

2) Determination of Propoxyphene in Biological Materials

In 1974 McBay and co-workers reported significantly improved methods for the detection of propoxyphene and propoxyphene metabolites in biological specimens. In their discussion, the authors summarize the fatality reports from the literature and then presented analysis data on 18 cases where death was attributed to propoxyphene (Table 1).

TABLE 1—Cases where death was attributed to propoxyphene.

Case No.	Sex	Age	Concentration of Propoxyphene		Blood	
			Blood, mg/100 ml	Liver, mg/100 g	Ethanol, mg/100 ml	Sabicylate, mg/100 ml
1	F	37	...	13	50	N.D.*
2	M	30	...	8	0	N.D.
3	F	31	1.5	30	0	N.D.
4	F	43	0.4	5.5	0	N.D.
5	M	24	0.7	12	0	N.D.
6	F	48	0.8	14	0	13 ^b
7	M	48	0.3	12	0	0
8	F	29	0.4	9.5	0	14 ^b
9	M	9	0.8	4	0	5
10	M	52	0.6	5	150	5
11	F	29	0.2	3	0	N.D.
12	F	44	0.7	22	50	12
13	M	50	0.5	7.5	160	N.D.
14	M	41	0.5	20	0	6
15	F	20	2.0	...	280	...
16	M	40	0.5	...	230	N.D.
17	F	50	0.6	17	0	6
18	F	37	0.2	1.5	220	0

- * N.D. = none detected, screening method.
- ^b Blood ethchlorvynol—3 mg/100 ml.
- ^c Blood theophylline—0.8 mg/100 ml.

From McBay et.al., 1974

In August, 1973, Dr. McBay contacted this office and in conversation with Dr. Zendzian of DEA was informed of the DEA estimate of 200 propoxyphene related deaths yearly. Dr. McBay considered this figure a gross underestimate and in support of his professional opinion provided a list of 15 "Darvon" related deaths for the first seven months of 1973 for the State of North Carolina. These deaths were not included in the reference paper.

VII 1) Medical Examiners Reports; Project DAWN

Project DAWN receives reports of deaths due to drug overdose from 334 medical examiners in 46 states and the District of Columbia. The resultant data has been analyzed by two different methods, a computer analysis and a direct examination of a complete printout of all medical examiner reports. It should be noted that the total of 1350 cases by direct examination is due to the fact that the complete printout covers a slightly different time base in what is essentially a continuous data collection effort.

1) Computer analysis

a. Motivation

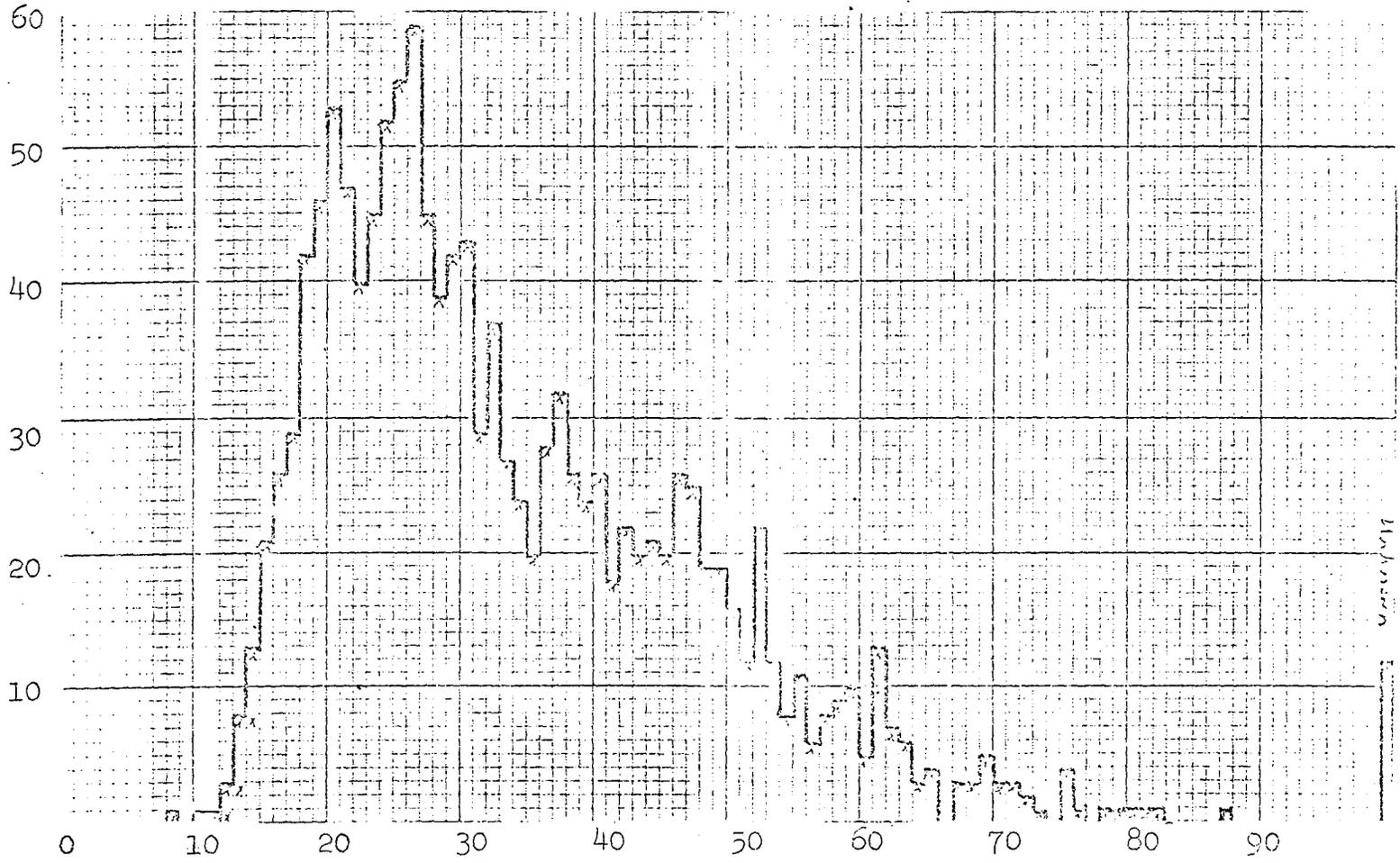
No Data	110
Psychic Effects/depression	147
Dependence	69
Self-destruction	481
Psychic effects & Dependence	3
Psychic effects & Destruction	6
Other	79
Unknown/no answer	<u>474</u>
Total	1369

b. <u>Sex</u>	
Male	626
Female	739
No answer	4
Total	<u>1369</u>

c. <u>Race</u>	
White	1005
Black	301
Other	33
Unknown/No answer	30
Total	<u>1369</u>

d. Age distribution
 Age distribution is plotted in the attached histogram.

e. <u>Manner of Death</u>	
Overdose-Accidental/Unexpected	365
Overdose-Suicide	559
Overdose-reason/unspecified	375
Drug contribution-Accidental/ Unexpected	12
Drug Contribution: Unspecified	38
Narcotism	1
Unknown/No answer	19
Total	<u>1369</u>



Age (Years)

Age Distribution of 1369 Medical Examiner Reports of deaths involving propoxyphene

f. Means of Drug Identification

Patients/Police Statement	124
Doctors Statement	716
Positive Clinical Response	2
Possession	307
Blood/tissue analysis	993
Urine analysis	351
Laboratory analysis/other	607
Nonreported	<u>13</u>
Total	3113*

*Total exceeds the number of cases since more than one drug was present in many cases and more than one means of identification may have been utilized for a single drug.

g. Drug Present

Of the 1369 computer analyzed cases 420 reported propoxyphene alone and 196 reported propoxyphene with alcohol. There were a total of 291 unique combinations of drugs of which only the first 16 in order of number are listed below since these cases and propoxyphene alone represent 69% of the total cases. Over forty individual substances appeared in the 949 cases in which propoxyphene was combined with other substances.

Grand Total	1369
D-propoxyphene	420
w/alcohol	196
w/diazepam	61
w/methadone	43
w/aspirin (may be Darvon w/ASA)	41
w/diazepam & alcohol	29
w/phenobarbital	27
w/methadone & alcohol	24
w/barbiturate sedative	16
w/morphine	16
w/chlordiazepoxide & alcohol	13
w/asprin & alcohol	13
w/secobarbital	12
w/chlordiazepoxide	12
w/pentobarbital	11
w/ flurazepam	10

h. Dose Form

Tablet, capsule or pill	1128
Liquid	4
Powder	1
Injectable liquid	7
Other	1
Unknown/No answer	228
Total	<u>1369</u>

i. Route of Administration

Oral	1182
Injection, Intravenous	8
Injection, Unspecified	5
Unknown/No answer	174
Total	1369

2) Direct analysis of detailed medical examiner reports

A complete printout of every medical examiner report (case) to DAWN which included the drug propoxyphene was obtained and examined in order to determine which of these deaths could be clearly attributed to propoxyphene. Propoxyphene concentrations in tissue samples were compared with the minimum concentrations in blood and liver (0.2 and 3.0 mg% respectively) which were reported by McBay et al in 1974 as indicative of death by propoxyphene overdose. 1350 reports were examined individually and the cases were classified in one of three classes, 1) Propoxyphene sufficient to cause death, 2) Propoxyphene not sufficient to cause death and 3) Unable to determine the contribution of propoxyphene to death.

1. Propoxyphene sufficient to cause death. In 666 (42%) cases a quantitative analysis of propoxyphene in blood and/or liver had been performed and blood concentrations in excess of 0.2 mg% and/or liver concentrations in excess of 3.0 mg% were reported. In these cases death could be attributed to propoxyphene alone however, it must be noted that in many of these cases other depressant drugs such as alcohol and various sedative-hypnotics were present in amounts which could be either strongly contributory to death or capable of causing death if they had been the only drug present.

2. Propoxyphene not sufficient to cause of death. In 193 (14%) cases a quantitative analysis of propoxyphene in blood and/or liver had been performed and blood or liver concentrations below 0.2 or 3.0 mg% respectively were reported. In many of these cases other drugs were present in sufficient concentrations to have been the cause of death or several depressant drugs were present which are known to express their toxic effects in an additive manner.

3. Unable to determine the contribution of propoxyphene to death. In 492 (36%) cases no quantitative analysis of propoxyphene was reported or where quantitative analysis were reported no standards for amounts compatible with cause of death were available. These include sources such as urine, gastric contents and brain.

VII m)

The NIDA Polydrug Program

The Polydrug project, sponsored by NIDA, was conceived for the purpose of gaining an insight into the nature and magnitude of non-narcotic drug abuse in the United States and making an assessment of the treatment needs of individuals misusing these drugs. A total of 14 medical based projects were funded in metropolitan areas throughout the United States. The field portion of this study has been completed and the data produced is presently being processed at NIDA.

Telephone contact was made with the principal investigators of eleven of these projects who were asked if propoxyphene abuse was found in any of their patients, and if any of these patients could be considered primary propoxyphene abusers. Summary case histories (without patient identification) were requested on the propoxyphene abusing patients.

Two of the projects (Brooklyn and Washington, D.C.) reported no propoxyphene abuse and one project (Houston) had identified propoxyphene as a narcotic and consequently did not admit patients with this problem into the program. One project (Piscataway, New Jersey) was unable to answer the question due to resignation of the principal investigator before the final report has been written. Due to time constraints, it proved impossible to contact three projects.

Of the seven projects reporting propoxyphene abuse, six sent case histories and summary information. Detroit reported by phone, that the project had seen 7-8 primary cases and 15-20 secondary abusers out of approximately 200 admissions, however, the project failed to provide additional information and these cases must be considered unsubstantiated at present. The cases reported by the remaining six projects are summarized below.

Boston reported that of "212 patients in an open-ended question about what drugs they were using on admission- 3.6% stated they were using Darvon; 4.8% said they had used Darvon either presently or at some time in the past: Two patients were detoxified using Darvon and these are people who stated an addiction to Darvon who were felt to require gradual detoxification". "My overall impressions about Darvon are that patients that abuse it are extremely ill psychiatrically. However, patients that use it chronically might comprise a great number of people in this country today."

Denver reported the largest number of cases. From a total of 347 patients, 10 individuals were identified whose primary drug of abuse was propoxyphene and an additional four individuals with whom propoxyphene was a secondary drug of abuse.

Although "patients frequently manifest anxiety, insomnia and irritability during the initial period of abstinence" which "resembled in some aspects a mild opiate withdrawal syndrome", the project medical personnel were unable to satisfy themselves as to the presence of a physiologic withdrawal syndrome. A summary of data on these cases is presented in Table I which was prepared by the principal investigator.

Minneapolis reported "one subject out of an N of 177 subjects, who reported a secondary problem with Darvon". This 37 year old male started with alcohol at age 15 and was presently using Valium daily and Darvon twice weekly in combination with sedatives.

Richmond reported one patient who was actively using Darvon at admission and 21 patients who had used Darvon out of a total of 150 patients. None of these individuals could be considered primary propoxyphene abusers.

San Francisco reported in detail two cases of primary propoxyphene abuse. One patient "a 24 year old white "street-wise female" was initially detoxified with Darvon-N (Propoxyphene napsylate) following 8 months of oral methadone. This detoxification initially appeared to be successful, however, she returned after a 21 month loss of contact using between 1500 & 2000 mg. of Darvon-N daily.

Table I

Characteristics of Propoxyphene Abusers

ADDICTION RESEARCH UNIT
DENVER GENERAL HOSPITAL
Denver, Colorado

Case No.	119	190	233	241	273	415	433	278	357	406	47	372	540	309
Age	26	27	60	38	30	20	27	38	33	24	35	41	48	43
Sex	M	M	F	M	F	F	M	M	M	M	F	F	M	F
Ethnicity	W	W	W	W	W	B	W	W	W	W	W	W	W	M.A.
Primary Darvon Abuser	x	x	x	x	x		x		x	x	x		x	
Secondary Darvon Abuser						x		x				x		x
Source:														
Single Physician			x					x						x
Multiple Physicians	x	x												
Illegal Prescription	x	x												
Street Buy										x				
Amount used Daily (mg.)	1500 to 2500		650 to 975	650 to 975		975	2500		1170	900 to 950	390 to 455		520 to 780	
Duration of Use (months)	48	48	4	12			12	8	48	24	180			

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This excessive drug use was developed over a six week period following prescription of Darvon-N for pain. The patient described the effect of Darvon-N as similar to methadone and visited other doctors to obtain additional Darvon-N. Following development of paranoid feelings, increasing difficulty with vision, increasing anxiety, difficulty sleeping, the patient returned for treatment.

The second case was a 26 year old "non-street-wise" female who was self-referred for Darvon detoxification. The patient was initially prescribed codeine for migraine headaches. This was switched to Darvon due to the patient's fear of codeine addiction. The patient initially took 5 tablets a day, usually in the evening but increased this to 18-20 tablets over a period of several years. During out-patient treatment with Darvon-N (100 mg. four times daily) the patient suffered a "seizure" and was admitted to the hospital for treatment and neurological evaluation. The patient signed out against medical advise and six months later was found to have resumed taking Darvon-N.

Seattle reported, in detail, two primary propoxyphene users from a total of 300 admissions. The drug appeared relatively unpopular among their patients.

The first case was a 54 year old white male who was maintained on 10 Darvon-N 100 mg. tablets daily for relief of pain due to a neck injury. The patient was referred by his physician who expressed concern over the patients "addiction". After thorough medical evaluation, it was decided that although the patients Darvon-N intake could be considered excessive, it was effective, the patient showed no signs of increasing his dose and he took no other drugs. Therefore, the patient was referred back to his physician with the recommendation that the physician continue providing him with Darvon-N indefinitely.

The second patient, a 27 year old white male had a long history of multiple drug use. He presented himself as having a barbiturate addiction, but was discovered to be also using Darvon 65 mg. on a daily basis.

VII n) Propoxyphene Napsylate Abuse

In 1972, Eli Lilly & Co. introduced the napsylate salt of propoxyphene to the drug market as Darvon-N. Shortly thereafter, DEA personnel heard rumors from California that this salt was being dissolved in vodka and injected intravenously. Propoxyphene napsylate is soluble in ethyl alcohol but there are definite dangers in injecting such a solution due to the toxic and tissue damaging properties of concentrated alcohol. Extremely discrete inquiries were undertaken to obtain hard information on this rumor while simultaneously avoiding having the inquiries themselves lead to the appearance of this type of abuse. No substantiating evidence could be obtained nor could any clear information be obtained as to the source of this rumor.

In August of 1974, Dr. Samuel L. Fox, Medical Director of the Drug Abuse Administration, Baltimore, Maryland, informed the Drug Abuse Section of the Food and Drug Administration of the abuse of propoxyphene napsylate (Darvon-N) combined with vodka which was occurring in the Maryland prison system. DEA was informed of this report and contacted Dr. Fox directly.

Dr. Fox stated that a serious drug abuse situation exists in the Maryland prison system which has involved the intravenous and oral abuse of Darvon (propoxyphene HCl) when more potent narcotic drugs were not available (see section b-5, page 42 of this report). Darvon is readily available in prison pharmacies and Dr. Fox had recommended that the relatively insoluble napsylate salt (Darvon-N) be used to preclude intravenous abuse. In late 1972 or early 1973, Dr. Fox learned that prisoners were dissolving Darvon-N in vodka (which was being smuggled into prison) and that the resultant "solution" was either drunk or injected intravenously for a quick high. Dr. Fox suggested that DEA contact Dr. Noel List (Assistant Professor, University of Maryland) for additional information.

Dr. List was contacted by DEA and provided the following information. Dr. List, in his capacity of Medical Director of the Glenwood Life Center, is involved in the treatment of drug abusing individuals particularly abusers of narcotic drugs. During the latter part of 1972, Dr. List was told by narcotic abusers that Darvon-N could be dissolved in vodka and injected intravenously.

This injection produced a mild heroin-like reaction and was used by short term prisoners to tide them over a heroin shortage. Dr. List has interviewed at least one narcotic abuser who had stated that he had used Darvon-N in this fashion. In early 1973, Dr. List informed staff members of Eli Lilly & Co. of this form of propoxyphene abuse.

The solubility of Darvon-N in vodka at room temperature was examined by the technical staff of DEA. A Darvon-N tablet placed in vodka (80 proof) disintegrates in about 5 minutes with mild agitation, producing a cloudy yellowish white suspension and a fine sludge. Filtration through cotton, a common procedure used by intravenous drug abusers, removed the coarser suspended material but the filtrate was an obvious suspension, part of which precipitated on standing. The filtrate was physically injectable though obviously capable of causing capillary damage in the lungs and other organs due to the suspended matter. The extracts prepared in this study contained from 9.7 to 12.4 mg/ml of propoxyphene. In addition, the solubility of a propoxyphene napsylate standard was determined to be 14.7 mg/ml in a 40% ethanol/water solution at room temperature.

VII o) Pilot Test of an Epidemiological Technique
for Detecting Abused Substances.

In 1975 DEA conducted a pilot test of an epidemiological technique for detecting abused substances in drug using populations (DEA 76-4). The pilot test was designed to assess the utility of the property of contagious transmission as an indicator of the abuse potential of twelve legally manufactured psychoactive drugs, and to assess the general usefulness of this approach to determining abuse liability. The epidemiological technique had been demonstrated previously in describing heroin epidemics. The twelve drugs studied were the amphetamines as a class, a synthetic narcotic, chlorphentermine, diethylpropion, fenfluramine, mazindol, methaqualone, pentazocine, phendimetrazine, phenmetrazine, phentermine and propoxyphene. Two additional drugs (phencyclidine and cocaine) which are known to be capable of contagious transmission as drugs of abuse were included, once field work began.

In this study, nine major cities were visited, and 935 treatment program clients were interviewed.

The study concluded that; "patterns of contagious transmission (epidemics of incidence of first use) were determined and described for cocaine, the amphetamines, propoxyphene, pentazocine, phenmetrazine, methaqualone, phencyclidine and hydromorphone. These patterns of "epidemicity" were shown to be relative to specific study sites and sub-populations within study sites".

In most of the individuals interviewed, the primary drug of abuse was heroin. A much smaller number of generally young individuals reported marihuana as their primary drug. For the purposes of this review, the items of interest are the secondary drugs of abuse and the place of propoxyphene among them.

Table 1 presents the ranking of secondary drugs by frequency of reports. Propoxyphene ranks fifth in frequency and was reported by 38% of the individuals interviewed.

The study concluded that "Propoxyphene ranks as a major abused drug, within absolute frequency of its use and also in its tendency to spread by contagious transmission. Its overall pattern is remarkable like that of phencyclidine in many places". Forty-eight percent of the propoxyphene users stated that they had first obtained their drug from

Table I

Ranking of Secondary Drugs By Frequency
Of Report (N-935 Interviews)
(Non-Medical Use Only)

<u>Rank</u>	<u>Drug & Schedule</u>	<u>Number of Users Reported</u>	<u>Percent</u>
1.	Cocaine (II)	743	80
2.	Amphetamines (II)	579	62
3.	Methaqualone (II)	430	46
4.	Hydromorphone (II)	372	40
5.	Propoxyphene (None)	357	38
6.	Phencyclidine (III)	323	34
7.	Pentazocine (None)	167	18
8.	Phenmetrazine (II)	146	15
9.	Meperidine (II)	44	4
10.	Oxycodon (II)	40	4
11.	Codeine (II)	19	2
12.	Diethylpropion (IV)	19	2
13.	Mazindol (III)	11	1
14.	Morphine (II)	9	1
15.	Chlorphentermine (III)	8	1
16.	Fenfluramine (IV)	5	-
17.	Diazepam (IV)	4	-
18.	Phentermine (IV)	3	-
19.	Oxymorphone (II)	3	-
20.	Phendimetrazine (III)	1	-

friends, peers or family members, 21% directly from medical sources, 9% from dealers and 21% by their own efforts (i.e., theft).

Copies of the final report of this study are available for review.

VIII DISCUSSION

Dextropropoxyphene was introduced to the medical world as a non-narcotic analgesic with a potency similar to codeine. Thus, it was implied that dextropropoxyphene lacked potential for abuse. In general, the analgesic drugs may be classified as either centrally or locally active. The majority of centrally acting agents are pharmacologically similar to morphine (i.e., the prototype narcotic analgesic) and thus may be suspected of having a potential for abuse as considered under the mission of BNDD. In contrast the locally active agents have never demonstrated potential for this type of abuse. Thus, in assessing the abuse potential of dextropropoxyphene it is necessary to determine if it is in fact a 'centrally acting narcotic analgesic', as this class of drugs is commonly identified in modern pharmacology (Drill 1965). The animal pharmacology of dextropropoxyphene is clearly indicative of a centrally acting analgesic. In the animal pain models, dextropropoxyphene is active in all cases while aspirin, a locally active agent, is active only in those tests that involve tissue damage. The central activity of dextropropoxyphene is most elegantly shown in the studies of LIM, et al. (1964), on the dog. There is no reason for scientific doubt that dextropropoxyphene is a centrally

acting analgesic in animals. Although in man the scientific study of the site of dextropropoxhene activity can never be conclusive, there is no reason to doubt that this drug is a centrally acting analgesic in man.

The ability of the narcotic antagonists to counteract certain specific activities of a drug are indicative of its morphine-like activity. Antagonism of specific effects of morphine (the prototype narcotic analgesic) by nalorphine (a narcotic antagonist) has been demonstrated to be a competitive reversible phenomenon with the two drugs acting at the same receptor. The interactions of morphine and nalorphine in man are shown in table 11.

Table 11

Table 17-1. Effects of morphine and nalorphine in non-tolerant human beings

Effect	Morphine alone	Nalorphine alone	Morphine plus nalorphine
Analgesia	U	U	X
Sedation	U	U	X
Respiratory depression	U	U	X
CSF pressure increase	U	U	X
Gastrointestinal and biliary spasm	U	U	X
Miosis	U	U	X
Euphoria	V	O	X
Diuresis	O	V	U
Antitussive action	U	U	A
Bradycardia	V	V	X
Hypotension	V	V	X

Key: U, usually occurs; V, variably occurs; O, opposite occurs; X, nalorphine antagonizes morphine; A, nalorphine additive with morphine.

From Drill's Pharmacology in Medicine
Joseph R. DiPalma, MD, ed, McGraw-Hill, 1965

In those species that normally exhibit excitation following morphine administration (cats, horses, etc.), nalorphine is a competitive reversible inhibitor of this effect.

The antagonistic effect of nalorphine is best demonstrated against the toxic effects of a suspected narcotic. Thus, nalorphine has been shown in animal studies to antagonize competitively the convulsant and lethal effects of dextropropoxyphene while pentobarbital, a non-narcotic depressant, antagonizes noncompetitively only the convulsant effects of dextropropoxyphene. In man nalorphine given before the onset of anoxic brain damage antagonizes the convulsant and respiratory depressant (i.e., lethal) effects of dextropropoxyphene. Studies of the effects of nalorphine on other pharmacological activities of dextropropoxyphene are not yet available. Thus, dextropropoxyphene acts in the central nervous system by interacting with the specific "morphine" receptor(s).

The physical dependence produced by the narcotic analgesics (of which morphine is the prototype) is characterized by the withdrawal syndrome. As described in Drill's Pharmacology in Medicine:

"In subjects addicted to morphine the initial symptoms of abstinence emerge 6 to 12 hours after the last dose and consist of an awareness of the impending illness and feelings of tiredness and weakness. After 12 hours certain signs of abstinence such as yawning, lacrimation, rhinorrhea, and perspiration emerge and the patient may enter a fitful, restless sleep. After 24 hours the patient becomes increasingly restless, twitching of various muscle groups appear, and the patient complains of back and leg pains and has hot and cold flashes as well as chills. At the same time other signs of disordered function of the autonomic nervous system appear, including fever, increase in both rate and depth of respiration, elevation of blood pressure, and dilation of previously constricted pupils. By 48 hours the abstinence syndrome has neared its peak and the patient is nauseated, retches and vomits, has diarrhea, eats and drinks very little, and loses weight rapidly. The patient lies in a fetal position, twitches and turns and covers himself with blankets even in hot weather. After 72 hours the abstinence syndrome begins to subside slowly and after 5 to 10 days most of the signs and symptoms have disappeared. The patient continues to complain of weakness, insomnia, restlessness, and muscle pains in legs and back for several weeks. It is not certain how much time is required for the addict to recover completely from his physical dependence.

In man, 4 to 6 months elapse before certain physiological variables approach a stable level and, even 6 months after withdrawal, superresponsivity of the autonomic nervous system to nociceptive stimuli has been reported.

This is the description of a maximal response; it must be remembered that physical dependence is dose-duration related so that an individual taking only minimal amounts of morphine will have only minimal symptomology. Similarly, some morphine-like analgesics having less intrinsic capability of producing physical dependence will produce a submaximal withdrawal syndrome. The symptoms of dextropropoxyphene withdrawal (yawning, lacrimation, rhinorrhea and perspiration) are those of a minimal morphine-type physical dependence. This minimal syndrome is apparently not readily precipitated by nalorphine at the doses used in the studies reviewed in this report.

The pharmacological properties in man of the prototype narcotic analgesic, morphine and dextropropoxyphene are compared in Table 12. The remarkable qualitative similarity, including side effects and idiosyncratic effects, of the two drugs is indicative of their close pharmacological relationship.

Indeed, there is no scientific reason to consider dextro-propoxyphene anything other than a narcotic analgesic.

It would appear that the manufacturer has already conceded this point. A recent advertisement for dextropropoxyphene (Darvon-N) states "The general pharmacological properties of propoxyphene are those of the narcotics as a group (see Warnings, Precautions and Adverse Reactions)." A copy of this advertisement is appended to this report.

Table 12

Comparison of the Pharmacological Activity and Side Effects of Morphine and Dextropropoxyphene

	morphine ¹⁾	dextropropoxyphene ²⁾
Analgesia	A	A
Sedation	S	S
Somnolence	S	S
Excitation	S	S
Insomnia	S	S
Dizziness	S	S
Headache	S	S
Warmth	S	
Itching	S	
Nausea	S	S
Vomiting	S	S
Constipation	S	S
Euphoria	S	S
Respiratory Depression	A	
Orthostatic Hypertension	S	
Tolerance	A	H
Physical Dependence	A	H
Psychological Dependence	S	S
Dermatitis	S	S

1) Goodman and Gilman

2) Recent Advertisement for Dextropropoxyphene (Darvon-N)

A = always with normal dose

S = sometimes with normal dose

H = higher than normal dose required

The pharmacological and toxicological properties that serve to classify dextropropoxyphene as a centrally acting narcotic analgesic include properties that give this drug an intrinsic potential for abuse. Continued use of dextropropoxyphene can produce a mild to moderate physical dependence, but the ability of a drug to produce physical dependence is not primary to its use as a drug of abuse. It is necessary that the drug possess some quality or qualities that make its use "attractive." Thus, the potential abuser must like taking the drug. It is not necessary that all people "like" using the drug, (not all people "like" heroin or beer) but that some individuals find the use of the drug so desirable that they are psychologically impelled to continue taking the drug and increasing the dose if necessary to continue experiencing the desired effect. Thus, the experienced addict reports "pleasant" morphine-like effects from dextropropoxyphene and in some circumstances is unable to distinguish between morphine and dextropropoxyphene. In addition, individuals having no previous experience with narcotics experience a feeling of euphoria when taking dextropropoxyphene. The feeling is so desirable to some individuals that they continue taking dextropropoxyphene. Such drug abusers may stabilize their intake of

dextropropoxyphene at abnormally high doses for long periods of time. The unpleasant side effects of very high doses do not cause the abuser to stop taking dextropropoxyphene but rather set a limit to his daily dose. This limitation of daily dose is similar to that seen in monkeys who self-administer dextropropoxyphene until they are unable to continue due to toxic convulsions. When they recover from their convulsions the monkeys return to their drug.

Dextropropoxyphene as a narcotic analgesic possesses an intrinsic capability for abuse and this potential has been realized by some individuals having access to excessive amounts of this drug. The scientific and clinical reports referred to earlier in this paper clearly show that some individuals engage in continued self-administration of excessive doses of dextropropoxyphene. In the case of intravenous abuse, injection continued despite the local damage that dextropropoxyphene causes to the veins. The potential for abuse and the actual existence of abuse of dextropropoxyphene are clearly established.

In conclusion the following points can be made concerning dextropropoxyphene as a drug of abuse.

1. Dextropropoxyphene is a centrally active narcotic analgesic with a spectrum of activity qualitatively similar to morphine the prototype narcotic analgesic.
2. Dextropropoxyphene produces a mild to moderate physical dependence of the morphine type. Unlike morphine, development of dextropropoxyphene dependence requires the administration of doses in excess of the recommended therapeutic dose.
3. Intravenous administration of dextropropoxyphene to experienced addicts produces "pleasant" morphine-like effects which cannot always be distinguished from those of morphine.
4. Dextropropoxyphene has properties which lead individuals to self-administer either orally or intravenously excessive amounts of the drug.
5. Tolerance develops to the "pleasant" effects of dextropropoxyphene as well as to other effects so that individuals can ingest or inject doses of the drug which would be in the lethal range for nontolerant individuals.

6. Self-administration of dextropropoxyphene in increasingly higher doses for the reasons noted in No. 3, 4, and 5 has produced physical dependence.
7. Intravenous self-administration of dextropropoxyphene in man utilized the pellet formulation of Darvon[®] which is no longer available but the new propoxyphene formulations are soluble in warm water and on a pharmacological basis can be utilized intravenously for the same effect.
8. Single doses of dextropropoxyphene in excess of 800 mg can be lethal if untreated and it is estimated that in excess of 200 individuals die yearly of dextropropoxyphene overdose in the United States.
9. Most abusers of dextropropoxyphene appear to obtain the drug by legal prescription but thefts of Darvon[®] from pharmacies and practitioners are being reported and the drug is available on the street at \$0.25-\$1.50 per capsule.

IX RECOMMENDATION FOR CONTROL

On the basis of scientific and clinical evidence that dextro-propoxyphene is a centrally acting narcotic analgesic capable of producing a mild to moderate physical and psychological dependence and that this drug has a history of abuse that continues to date, it is recommended that alpha-d-propoxyphene (alpha--4 dimethylamino-1,2-diphenyl - 3-methyl-2-propionoxybutane) be controlled under Public Law 91-513.

In considering the 8 points for control of a drug:

Sec. 201.

(c) In making any finding under subsection (a) of this section or under subsection (b) of section 202, the Attorney General shall consider the following factors with respect to each drug or other substance proposed to be controlled or removed from the schedules:

(1) Its actual or relative potential for abuse.

(1) Dextropropoxyphene produces euphoria, mild to moderate physical dependence and has been abused both orally and intravenously.

(2) Scientific evidence of its pharmacological effect, if known.

(3) The state of current scientific knowledge regarding the drug or other substance.

(2) & (3) Current scientific (i.e., pharmacological) evidence

clearly equates dextropropoxyphene to an "opiate" as defined under Public Law 91-513.

- (4) Its history and current pattern of abuse.
- (5) The scope, duration, and significance of abuse.
- (4) & (5) The history of propoxyphene abuse extends from shortly after its introduction to the market place where it is presently among the most commonly prescribed drugs. Abuse is mainly by the oral route with legally obtained drug (i.e., by prescription), although intravenous abuse occurs and the drug is in the illegal market.
- (6) What, if any, risk there is to the public health.
- (6) As one of the most commonly prescribed drugs, dextropropoxyphene is a significant cause of death by overdose.
- (7) Its psychic or physiological dependence liability.
- (7) Dextropropoxyphene can produce a mild to moderate psychic and/or physical dependence.
- (8) Whether the substance is an immediate precursor of a substance already controlled under this title.
- (8) N/A Dextropropoxyphene cannot be converted readily into any controlled drug.

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Exhibit I



Your written assurance of quality

Each prescription you issue is an exercise of your professional judgment. The drug you prescribe is vital to your patient's health and well-being. What may seem to be minor differences in dosage form, particle size, solubility, and rate of absorption may make major differences in therapeutic efficacy. When the choice is yours, you want to prescribe the best.



101-138

Eli Lilly and Company • Indianapolis, Indiana 46206

DARVON® COMPOUND-65 (65 mg. propoxyphene hydrochloride, 227 mg. aspirin, 162 mg. phenacetin, and 32.4 mg. caffeine)

Actions: Propoxyphene hydrochloride is an analgesic. The combination of propoxyphene hydrochloride with aspirin and/or phenacetin results in greater analgesia than that achieved by either drug administered alone. Propoxyphene hydrochloride is structurally related to the narcotic analgesics methadone and isomethadone, and its general pharmacologic properties are those of the narcotics as a group.

In most individuals, recommended doses of propoxyphene hydrochloride have not caused clinically significant alterations of respiration, blood pressure, or pulse rate.

Indication: For the relief of mild to moderate pain.

Contraindications: Hypersensitivity to propoxyphene hydrochloride or to the other ingredients (aspirin, phenacetin, caffeine) in the propoxyphene hydrochloride combination products.

Concomitant administration with orphenadrine-containing compounds.

Warnings: Salicylates should be used with caution in the presence of peptic ulcer.

Phenacetin may damage the kidneys when used in large amounts or taken over a long period of time.

Propoxyphene hydrochloride may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

Use in Pregnancy:—The safety of the use of this agent during pregnancy has not been established. The potential hazards of the drug must be weighed against the possible benefits.

Use in Children:—This agent should not be used in children, since adequate data to establish safe conditions of use are lacking.

Drug Dependence:—Tolerance, psychological dependence, and physical dependence have been reported; the abuse liability of propoxyphene hydrochloride is qualitatively similar to that of codeine although quantitatively less. Darvon (propoxyphene hydrochloride, Lilly) will not support morphine dependence.

Precautions: Patients who have received narcotic drugs for long periods of time may have developed physical dependence, and the sudden substitution of ordinary doses of propoxyphene hydrochloride may result in an acute withdrawal syndrome. These symptoms may be avoided by gradually reducing the dose of the prior medication as propoxyphene hydrochloride is substituted.

Adverse Reactions: Dizziness, headache, sedation, somnolence, paradoxical excitement, insomnia, skin rashes, and gastro-intestinal disturbances (including nausea, vomiting, abdominal pain, and constipation) may occur with the recommended doses of the drug.

Euphoria may occasionally occur.

Administration and Dosage: Propoxyphene hydrochloride with aspirin, phenacetin, and caffeine is given orally. The usual dose is 65 mg. of propoxyphene hydrochloride, 227 mg. of aspirin, 162 mg. of phenacetin, and 32.4 mg. of caffeine three or four times daily.

How Supplied: Pulvules® Darvon® Compound-65, containing 65 mg. propoxyphene hydrochloride, 227 mg. aspirin, 162 mg. phenacetin, and 32.4 mg. caffeine are supplied in bottles of 100 and 500, in 10 strips of 10 individually labeled blisters each containing 1 Pulvule (D1165), and in strip packages of individual sealed Pulvules (DS1000).

For complete prescribing information and overdosage treatment, consult the package literature or PDR.

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Exhibit II

whenever an
analgesic with aspirin
is preferred

dosage:
1 tablet 3 or 4 times daily

Useful for patients
who may be sensitive
to aspirin

dosage:
1 tablet 3 or 4 times daily

Actions: Propoxyphene napsylate is a water-insoluble salt of propoxyphene; as such, it differs from propoxyphene hydrochloride (Darvon[®]) in that it allows more stable liquid dosage forms and tablet formulations of Darvon-N and Darvon-N with aspirin. The pharmacologic properties of propoxyphene napsylate are similar to those of propoxyphene hydrochloride, and these drugs produce mild to moderate analgesia. However, because of differences in molecular weight, a dose of 100 mg. of propoxyphene napsylate is required to supply an amount of propoxyphene equivalent to the amount present in 65 mg. of propoxyphene hydrochloride. The general pharmacologic properties of propoxyphene are those of the narcotics as a group (see Warnings, Precautions, and Adverse Reactions).

Indication: For the relief of mild to moderate pain.

Contraindications: Hypersensitivity to propoxyphene napsylate and, in the combination product, to aspirin.

This agent should not be used in children, since adequate data to establish safe conditions of use are lacking.

Warnings: Propoxyphene napsylate may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

Salicylates should be used with caution in the presence of peptic ulcer.

Use in Pregnancy:—The safety of the use of this agent during pregnancy has not been established.

Drug Dependence—Tolerance, psychological dependence, and physical dependence have been reported; the abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less. Propoxyphene will not support morphine dependence.

Precautions: Patients who have received narcotic drugs for long periods of time may have developed physical dependence, and the sudden substitution of ordinary doses of propoxyphene napsylate may result in an acute withdrawal syndrome. These symptoms may be avoided by gradually reducing the dose of the prior medication as propoxyphene napsylate is substituted for pain relief.

Salicylates present in Darvon-N with A.S.A. may enhance the effect of anticoagulants and inhibit the uricosuric effect of probenecid. In large doses, salicylates may also decrease insulin requirements.

Adverse Reactions: Dizziness, headache, sedation, somnolence, paradoxical excitement, insomnia, skin rashes, and gastro-intestinal disturbances (including nausea, vomiting, abdominal pain, and constipation) may occur with the recommended doses of propoxyphene. Euphoria may occasionally occur.

Salicylates present in the combination product may induce hypersensitivity, urate kidney stones, chronic gastro-intestinal blood loss, tinnitus, nausea, and vomiting.

Administration and Dosage: Preparations of Darvon N are given orally.

The usual adult dose of Darvon N is 100 mg. three or four times daily.

The usual adult dose of Darvon N with A.S.A. is 1 tablet, which contains 100 mg. of propoxyphene napsylate and 325 mg. of aspirin, three or four times daily.

How Supplied: Tablets Darvon-N[®] (propoxyphene napsylate, Lilly), 100 mg., in bottles of 100 and 500 and in Identii-Dose[®] (unit dose medication, Lilly) in boxes of 100.

Tablets Darvon-N[®] with A.S.A. (propoxyphene napsylate with aspirin, Lilly), each combining 100 mg. propoxyphene napsylate and 325 mg. aspirin, in bottles of 100 and 500 and in Identii-Dose in boxes of 100. 10-157121

Additional information available to the profession on request.
Eli Lilly and Company
Indianapolis, Indiana 46205



10157

DARVON®
(propoxyphene hydrochloride)
Capsules, U.S.P.

**DARVON® COMPOUND and
DARVON® COMPOUND-65**
(propoxyphene hydrochloride, aspirin,
phenacetin, and caffeine)

DARVON® WITH A.S.A.®
(propoxyphene hydrochloride and aspirin)
Capsules, N.F.

Description: Darvon® (propoxyphene hydrochloride, Lilly) is a synthetic analgesic. It is an odorless white crystalline powder with a bitter taste. It is freely soluble in water. Chemically, it is *α-(+)-4-(Dimethylamino)-2-methyl-1,2-diphenyl-3-butanol Propionate Hydrochloride*.

Actions: Propoxyphene hydrochloride is an analgesic. The combination of propoxyphene hydrochloride with aspirin and/or phenace-

tin results in greater analgesia than that achieved by either drug administered alone. Propoxyphene hydrochloride is structurally related to the narcotic analgesics methadone and isomethadone, and its general pharmacologic properties are those of the narcotics as a group.

In most individuals, recommended doses of propoxyphene hydrochloride have not caused clinically significant alterations of respiration, blood pressure, or pulse rate.

Indication: For the relief of mild to moderate pain.

Contraindications: Hypersensitivity to propoxyphene hydrochloride or to the other ingredients (aspirin, phenacetin, caffeine) in the propoxyphene hydrochloride combination products.

Concomitant administration with orphenazine-containing compounds.

Warnings: Salicylates should be used with caution in the presence of peptic ulcer.

Phenacetin may damage the kidneys when used in large amounts or taken over a long period of time.

Propoxyphene hydrochloride may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

Use in Pregnancy—The safety of the use of this agent during pregnancy has not been established. The potential hazards of the drug must be weighed against the possible benefits.

Use in Children—This agent should not be used in children, since adequate data to establish safe conditions of use are lacking.

Drug Dependence—Tolerance, psychological dependence, and physical dependence have been reported; the abuse liability of propoxyphene hydrochloride is qualitatively similar to that of codeine although quantitatively less. Darvon® (propoxyphene hydrochloride, Lilly) will not support morphine dependence.

Precautions: Patients who have received narcotic drugs for long periods of time may have developed physical dependence, and the sudden substitution of ordinary doses of propoxyphene hydrochloride may result in an acute withdrawal syndrome. These symptoms may be avoided by gradually reducing the dose of the prior medication as propoxyphene hydrochloride is substituted.

Adverse Reactions: Dizziness, headache, sedation, somnolence, paradoxical excitement, insomnia, skin rashes, and gastro-intestinal disturbances (including nausea, vomiting, abdominal pain, and constipation) may occur with the recommended doses of the drug.

Euphoria may occasionally occur.

Administration and Dosage: A narcotic prescription is not required. Darvon® (propoxyphene hydrochloride, Lilly) is given orally. The usual dose is 65 mg. three or four times daily.

Propoxyphene hydrochloride with aspirin is given orally. The usual dose is 65 mg. of propoxyphene hydrochloride and 325 mg. of aspirin three or four times daily.

Propoxyphene hydrochloride with aspirin, phenacetin, and caffeine is given orally. The usual dose is 65 mg. of propoxyphene hydrochloride, 227 mg. of aspirin, 162 mg. of phenacetin, and 32.4 mg. of caffeine three or four times daily.

Overdosage: Manifestations of accidental or intentional overdosage with propoxyphene are similar to those of narcotic overdosage and include convulsions (more common than is usually noted in cases of narcotic poisoning), coma, respiratory depression, and circulatory collapse. When combination products

containing salicylates as well as propoxyphene have been ingested, the clinical picture may be complicated by salicylism.

Analeptic drugs (for example, caffeine or amphetamine) should not be used because of their tendency to precipitate fatal convulsions. Intravenously administered narcotic antagonists (nalorphine and levallorphan) are the drugs of choice to reverse signs of intoxication. These agents should be given repeatedly until the patient's status remains satisfactory. Gastric lavage also may be helpful. In addition, supportive measures, such as assisted oxygenation and intravenous fluids, should be used as indicated.

Dialysis is of little value with respect to propoxyphene alone; salicylates and phenacetin are dialyzable.

How Supplied: (1) *Pulvules,® Darvon® (Propoxyphene Hydrochloride Capsules, U.S.P.):* No. 364, 1102, 32 mg. (No. 4, Light-Pink Opaque), and No. 365, 1103, 65 mg. (No. 3, Light-Pink Opaque), in bottles of 100 and 500, in 10 strips of 10 individually labeled blisters each containing 1 Pulvule (ID100), and in strip packages of individually sealed Pulvules (DS1000).

(2) *Pulvules No. 368, Darvon® Compound (propoxyphene hydrochloride, aspirin, phenacetin, and caffeine, Lilly), H05* (No. 0, Light-Pink Opaque Body, Light-Gray Opaque Cap),* in bottles of 100 and 500, in 10 strips of 10 individually labeled blisters each containing 1 Pulvule (ID100), and in strip packages of individually sealed Pulvules (DS1000). Each Pulvule contains 32 mg. propoxyphene hydrochloride, 227 mg. aspirin, 162 mg. phenacetin, and 32.4 mg. caffeine.

(3) *Pulvules No. 369, Darvon® Compound-65 (propoxyphene hydrochloride, aspirin, phenacetin, and caffeine, Lilly), H06* (No. 0, Red Opaque Body, Light-Gray Opaque Cap),* in bottles of 100 and 500, in 10 strips of 10 individually labeled blisters each containing 1 Pulvule (ID100), and in strip packages of individually sealed Pulvules (DS1000). Each Pulvule contains 65 mg. propoxyphene hydrochloride, 227 mg. aspirin, 162 mg. phenacetin, and 32.4 mg. caffeine.

(4) *Pulvules No. 366, Darvon® with A.S.A.® (Propoxyphene Hydrochloride and Aspirin Capsules, N.F.), 1104* (No. 0, Red Opaque Body, Light-Pink Opaque Cap),* in bottles of 100 and 500 and in 10 strips of 10 individually labeled blisters each containing 1 Pulvule (ID100). Each Pulvule contains 65 mg. propoxyphene hydrochloride and 325 mg. aspirin.

[660771]

[Shown in Product Identification Section]
Pulvules No. 364, 32 mg.—100's—FSN 6505-660-1720; 500's—FSN 6505-725-6392
Pulvules No. 365, 65 mg.—500's—FSN 6505-958-2364

Pulvules No. 368, Darvon Compound—
500's—FSN 6505-967-8735
Pulvules No. 369, Darvon Compound-65—
500's—FSN 6505-784-4976

Actions: Propoxyphene napsylate is a water-insoluble salt of propoxyphene; as such, it differs from propoxyphene hydrochloride (Darvon[®]) in that it allows more stable liquid dosage forms and tablet formulations of Darvon-N[™] (propoxyphene napsylate, Lilly) and Darvon-N with aspirin. The pharmacologic properties of propoxyphene napsylate are similar to those of propoxyphene hydrochloride, and these drugs produce mild to moderate analgesia. However, because of differences in molecular weight, a dose of 100 mg. of propoxyphene napsylate is required to supply an amount of propoxyphene equivalent to the amount present in 65 mg. of propoxyphene hydrochloride. The general pharmacologic properties of propoxyphene are those of the narcotics as a group (see Warnings, Precautions, Adverse Reactions, and Overdosage).

Indication: For the relief of mild to moderate pain.

Contraindications: Hypersensitivity to propoxyphene napsylate and, in the combination product, to aspirin.

This agent should not be used in children, since adequate data to establish safe conditions of use are lacking.

Warnings: Propoxyphene napsylate may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

Salicylates should be used with caution in the presence of peptic ulcer.

Use in Pregnancy:—The safety of the use of this agent during pregnancy has not been established.

Drug Dependence:—Tolerance, psychological dependence, and physical dependence have been reported; the abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less. Propoxyphene will not support morphine dependence.

Precautions: Patients who have received narcotic drugs for long periods of time may have developed physical dependence, and the sudden substitution of ordinary doses of propoxyphene napsylate may result in an acute withdrawal syndrome. These symptoms may be avoided by gradually reducing the dose of the prior medication as propoxyphene napsylate is substituted for pain relief.

Salicylates present in Darvon-N with A.S.A. may enhance the effect of anticoagulants and inhibit the uricosuric effect of probenecid. In large doses, salicylates may also decrease insulin requirements.

Adverse Reactions: Dizziness, headache, sedation, somnolence, paradoxical excitement, insomnia, skin rashes, and gastro-intestinal disturbances (including nausea, vomiting, abdominal pain, and constipation) may occur with the recommended doses of propoxyphene. Euphoria may occasionally occur.

Salicylates present in the combination product may induce hypersensitivity, urate kidney stones, chronic gastro-intestinal blood loss, tinnitus, nausea, and vomiting.

Administration and Dosage: Preparations of Darvon-N[™] (propoxyphene napsylate, Lilly) are given orally.

The usual adult dose of Darvon-N is 100 mg. three or four times daily.

The usual adult dose of Suspension Darvon—

Lilly—Cont.

N, containing 50 mg. per 5 ml., is 10 ml. three or four times daily.

The usual adult dose of Darvon-N with A.S.A. is 1 tablet, which contains 100 mg. of propoxyphene napsylate and 325 mg. of aspirin, three or four times daily.

Overdosage: Manifestations of accidental or intentional overdosage with propoxyphene are similar to those of narcotic overdosage and include convulsions (more common than is usually noted in cases of narcotic poisoning), coma, respiratory depression, and circulatory collapse. When combination products containing salicylates as well as propoxyphene have been ingested, the clinical picture may be complicated by salicylism.

Analeptic drugs (for example, caffeine or amphetamine) should not be used because of their tendency to precipitate fatal convulsions. Intravenously administered narcotic antagonists (naloxone, nalorphine, and levallorphan) are the drugs of choice to reverse signs of intoxication. These agents should be given repeatedly until the patient's status remains satisfactory. Gastric lavage also may be helpful. In addition, supportive measures, such as assisted oxygenation and intravenous fluids, should be used as indicated.

Dialysis is of little value with respect to propoxyphene alone; salicylates are dialyzable.

How Supplied: (R) Tablets Darvon-N[™] (propoxyphene napsylate, Lilly), No. 1882, C52,* 50 mg., Specially Coated, Yellow, in bottles of 100 and 500; No. 1883, C53,* 100 mg., Specially Coated, Orange, in bottles of 100 and 500 and in 10 strips of 10 individually labeled blisters each containing 1 tablet (DB100).

(R) Suspension No. M-135, Darvon-N[™] (propoxyphene napsylate, Lilly), W71,* 50 mg. per 5 ml., in 16-oz. bottles.

(R) Tablets No. 1884, Darvon-N[™] with A.S.A.® (propoxyphene napsylate with aspirin, Lilly), C54,* Specially Coated, Dark-Orange, in bottles of 100 and 500 and in 10 strips of 10 individually labeled blisters each containing 1 tablet (DB100). Each tablet contains 100 mg. propoxyphene napsylate and 325 mg. aspirin.

(071571)

(Shown in Product Identification Section)

DARVON-N[™]
(propoxyphene napsylate)

DARVON-N WITH A.S.A.®
(propoxyphene napsylate with aspirin)

Description: Darvon-N[™] (propoxyphene napsylate, Lilly) is a synthetic, odorless, white crystalline solid with a bitter taste. It is very slightly soluble in water and soluble in methanol, ethanol, chloroform, and acetone. Chemically, it is α -(+)-4-(Dimethylamino)-3-methyl-1,2-diphenyl-2-butanol Propionate (ester) 2-Naphthalene-sulfonate (salt) Hydrate. It is structurally related to the narcotic methadone.

Continued on next page

UNITED STATES GOVERNMENT

DEPARTMENT OF JUSTICE

Memorandum

Exhibit IV

TO : Frederick M. Garfield, Assistant Director
Office of Scientific Support, SCI

DATE: NOV 26 1971

FROM : Chief Chemist
Special Testing and Research Laboratory, SCILR

SUBJECT: Darvon and Talwin

As you requested in your memorandum of October 15, 1971, we have undertaken a study to determine the ease of isolation of the active ingredients of various dosage forms of Darvon and Talwin. The testing of Talwin and Darvo-Tran was performed on material we purchased from a local pharmacy in November of this year. The other products were obtained from the U.S. Food and Drug Administration which had obtained them from Eli Lilly and Company as NDA submissions.

The products tested and the results we obtained are as follows:

Talwin: Lot No. 464HF; Each tablet contains pentazocine, as hydrochloride, equivalent to 50 mg. base.

The pentazocine hydrochloride may be readily isolated from the excipients by treating the crushed tablet material with either chloroform, ethanol, or warm water. Recovery studies showed 100% extraction of pentazocine hydrochloride by heating the crushed tablet material in water to about 60°C for five minutes, cooling, and filtering. The filtrate containing the pentazocine was clear and could be used for injection.

Pulvule #392: Lot CT-1613-8A, NDA Sample; Propoxyphene napsylate, 100 mg. (Presumably identical to Darvon N).

Although propoxyphene napsylate is not very soluble in cold water, by heating the powder in water at 80-90°C for five minutes, cooling, and filtering, 100% recovery of the active ingredient was obtained. The filtrate was clear and could be used for injection.

Pulvule #393: Lot CT-1614-8A, NDA Sample; Propoxyphene napsylate, 100 mg., with aspirin, 325 mg. (Presumably identical to Darvon N with ASA).

When this material was treated as in #392, above, 93% of the propoxyphene napsylate was recovered, but it was contaminated with 81% of the aspirin.

The propoxyphene salt could be isolated by a preliminary ether wash of the material to remove the aspirin followed by heating the residue in water and filtering. Some of the propoxyphene is lost in the ether wash, and the recovery of the propoxyphene by this procedure was 69%.

Pulvule #395: Lot CT-1611-8A, NDA Sample; Propoxyphene napsylate, 100 mg.; aspirin, 227 mg., phenacetin, 162 mg., and caffeine, 32.4 mg. (Presumably identical to Darvon N Compound).

When this material is heated with water and filtered, the filtrate contains 88% of the aspirin, 62% of the phenacetin, 83% of the caffeine and 80% of the propoxyphene napsylate. Preliminary treatment with ether as in #393, above, removes all but traces of the aspirin and phenacetin. By washing the residue of the ether treatment with cold water prior to extraction of the propoxyphene napsylate with hot water, all but traces of the caffeine are removed and the propoxyphene napsylate is isolated. Recovery by this procedure is 67%.

Darvon 65: Lot 3HE83A; Propoxyphene hydrochloride, 65 mg.

The propoxyphene hydrochloride can be easily isolated from this product by dissolving the powder in water and filtering. Recovery was 90% and the filtrate was clear and could be used for injection.

Darvon with ASA: Lot 4SH93C; Propoxyphene hydrochloride, 65 mg., and aspirin, 325 mg.

As with the napsylate salt, direct aqueous dissolution and filtering carries most of the aspirin along with the propoxyphene. Preliminary washing with ether will remove all but traces of the aspirin and the propoxyphene hydrochloride is then easily removed. Recovery using this procedure is only 58% since some of the propoxyphene hydrochloride is removed in the ether wash.

Darvon Compound 65: Lot 4UD03A; Propoxyphene hydrochloride, 65 mg., aspirin, 227 mg., phenacetin 162 mg., and caffeine 32.4 mg.

This material behaves essentially the same as #395, above, with one exception. The caffeine cannot be removed from the propoxyphene hydrochloride with a cold water wash since both compounds are soluble in cold water. The recovery of propoxyphene hydrochloride was 40-60% and caffeine 100% using preliminary ether wash followed by dissolution in water and filtering. Only traces of phenacetin and aspirin were present.

Darvo-Tran: Lot 4LL70A; Propoxyphene hydrochloride 32 mg., aspirin 325 mg., and phenaglycodol, 150 mg.

When this material was dissolved in water at room temperature and filtered, the filtrate contained 94% of the propoxyphene hydrochloride, 66% of the aspirin, and 41% of the phenaglycodol. Using a preliminary ether extract prior to dissolving in water, less than 5% of both the phenaglycodol and aspirin were present with the propoxyphene; however, recovery of the propoxyphene was only 29-36%.

CONCLUSION

Talwin: The active ingredient, pentazocine hydrochloride, can be easily isolated from the dosage form by simply dissolving the crushed tablet material in water and filtering. The resulting solution is clear and free-flowing and could be used for injection.

Darvon: For all practical purposes, there is little or no difference between the hydrochloride and napsylate salts of propoxyphene in regard to their abuse potential. Although the napsylate is not very soluble in cold water, its solubility in hot water approximates that of the hydrochloride and it is common practice for the abuser to heat preparations to solubilize the drug.

Therefore, either salt of propoxyphene is easily isolated from those dosage forms containing no other active ingredient(s) by dissolving the powder in warm water and filtering. No breakdown of propoxyphene was detected when subjected to heating under the conditions described. The presence of methylcellulose in the napsylate preparations causes no difficulty in the dissolution of the powder or viscosity of the filtrate. The resulting solution is clear, free-flowing, and could be used for injection.

*Memorandum*EXHIBIT V

TO : Mr. Ernest A. Carabillo, Jr.
Chief, Special Programs Division

DATE:

FROM : Laboratory Director
Special Testing and Research Laboratory

SUBJECT: Propoxyphene Solubility

As requested in your memo of 11/26/75, we conducted a study of the solubility and resultant availability of Propoxyphene Napsylate (Darvon-N) from 100-milligram tablets. The tablets used were a commercially available dosage form of Darvon-N (Lot No. 7 KH 43A), and the standard propoxyphene napsylate represented Lot No. 177-135-0D-54.

To determine recoveries, a counted number of tablets (ranging from 1-4) were extracted with either 5.0 or 10.0 ml of water, heating for 5-6 minutes to 70-80°C. The tablets readily disintegrated within a few seconds. After cooling to room temperature, the material was filtered through a cotton pledget about 0.5 cm in the neck of a small funnel. The volume of fluid recovered was measured, the material centrifuged and an aliquot of the supernatant liquid taken for analysis by UV spectrophotometry. One hundred milligrams of propoxyphene napsylate standard was treated in a similar fashion. Results are tabulated below:

<u># tablets extracted</u>	<u>ml H₂O used</u>	<u>ml fluid recovered</u>	<u>concentration of propoxyphene napsylate in filtrate (mg/ml)</u>
1	5.0	2.9	3.0
2	5.0	2.0	4.3
3	5.0	1.4	5.0
4	5.0	1.0	6.5
1	10.0	8.2	2.9
2	10.0	7.8	3.2
3	10.0	6.4	3.1
4	10.0	6.2	4.1
Standard (100 mg)	5.0	3.5	2.3

The fluid recovered was free-flowing and viscosity would not be a factor in use of the filtrate for injection. When the clear solutions were allowed to stand for 1-2 hours, however, precipitation of some additional material occurred, which could lead to problems with intravenous use.

The results indicate that supersaturation of propoxyphene napsylate in water occurs at elevated temperatures. Hence, the maximum concentration which can be obtained cannot be determined with any precision unless all parameters are handled identically. Since such a treatment cannot be expected in the "real world," we have considered such an approach to be beyond the scope of this study.

I hope the above results provide the information you need for your work. If you have any questions, please let me know.

Stanley P. Sobol