# This Week's Citation Classic ®

**Janssen P A J, Niemegeers C J E & Dony J G H.** The inhibitory effect of fentanyl and other morphine-like analgesics on the warm water induced tail withdrawal reflex in rats. *Arzneim.-Forsch.—Drug Res.* 13:502-7, 1963.
[Research Laboratorium Dr. C. Janssen, Beerse, Belgium]



A new assay for the study of morphine-like analgesics, the warm water induced tail withdrawal reflex in rats, is described in detail Based on the results obtained in this relatively simple test with a large number of well-known narcotic analgesics, the intensity, onset, peak, duration of action, and safety of the new narcotic fentanyl was predicted [The *SCI* ® indicates that this paper has been cited in more than 315 publications.]


## New Assay for the Most Popular Narcotic Analgesic


**Paul A.J. Janssen and**
**Carlos J.E. Niemegeers**
**Janssen Research Foundation**
**Turnhoutseweg 30**
**B-2340 Beerse**
**Belgium**


The evaluation of opiate-like analgesics in the early 1960s was mostly performed using a classical test in mice, introduced by N.B. Eddy: inhibition of paw licking on a hot plate. With the introduction of neuroleptics, the hot plate test could no longer be considered a specific test for opiate-like analgesics since chlorpromazine and haloperidol inhibited the licking reflex at lower doses than morphine and meperidine.[1] The development of a simple, specific, and harmless test for analgesia in rats could greatly improve predictions on clinical effectiveness and safety of narcotic analgesics, particularly for their use in anesthesia. Exposure of the distal part of the rat's tail to water at a constant temperature of 55° C was found appropriate. Tail withdrawal in untreated rats usually occurs within two to four seconds. Even with doses of narcotics, producing surgical analgesia, repeated measurements do not cause damage of the tail, because contact time is deliberately limited to 10 seconds. Using this method, reliable results were obtained for intensity, onset, peak, duration of action, and safety of fentanyl and other well-known morphine-like analgesics.

Because fentanyl respects cardiovascular and autonomic stability, it became the most widely used narcotic in anesthesia, either as a mono-anesthetic or in combination with droperidol (dehydrobenzperidol) in neuroleptanalgesia. Today the worldwide interest in fentanyl is reflected in more than 10,000 scientific publications. This paper could thus have been cited for the description of fentanyl's effectiveness and safety. The tail withdrawal reflex, however, also was the basic test for more recently developed narcotics, such as carfentanil,[2] sufentanil,[3] and alfentanil.[4] Carfentanil, the most potent analgesic known, has been selected for veterinary use, more specifically for the immobilization and care of wild animals. Alfentanil and sufentanil were developed because the requirements in anesthesia for maximal safety and comfort of the patient, as well as for minimal postoperative complications, called for a more extended range of potent safe analgesics. Both compounds were developed to increase the flexibility of use and to cover the wide range of surgical interventions from very short (alfentanil) and minor to very long and severe (sufentanil). Using the tail withdrawal reflex in rats, narcotic analgesics were developed with a wide range of applications in surgery and care of animals and man.


1. Janssen P A J, Van de Westeringh C, Jageneau A H M, Demoen P J A, Hermans B K F, Van Daele G H P, Schellekens K H L, Van der Eycken C A H & Niemegeers C J E. Chemistry and pharmacology of CNS depressants, related to 4-(4-hydroxy-4-phenyl-piperidine) butyrophenone Part I Synthesis and screening data in mice. *J. Med. Pharmaceut. Chem.* 1:281-97, 1959 (Cited 135 times.)
2. Stanley T H. New developments in opioid drug research for alleviation of animal pain *J. Amer. Vet. Med. Assn.* 191:1252-3, 1987
3. Niemegeers C J E, Schellekens K H L, Van Bever W F M & Janssen P A J. Sufentanil, a very potent and extremely safe intravenous morphine-like compound in mice, rats and dogs *Arzneim.-Forsch.—Drug Res.* 26:1551-6, 1976 (Cited 60 times)
4. Niemegeers C J E & Janssen P A J. Alfentanil (R 39 209), a particularly short acting intravenous narcotic analgesic in rats. *Drug Develop. Res* 1:83-8, 1981 (Cited 60 times)



Received October 30, 1990