An assessment of dependence potential is required for new CNS-active substances since the adoption of the guideline on non-clinical dependence investigation by EMEA in 2006 [1, 2]. One of the tests recommended in the guidelines is the Drug Discrimination (DD) test. The more used method is done in a Skinner box, the animal will have to discriminate between the test item and the vehicle by pressing on different levers. The limitation of this method is that several months are needed to evaluate a substance. The purpose of this study was to develop an optimised method, i.e. a test with a reduced duration and good predictability and robustness.

DD test is based on the comparison of the stimulus effect induced by a new drug and the stimulus effect induced by a well know dependency inductor drug. If the stimuli are similar, the animal will adopt the same behaviour when dosed with the New Chemical Entity (NCE) as with the training drug suggesting a dependency induction. For the DD apparatus, a device with 2 compartments with an electrified floor, derived from our device used for the Conditioned Place Preference test which allows detection of reinforcing properties of cocaine in 5 days [3] and by the device described by Torbjörn [4]. In a first phase the animal is conditioned to the training drug (cocaine), i.e. the animal has to go to the drug compartment when dosed with cocaine and in the vehicle compartment when dosed with saline. In a second phase, NCE is tested. If the NCE induces a similar feeling compared to the training drug then the animal will go into the drug compartment.

### Material and methods

**Animals:** Male Wistar rats, 200-250g (Dépré breeding centre, France).

**Apparatus:** A device with 2 compartments, separated by a transparent wall, one dedicated to the drug and the other one to the vehicle, was used. The floor was electrified. A white tube was placed in the vehicle compartment and a white box in the drug compartment (see Figure 1).

**Experimental procedure:** the test was done in 2 steps:

**Training phase:** the objective is that the animal discriminates between saline and cocaine (5 mg.kg, i.p): 10 animals were included in the study. Each animal was dosed 2 times per day for 5 days per week according to a predefined planning (see Table 1).

15 min after each i.p. injection, the animal was put in the vehicle compartment. Ten seconds later a sound signal was activated. Two seconds later, if the animal was in the correct compartment, no electric shock was delivered. If the animal was in the wrong compartment, an electric shock was given in order that the animal went to the correct compartment. Three trials were done per session.

When the performance criterion was established, i.e. 80% of good responses, the evaluation with the NCE was started.

**Testing phase:** the objective is to identify if the NCE induces a similar behaviour to cocaine: the animal was dosed with the vehicle or the NCE and put in the tube compartment. Ten seconds after the sound signal was activated, the position of the animal was noted 2 s later. Only one trial was done per session. The test sessions were interspersed in training sessions to confirm that the animal was always able to discriminate between cocaine and saline.

### Results

At the beginning of the test 10 rats were included; after 22 days of training, the performance criteria, i.e. 80% of good answers was achieved with 6 rats. Two rats were removed over the first days because they refused to stay in the arena. The 2 other ones were removed from D8 because of their low performance. 80% of good answers were achieved quickly for the vehicle, around D13. For cocaine 2 consecutive days with a satisfactory performance was achieved from D22.

Amphetamine was tested as increasing doses at 0.3 and 1 mg.kg, i.p. Amphetamine at 1mg.kg is discriminated as being similar to cocaine. Test sessions with amphetamine were interspersed in training sessions to confirm that the animals were always able to discriminate cocaine and saline.

Morphine was tested as increasing doses from 1 up to 10 mg.kg, i.p. Morphine did not share cocaine discriminative stimulus effects. Results obtained with the vehicle and cocaine were satisfactory showing that the animals were always able to discriminate between cocaine and saline.

### Conclusion

These first results suggest that the method is sensitive enough to detect any drug discrimination paradigm. The main advantage is the short duration of the evaluation: about 6 weeks.

### References

1. CHMP/EMEA, Guideline on the non-clinical investigation of the dependence potential of the medical products, 2006
3. Psychological dependence assessment using Conditioned Place Preference (CPP) test in the rat, poster, SPL, 2009
5. Self Administration in cynomolgus monkeys (Macaca fascicularis), poster, SPL, 2010