P-233

鼻部吸入暴露処置の雌性ラットの性周期に及ぼす影響

○平嶋 昂, 涌生 聖, 佐藤ゆかり, 大竹 誠司 株式会社LSIメディエンス 創薬支援事業本部 試験研究センター 鹿島安全性第1研究部

Effect of nose-only inhalation exposure on estrous cycle in female rats

OTakashi Hirashima, Kiyoshi Wako, Yukari Sato, Seiji Ootake Kashima Safety Assessment Department A, Nonclinical Research Center, Drug Development Service Segment, LSI Medience Corporation

E-mail: hirashima.takashi@ma.medience.co.jp

Objective

Reproductive toxicity studies are widely conducted to evaluate effects of medicines and chemicals on reproductive performance. Nose-only inhalation exposure is one of the dosing routes in reproductive toxicity studies of inhalation medicines and/or volatile chemicals. We have observed prolonged estrous cycles by nose-only inhalation exposure in reproductive toxicity studies in rats. An altered estrous cycle returned to the pre-exposure period cycle during the exposure period. This result suggests that animals may acclimatize to the effects of nose-only inhalation exposure on estrous cycle. Restraining during nose-only inhalation exposure causes stress in animals but is an essential operation. Stress is a well-known factor that affects the estrous cycle. The purpose of this study was to obtain basic data that may help in the performance of reproductive toxicity studies by nose-only inhalation exposure in rats.

Materials and Methods

-Test system

Crl:CD(SD) rats, female, 8 weeks of age (confirmed with estrous onset)

Nose-only inhalation exposure

Flow-past type nose-only inhalation exposure chamber

Clean air, 6 hours/day, 7 days/week, 28 days

Observation and measurements

Clinical observation: Before and after exposure

Body weight: Once a week

Estrous cycle:

From 14 days before exposure to the end of a 28-day exposure period

Once every morning, vaginal smear, eosin/thionin staining,

4 phases (diestrus, proestrus, estrus, and metestrus)



←	←		Monitoring of Estrous Cycle							
L	Pre-Exposure			Nose-Only Inhalation				ure		
-14	-7	7	1		7	14	2	1	28	(Days)

E

Results

Fig. 1 Estrous cycle from 14 days before exposure to the end of a 28-day exposure period Pre-exposure Exposure period 25 | 26 23 24 27 | 28 19 20 22 50102 50103 E E 50104 50105 Ε Ε Ε Е Ε Ε 50109 50110 Ε 50111 50112 Ε E 50114 Ε 50116 Ε 50117

50120 E Е Prolonged estrous cycle from 4-day cycle, E: Estrous, : 4-day cycle : 5-day or more cycles

Fig.1, 2 Nine of 15 animals indicated prolonged estrous cycle from 4-day cycle during exposure period. Few animal indicated 8- to 12-day cycles. Returning to 4-day cycle was observed in 4 animals within 2 weeks of exposure and in 1 animal within 3 weeks of exposure.

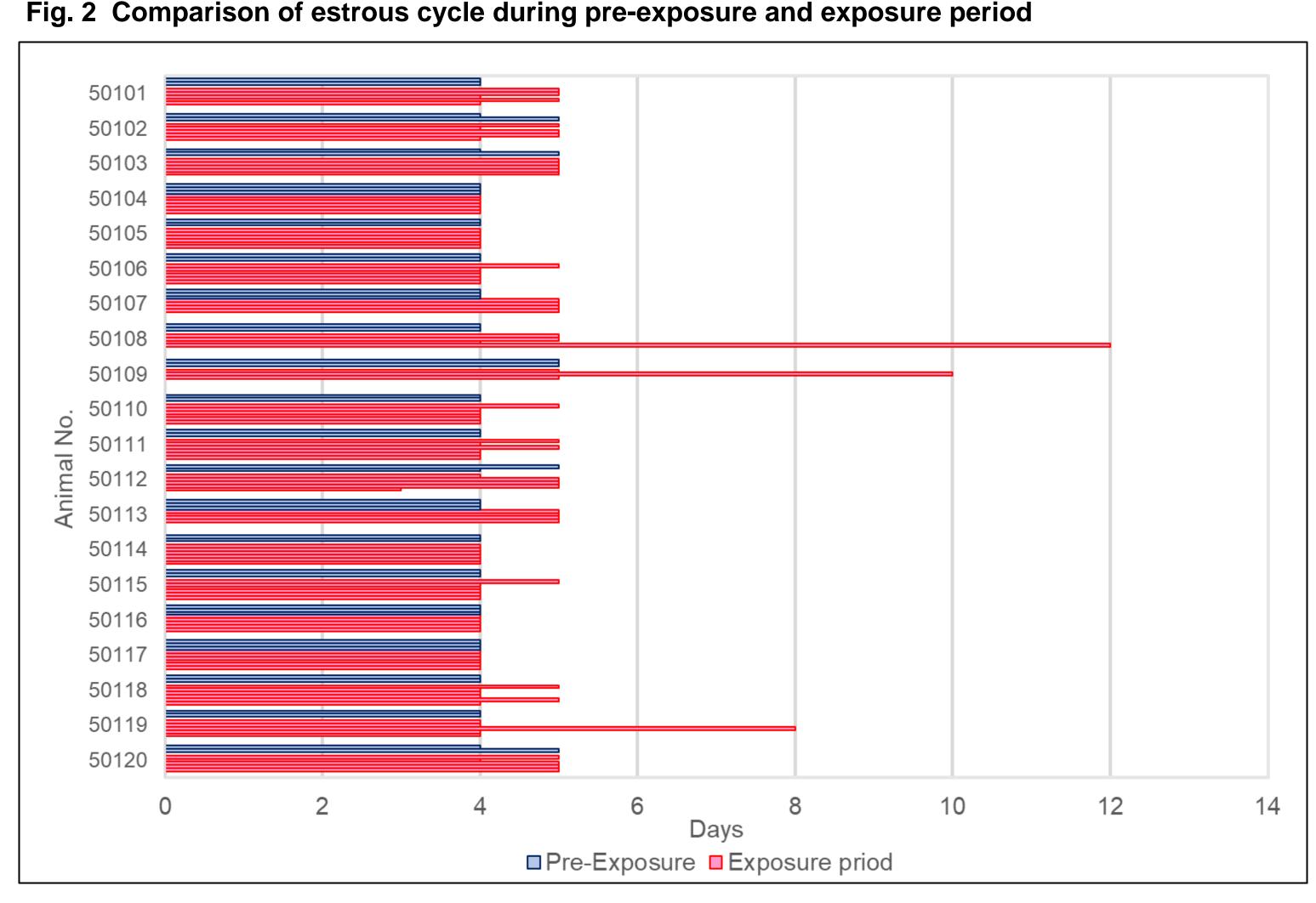


Fig. 3 Body weight

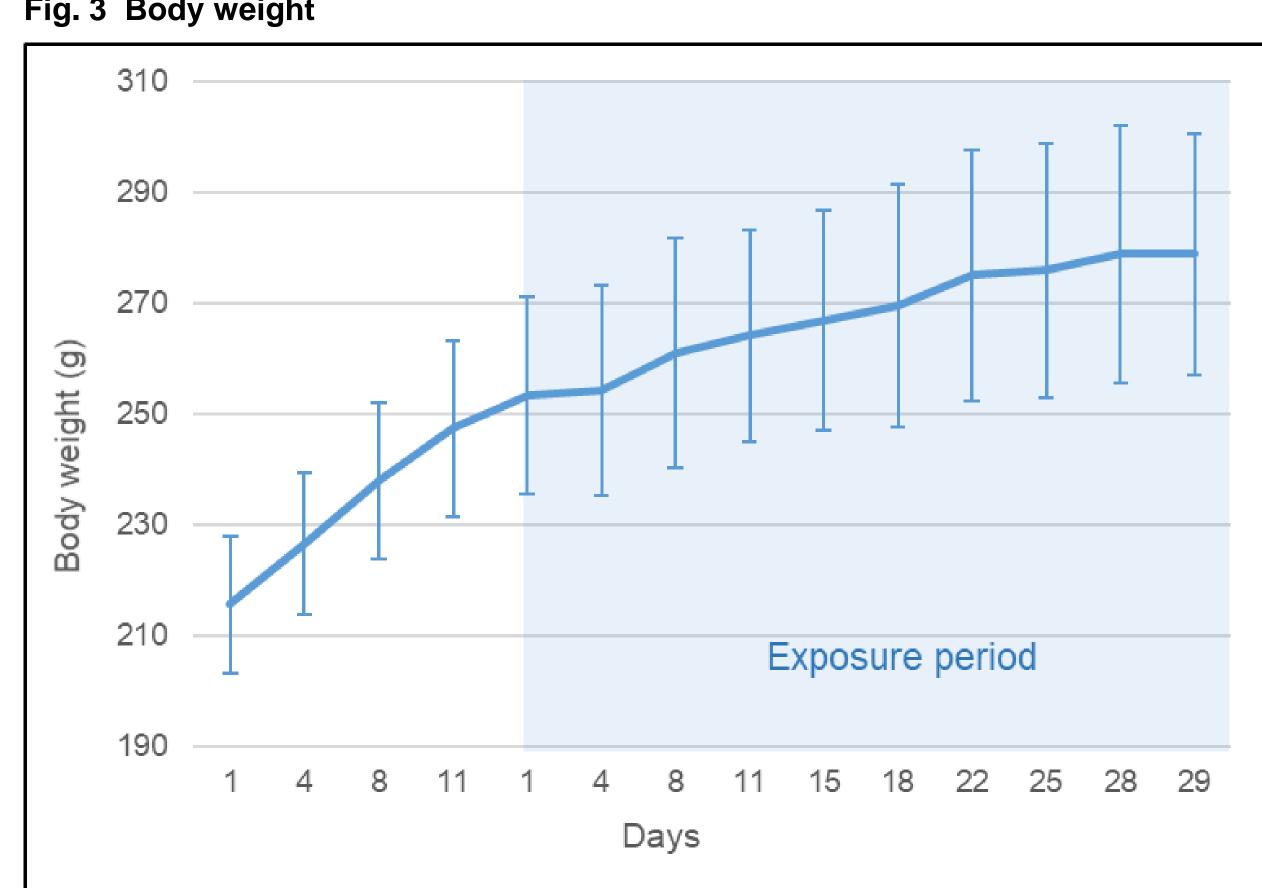


Fig.3 The body weight gain was suppressed at the initiation of exposure. The body weight was increased over the entire exposure period. No abnormalities in clinical signs were observed in any animal.

Discussion

This study clarified that operation of nose-only inhalation exposure affected the estrous cycle. Since it is well known that stress affects the estrous cycle, the alteration of the estrous cycle in this study was considered to be the result of the stress caused by restraint with a restraint tube during nose-only inhalation exposure. Approximately half of the females that indicated prolonged estrous cycle returned to normal estrous cycle within 2 or 3 weeks of the exposure period. Moreover, abnormal estrous cycle was observed only 3 of 20 animals. These results suggest that female SD rats acclimatized to the stress by restrainer for nose-only inhalation exposure within 2 or 3 weeks.

For the next examination, we would like to examine the effects of estrous cycle change by nose-only inhalation exposure on the days required until copulation, copulation index, and fertility index, and the effects of acclimation to stress caused by nose-only inhalation on the above factors.