ANNEX TO EXPERT STATEMENT

The human relevance of the observed lethality of Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide (called Silanamine by RAC) (CAS # 68909-20-6) in acute toxicity testing using inhalation exposure in rats

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Main differences in the nasal anatomy of rat compared to human (see ref. 3)

- Absent atrioturbinates in human whilst present in rat
- No nasoturbinate present in human but in rats
- No septal windows in human but present in rats
- No nasopalatine duct in adult human whilst present in rats
- 4 paranasal sinuses in human, but only 1 in rats
- No transverse lamina and olfactory recess in human but present in rats.

Issues with deposition of inhaled particles

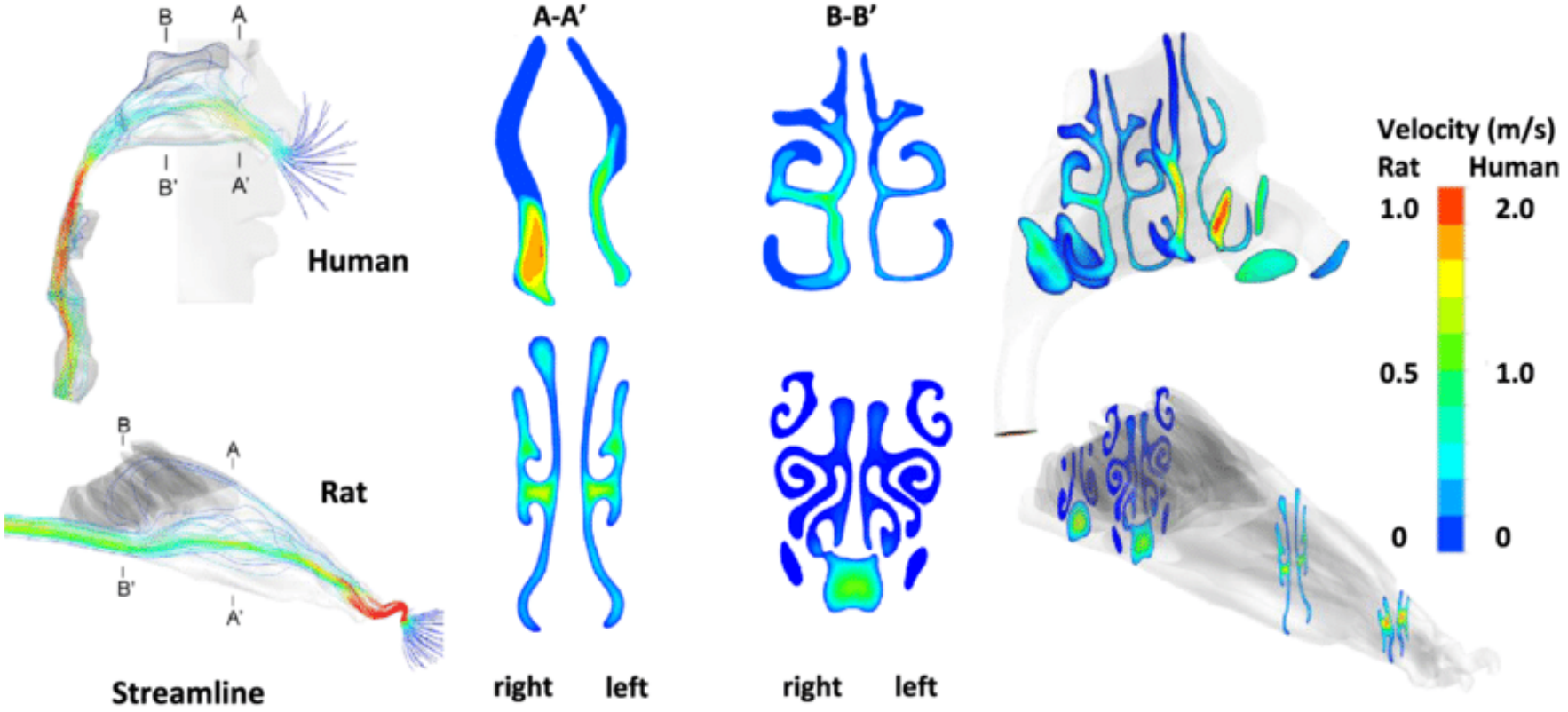
Regional deposition dose of inhaled nanoparticles in a human and rat olfactory region depend on particle size and breathing rate. Regional deposition of nanoparticles in human and rat nasal cavity is extremely low, with the highest deposition (< 3.5 and 8.1%) related to high diffusivity particles of 1.5 nm and 5 nm, respectively. There is significant filtering of extremely small particles (< 2 nm) by abrupt sharp turns at front of the rat nose. Only a small portion of inhaled nanoparticles reaches the rat olfactory region when compared to human (1.25 to 45%). However, for larger nanoparticles (> 3 nm), a significantly higher percentage of reaches rat nasal olfactory region (2 to 32 folds [1]).

Main differences in anatomy of the lower airways in rat compared to human

- Rodents have a monopoidal branching of the airways, whereas primates have a bipodal-tripodal branching;
- There is significantly more heterogeneity in the alveolar duct branching pattern within the alveolar region in rats;
- Within the alveolar duct system of the rat, the branching system is complex, with as few as 3 and up to 13 branches contained in a single ventilatory unit (ventilatory unit is defined to be the collection of alveoli and alveolar ducts distal to a single bronchiolar-alveolar duct junction).

- The alveolar duct branching system of the rat is so complex in three dimensions that multiple branches may occur within the distance of a single alveolus, which for the rat is only about 100 pm;
- The size of the average ventilatory unit increases only about 5- to 10-fold from rodent to primate;
- A ventilatory unit is typically about 17.5 alveolar diameters in size. However, there are significant differences in ventilatory unit volume within a given species, e.g., among the 140 rat ventilatory units studied, luminal gas volume varied from 0.2 to 3.4 mm3 due to differences in the number of alveoli in each ventilatory unit, as determined by morphometric analyses of vascular per fusion fixed lungs;
- Allometric studies of alveolar size have been conducted for mouse, rat, rabbit, and human lung. A scaling factor of 0.53 was found to relate increases in the number of alveoli per lung with increasing body weight [2].
- The volume of reactive macrophages may fill the alveolar volume in a rat completely. This is not the case in human, i.e., the volume of macrophage in humane may reach the same size, however, the alveolar volume is higher. A possible inhalation of particles into the lower airways of human would therefore cause activation of macrophages and exhalation by coughing.

The above-mentioned facts result in a different distribution of a test item within the lungs. The alveolar lumen is larger in human. Involved cells are differently distributed. Coughing off material from lower airways is easy for human but not for rats.



Sample cross sections of nasal and olfactory channels in rats and humans including predicted airflows [1]

References

[1] Tian L, Shang Y, Chen R, Bai R, Chen C, Inthavong K, Tu J. Correlation of regional deposition dosage for inhaled nanoparticles in human and rat olfactory. Particle Fiber Toxicol. 2019. 16:6. https://doi.org/10.1186/s12989-019-0290-8

[2] Miller FJ, Mercer RR, Crapo JD (1993). Lower Respiratory Tract Structure of Laboratory Animals and Humans: Dosimetry Implications. Aerosol Sci Tech 18: 257-271.

[3] Chamanza R, Wright JA. A Review of the Comparative Anatomy, Histology, Physiology and Pathology of the Nasal Cavity of Rats, Mice, Dogs and Non-human Primates. Relevance to Inhalation Toxicology and Human Health Risk Assessment. J Comp Pathol. 2015 Nov;153(4):287-314.