.0%, resp.) Approx. 0.5% were detected in the lung-associated lymph nodes, however, the test items were not detectable in other organs/tissues. Separation of leukocytes and cell-free supernatant of a broncholaveolar lavagate by centrifugation revealed that the Be-7 Printex® 90 activity was completely located in the cell sediment indicating total engulfment by alveolar macrophages. - Approx. 0.3 mg of Be-7 Monarch® 1000 and Be-7 Printex® 90 were administered to rats by oral gavage. Within 3 days post-treatment 98% and 99% of the retained doses were detected in feces. - In conclusion, the results of both administration modes indicate that the two carbon black grades acted as microscaled agglomerates, not as nanosized aggregates, and displayed no potential for translocation. In the instillation study besides lungs, Be-7 Printex® 90 and Be-7 Monarch® 1000 were detected at very small amounts only in LALN; this finding is consistent with the behaviour of poorly soluble particles. Overall, carbon black was not systemically available after deposition in lungs or stomach.

3659 Fate of Gold and Silver Nanoparticles in Organs after Subacute Co-inhalation Exposure to Gold and Silver Nanoparticles of Similar Sizes

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The toxicokinetics of nanomaterials, including studies on the absorption, distribution, metabolism, and elimination (ADME) of nanomaterials, are essential in assessing their potential health effects. The fate of nanomaterials after inhalation exposure to multiple nanomaterials is not clearly understood. Male Sprague-Dawley rats were exposed to similar sizes of silver nanoparticles (AgNPs, 10.86 nm) and gold nanoparticles (AuNPs, 10.82 nm) for 28 days (6-hr/day, 5-days/week for 4 weeks) either separately or combined using a nose-only inhalation system. The mass concentrations sampled from the breathing zone were AuNP 19.34 ± 2.55 μg/m^3 and AgNP 17.38 ± 1.88 μg/m^3 for the separate exposure and AuNP 8.20 μg/m^3 and AgNP 8.99 μg/m^3 for the co-exposure. The lung retention and clearance were previously determined on exposure day 1 (E-1, 6-hr) and on post-exposure days 1, 7, and 28 (PEO-1, PEO-7, and PEO-28) (Kim et al., 2021). In addition, the fate of the nanoparticles, including their translocation and elimination from the lungs to major organs, was determined during the post-exposure observation period. After subacute inhalation, the AuNP translocation to extrapulmonary organs included the liver, kidneys, spleen, testes, epididymis, olfactory bulb, hilar and brachial lymph nodes, and brain (is that cerebrum and cerebellum, or cerebrum only?) and showed biopersistence, regardless of single exposure or co-exposure, with similar retention half-times. In contrast, the tissue translocated tissue Ag was rapidly eliminated, regardless of single or co-exposure, except for continual accumulation in the olfactory bulb and brain that persisted until PEO-28. This co-exposure study of AuNPs and AgNPs indicated that soluble AgNPs and insoluble AuNPs translocate differently, probably due to soluble AgNPs being dissolved into Ag ions when translocating to extrapulmonary organs where they were rapidly removed from most of them, except for the brain and olfactory bulb. In contrast, the insoluble AuNPs were continually translocated to extrapulmonary organs and not rapidly eliminated.

3660 Effect of Inhalation Exposure to Cellulose Nanocrystals on Reproductive Outcomes of Male Mice

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Crystalline nanocelluloses (CNC) have good electrical, optical, and mechanical properties which make them desirable for industrial applications. We investigated adverse reproductive outcomes due to inhalation exposure to CNC aerosol, generated from a bulk supply of wood pulp derived cellulose nanocrystals. C57BL6/J male mice were exposed to precise concentration of airborne CNC (5 mg/m^3, 5 h/day, 5 days/week for 1st and 2nd week and 4 days/week for 3rd week). Cauda epididymal sperm samples, testes and serum were collected to evaluate sperm alterations, oxidative stress, changes in the hormonal levels and inflammatory cytokine responses and perform testes histopathology at 24 h, 2-, 6- and 12-months post exposure. CNC inhalation significantly elevated abnormality in sperm heads and tail/mid-piece as well as reduced the number of motile sperm at all time points of recovery. Sperm DNA integrity assessed as DNA fragmentation index was significantly elevated only 24h post CNC inhalation and then reduced to the air-control level. Interstitial edema and occasional dystrophic seminiferous tubules with arrested spermatogenesis and degenerating spermatocytes were found in testes 6- and 12-month post inhalation while no changes were seen at the early time points. CNC inhalation produced significant imbalance in the levels of testosterone (throughout the recovery time of 2-12 month) and luteinizing hormone (only at 12-month post exposure). Assessment of testicular oxidative damage showed significantly higher amounts of protein carbonyls at all time points of recovery. A hierarchical cluster analysis of 23 cytokines/chemokines/growth factors of the testes separated inflammatory cytokines (G-CSF, IL-6, IL-12p70 and MIP-1α) and revealed patterns that differentiate early responses from later time points. Serum cytokines at the later time points clustered together in the close proximity to the 24h acute response. Overall, these results demonstrate that CNC inhalation exposure induces sustained male reproductive toxicity observed up to 12 months of recovery.

3661 Preliminary Report of the Two-Year, Every Four-Week-Interval Intermittent Whole Body Inhalation Study of the Multiwalled Carbon Nanotube in Male Mice

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In a whole-body inhalation toxicology study on gaseous test substance, the lungs are exposed to a same concentration throughout the study. In contrast, in a particulate matter inhalation study, especially when the particle is biopersistent, and concentration of the aerosol of the particle is constant throughout the inhalation study, the lung burden or the amount of the perticle deposited in the lung gradually increases over time, from zero to a certain amount at the end of the study. If the lung toxicity is induced by the deposited particles, the particulate matter inhalation gives small effects at the beginning and larger effects towards the end of the study. If compared with the study of gaseous test substance, the particulate matter study has half of the "area under the curve (AUC)" of the lung tissue concentration-time curve. We started a project to seek for the experimental conditions to make the lung burden constant during the two-year period by boosting it at the beginning of the study followed by intermittent maintenance exposure. In order to compare lung conditions with the conventional protocol, we first initiated a 4-week intermittent exposure 2-year inhalation study without initial boost, mimicking the increment of lung burden of the rat study reported by Kasai et al., 2016. Male C57BL/6 mice were exposed to 53 micrometer mesh-filtered Mitsui MWNT-7 aerosol by Taquann system (J. Toxicol. Sci. 2013) at the mass concentrations of 2.6±0.1 and 5.0±0.1mg/m3, 6 hours per day, once every 4 weeks. MMAD was ca. 500 nm. Here, we report the finding of 24 months preliminary data. Average lung weight of control, low and high dose groups were 165.6±8.8 microgram, 336.2±25.2 microgram, and 369.4±25.5 microgram, respectively. Histologically, advanced precipitation of MWNT-7 with chronic granulomatous foreign body responses and fibrosis in a form of respiratory bronchiolitis was observed along with terminal bronchial epithelial proliferative changes were observed. Lymphatics and pleural inflammatory/fibrotic lesions were also observed. At least two epithelial neoplasms were identified in the low dose group. Further details will be presented. *Health and Labour Sciences Research Grant, Japan.*

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