An original method to interpret neurobehavioral data generated by the Irwin test in the mouse

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The Irwin test is a systematic observational procedure for assessing and scoring the effects of drugs on the behavioral and physiological state of rodents. This method described by Irwin (1962, 1968) [1] is part of the safety pharmacology core battery recommended by the ICH (International Committee for Harmonization) to detect potential adverse effects of candidates on the central nervous system (CNS) before human testing. When applied at an early stage of drug development, this test is particularly suitable to: a) screen and select compounds against unwanted CNS effects, b) understand the mechanisms underlying these effects, c) help improving the structure-activity relationship, and d) possibly, reveal novel therapeutical effects. By using an appropriate dose range for each test molecule, it is possible to obtain information on its pharmacological profile, on the intensity and the duration of its effects, and on the specificity of these effects ("on- or off-target" effects). At UCB Pharma, we refined the original Irwin test to better fit to the 3R's rules, by reducing the number of animals per dose, and by avoiding too high doses which could induce severe signs or lethality. NMRI mice of around 20 g receive the test compound by intraperitoneal route (n=3 per dose) and are observed at 0, 5, 15, 30, 60 and 120 minutes after drug administration. At each observation time, 53 parameters are scored using a rigorous standardized procedure based on that described by Irwin, 1968. These parameters are distributed as followed: 15 items for the behavioral profile, 21 items for the neurological profile and 17 items for the autonomic profile. A minimal active dose can be determined for each parameter. The originality of our interpretation of the data, collected as scores, is that some of them (36 items) are categorized into 5 fundamental activities: Central Activity (CA), Central Reactivity (CR), Neurovegetative Reflexes (NR), Neuromotor Tonus (NT), and Autonomic System (AS). A large set of reference substances, reflecting a large panorama of different pharmacological activities, were screened in this Irwin test. After a close scrutiny of the affected behavioural parameters with these reference substances, we developed an algorithm for the interpretation of their effects (increase or decrease) on the 5 "fundamental" systems (CA, CR, NR, NT and AS). Each new substance tested with unknown target, affecting some of the 53 items, can be submitted to the algorithm, in order to identify its physiological and pharmacological activities, and compare its profile with that of products already known.

References

1. Irwin, S. (1968). Comprehensive observational assessment: Ia. A systematic, quantitative procedure for assessing the behavioral and physiological state of the mouse. *Psychopharmacologia (Berl.),* **13,** 222-257.

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