

ORAL TWO-GENERATION REPRODUCTION STUDY WITH NM-200 SYNTHETIC AMORPHOUS SILICA IN WISTAR RATS

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INTRODUCTION

Nanomaterials form an important class of technological materials that have numerous novel and useful properties. The expected growth in production and use of such materials increased the likelihood of human and environmental exposure. Current test guidelines on developmental and reproductive toxicity are generally able to determine hazards but their specific application to nanomaterials needs to be evaluated.

In this project, standard OECD test methods (OECD guidelines 414 and 416) were applied for nanomaterials hazard testing and necessary modifications and supplementations to these tests will be recommended.

The results of the prenatal developmental toxicity with NM-200 synthetic amorphous silica, performed at the BASF laboratories, are presented separately.

MATERIALS AND METHODS

In the present two-generation study, 28 male and 28 female Wistar Han rats per group were treated by oral gavage with NM-200 Synthetic Amorphous Silica particles (supplied by Joint Research Centre, Italy) at dose levels of 0, 100, 300 and 1000 mg/kg body weight/day for two consecutive generations. The silica particles were tested 'as is' and aggregates were not artificially broken down and analysed by Dynamic Light Scattering (DLS) and once by analytical ultracentrifugation (AUC).

Body weight and food consumption were measured throughout the entire study. Reproductive- (including estrus cycle evaluation and sperm analysis) and developmental- (including sexual maturation) parameters were measured. At sacrifice (reproductive) organs and tissues were sampled for histopathology and silica distribution measurements.

RESULTS

Analysis of the NM-200 Synthetic Amorphous Silica dispersions showed agglomeration of particles (up to 1600 nm). No effects were observed on body weights and food consumption, reproductive parameters (Table 1), organ weights (Table 2), sperm parameters, estrous cycle, pup weights, sexual maturation parameters (Table 3).

F0-generation	Control	Low dose	Mid dose	High dose
	0 mg/kg BW	100 mg/kg BW	300 mg/kg BW	1000 mg/kg BW
Mating index (%)	100	100	100	100
Female fecundity index (%)	100	100	96	96
Female fertility index (%)	100	100	96	96
Gestation index (%)	100	96	100	100
Pups delivered (per litter)	10.26 ± 0.55	10.71 ± 0.44	11.33 ± 0.38	11.00 ± 0.28
Stillborn pups (%)	3.2	2.0	4.2	1.3
Pup viability index day (%)	93	94	92	98
Post implantation loss (%)	8.6 ± 2.6	10.5 ± 3.7	9.5 ± 2.5	10.1 ± 2.5

Table 1: Reproductive parameters of the F0-generation. Data from the F1-generation are not yet available.

Males	Terminal body weight	Brain	Epididymes	Kidneys	Liver	Pituitary	Prostate	Seminal vesicles	Spleen	Testes	Thyroid
Control	406.2	2.043	1.201	2.363	12.021	0.016	1.001	1.326	0.741	3.484	0.025
Low dose	397.0	2.037	1.218	2.348	11.434	0.016	0.946	1.269	0.640	3.565	0.025
Mid dose	400.5	2.058	1.276	2.336	11.823	0.016	1.003	1.275	0.661	3.588	0.025
High dose	400.3	2.050	1.242	2.377	11.774	0.015	0.966	1.276	0.665	3.542	0.026

Females	Terminal body weight	Brain	Kidneys	Liver	Pituitary	Prostate	Seminal vesicles	Spleen	Testes
Control	275.5	1.873	1.841	12.448	0.096	0.016	0.625	0.020	0.523
Low dose	274.7	1.892	1.843	12.529	0.094	0.015	0.606	0.020	0.608
Mid dose	274.9	1.886	1.823	12.531	0.098	0.015	0.623	0.020	0.611
High dose	277.7	1.877	1.806	12.942	0.089	0.016	0.596	0.020	0.545

Table 2: Absolute organ weights (grams) of male and female F0-generation animals (Control 0 mg/kg body weight; Low dose 100 mg/kg body weight; Mid dose 300 mg/kg body weight; High dose 1000 mg/kg body weight (N = 28))

Sexual maturation	Control	Low dose	Mid dose	High dose
	0 mg/kg BW	100 mg/kg BW	300 mg/kg BW	1000 mg/kg BW
Testes descending	26.18 ± 0.30	26.36 ± 0.30	25.71 ± 0.30	25.89 ± 0.35
Preputial separation	43.46 ± 0.30	44.29 ± 0.70	44.29 ± 0.58	45.29 ± 0.82
Vaginal opening	35.21 ± 0.56	35.36 ± 0.90	35.21 ± 0.55	35.57 ± 0.52

Table 3: Sexual maturation parameters of F1-generation pups.

CONCLUSION

Oral administration of NM-200 synthetic amorphous silica had no effect on reproductive performance of Wistar rats and on the development of the offspring. The systemic distribution of the silica particles will be studied in various 'route-of-administration' organs. Measuring uptake and organ burdens could be a valuable addition to OECD standard test guidelines when applied to the hazard assessment of nanomaterials.

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