

# Publication

## Ventilatory function assessment in safety pharmacology: Optimization of rodent studies using normocapnic or hypercapnic conditions.

S. Goineau, S. Rompion, P. Guillaume and S. Picard.

*Toxicol. Appl. Pharmacol.*, 247, 191–197, 2010.

<http://www.ncbi.nlm.nih.gov/pubmed/20600212>

### *Abstract*

Although the whole body plethysmography for unrestrained animals is the most widely used method to assess the respiratory risk of new drugs in safety pharmacology, non-appropriate experimental conditions may mask deleterious side effects of some substances. If stimulant or bronchodilatory effects can be easily evidenced in rodents under standard experimental conditions, i.e. normal air breathing and diurnal phase, drug-induced respiratory depression remains more difficult to detect. This study was aimed at comparing the responsiveness of Wistar rats, Duncan Hartley guinea-pigs or BALB/c mice to the respiratory properties of theophylline (50 or 100 mg/kg p.o.) or morphine (30 mg/kg i.p.) under varying conditions (100% air versus 5% CO<sub>2</sub>-enriched air, light versus dark day phase), in order to select the most appropriate experimental conditions to each species for safety airway investigations. Our results showed that under normocapnia the ventilatory depressant effects of morphine can be easily evidenced in mice, slightly observed in guinea-pigs and not detected in rats in any day phase. Slight hypercapnic conditions enhanced the responsiveness of rats to morphine but not that of guinea-pigs and importantly they did not blunt the airway responsiveness of rats to the stimulation and bronchodilation evoked by theophylline, the most widely used reference agent in safety pharmacology studies. In conclusion, hypercapnic conditions associated with the non-invasive whole body plethysmography should be considered for optimizing the assessment of both the ventilatory depressant potential of morphine-like substances or the respiratory stimulant effects of new drugs in the rat, the most extensively used species in rodent safety and toxicological investigations.