

Suggestion for an international nonproprietary name for each of the above-named drugs will be submitted at a later date.

EXHIBIT B

(This letter is from Mr. Anslinger, U.S. Commissioner of Narcotics to WHO. Dr. Eddy's study is attached.)

There are enclosed two copies of reports on the above-named drugs (identified as Enclosures A to E respectively) submitted by Dr. Nathan B. Eddy of the National Institutes of Health, United States Public Health Service, Bethesda, Maryland, U.S.A.

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Representative of the United States on
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United Nations.*

Enclosures.

ADDICTION LIABILITY OF ALPHA-4-DIMETHYLAMINO-1,2-DIPHENYL-3-METHYL-4-
PROPIONYLOXYBUTANE (LILLY 16298, PROPOXYPHENE)

A. EFFECTS OF SINGLE DOSES IN NONADDICTED PATIENTS

Since this drug is very irritating, only the oral route was used. The compound was administered in single doses to 13 nontolerant former addicts in doses ranging between 50 to 400 mg. Table I shows the results of 25 trials. It is evident that this compound is fairly inert. Even the two subjects who were given a dose of 200 mg. at 8:30 a.m. followed by 400 mg. at 9:00 a.m., said "It is like water," although both complained of a slight headache. One subject who received 150 mg. one week and 200 mg. the following week, complained of diarrhea on both occasions.

B. SUPPRESSION OF SYMPTOMS OF ABSTINENCE FROM MORPHINE

Eleven subjects who had been stabilized in 240-280 mg. of morphine daily were given a total dose of 1200 mg. of No. 16298 during the first 24 hours after abrupt withdrawal of morphine. The drug was administered orally, in doses of 200 mg. at intervals of four hours, except at night when the interval was six hours. In a similar study using the same patients, the dose was increased to a total of 2400 mg. given in divided doses of 400 mg. In a control experiment, the same subjects were given placebo capsules which resembled the No. 16298 capsules on a comparable schedule.

In a positive control experiment, nine of these 11 subjects were given morphine injections on a four-hour schedule and they were informed only that another compound was being tested. The results of this experiment with the 400 mg. dose of No. 16298 (2400 mg. in 24 hours) are illustrated in Figure 1. Intensity of abstinence was reassured by the Himmelsbach scoring system, beginning at the 14th hour of abstinence and continuing at hourly intervals to the 24th hour. The figure illustrates that when morphine was given the score fluctuated between 3 to 8 points. When placebo injections were given instead of morphine the intensity of abstinence rose to 30 points at the end of 24 hours. When No. 16298 was administered in doses of 400 mg., every four hours, the intensity of abstinence was significantly reduced beginning with the 14th hour and continuing through the 24th hour. Two of 9 subjects to whom this dose was given showed excessive sedation and a depressed respiration of Cheyne-Stokes type. It was necessary to reduce the dose to 200 mg. twice for one patient and once for the other patient. Although all the other patients who received this high dosage showed depressed respiration, it did not become sufficiently serious to warrant discontinuation of the experiment. With the 200 mg. dose (total 1200 mg.) the abstinence scores from the 14th through the 24th hour were as follows: 14, 13, 14, 15, 16, 17, 18, 20, 20, and 23. These scores are very similar to those obtained with a 400 mg. dose except at the 14, 15, and 16th hour of abstinence. With the small dose, there was no serious depression of respiration but definite sedative effects were present.

All of the patients in whom No. 16298 was substituted stated that it was beneficial in that they slept more and were less nervous than they had been when no medication was given. None of them stated, however, that the effect of the com-