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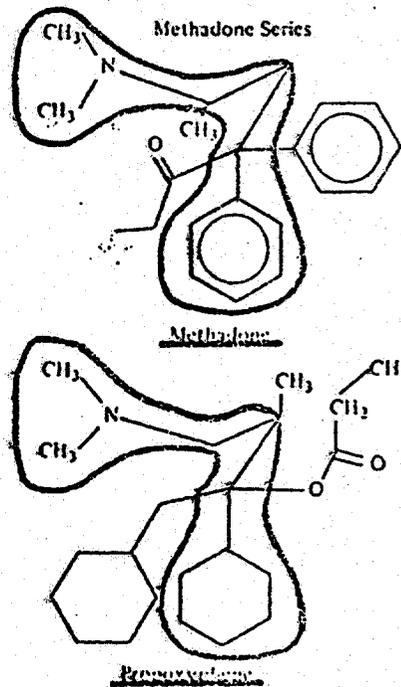
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November 21, 1978

Joseph Califano  
Secretary  
Department of Health, Education, and Welfare  
Humphrey Building, Room 615-F  
200 Independence Avenue, S.W.  
Washington, D.C. 20201

Dear Secretary Califano:

According to recent information we have obtained from the Drug Enforcement Agency (DEA), Department of Justice, the narcotic propoxyphene (as in Darvon)--closely related to methadone<sup>1</sup>--leads all other prescription drugs in the United States in drug-related deaths. In 14 U.S. cities (see page 3) there were more propoxyphene (DPX)-related deaths than morphine and heroin-related deaths in 1977.



SIMILARITY BETWEEN  
PROPOXYPHENE (DPX)  
AND  
METHADONE

TRACER

<sup>1</sup>The above figure is from the Second Edition (1978) of Clinical Pharmacology by Melmon and Morrelli, MacMillan Publishing Co., Inc., New York.

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Because propoxyphene is of so little value as a pain-killer--although Americans spent about 140 million dollars in 1977 for the Lilly-manufactured Darvon drugs<sup>1</sup>--is so widely abused and is so lethal, I urge you to either:

- a) Ban immediately the marketing of propoxyphene as an imminent hazard under the Food, Drug and Cosmetic Act, 21 U.S.C. §355(e), and make it available only as an investigational drug for treating narcotics addicts<sup>2</sup> or, in the alternative,
- b) Support our petition<sup>3</sup> (see enclosure) to reschedule DPX as a Schedule II narcotic which would impose production quotas and prohibit refills of prescriptions.

The following information is excerpted from our Drug Enforcement Agency petition:

• During 1977 alone there were 589 propoxyphene (DPX)-related deaths reported to DEA from their Drug Abuse Warning Network (DAWN) which collects data from only 1/3 of the population of this country.

• In the past 4 years (1974-1977), there have been 2,154 DPX-related deaths reported to DEA. Most recently, as heroin has become somewhat better controlled, DPX-related deaths have even surpassed heroin and morphine-related deaths in many cities. In 14 of the 23 metropolitan areas for which data comparing DPX-related deaths with heroin/morphine deaths are available, propoxyphene (DPX) was associated with more deaths than heroin/morphine in the first half of 1977. The cities are Boston, Buffalo, Cleveland, Dallas, Denver, Indianapolis (home of Lilly, producer of Darvon and other propoxyphene drugs), Miami, Minneapolis, New York, Oklahoma City, Philadelphia, Phoenix, San Antonio and Seattle.

- 1 Propoxyphene is also available as a generic drug but most sales are for Lilly products including Darvon, Darvocet, Darvocet-N, Darvon-N, Darvon Compound 65, etc.
- 2 DPX is currently approved by FDA as an investigational drug for treating narcotic addiction.
- 3 Under the Controlled Substances Act, 21 U.S.C. §811(a), the Department of Justice is being petitioned by Health Research Group today to move propoxyphene to Schedule II.

● DPX DEATH RATES IN U.S. CITIES

In order to compare various U.S. metropolitan areas in terms of DPX-related deaths, the number of such deaths for each area between July 1973 and December 1977 was divided by population (in millions) of that area. These results can be seen in Table 2.

TABLE 2

PROPOXYPHENE(DPX-AS IN DARVON)DEATH RATES  
FOR U.S. METROPOLITAN AREAS<sup>a</sup>

nk	Area	DPX-Related Deaths (7/73-12/77) <sup>b</sup>	Population <sup>d</sup> (In Millions)	Deaths/Million People
	Phoenix	81	1.218	66.5
	San Francisco	189	3.129	60.4
	San Diego	95 <sup>c</sup>	1.588	59.8
	Dallas	80	1.690	47.3
	Denver	61	1.387	44.0
	Los Angeles	276	6.945	39.7
	Cleveland	78	1.975	39.5
	San Antonio	37	.949	39.0
	Miami	52	1.439	36.1
	Buffalo	46	1.327	34.7
	Detroit	132	4.174	31.6
	Oklahoma City	21	.683	30.7
	Philadelphia	133	4.797	27.7
	Boston	72	2.731	26.4
	New York City	274	11.316	24.2
	Chicago	151	6.983	21.6
	Atlanta	32	1.532	20.9
	Washington, DC	60	2.936	20.4
	Indianapolis	15	1.147	13.1
	Minneapolis	20	1.846	10.8
	Seattle	14	1.411	9.9
	Kansas City	11	1.268	8.7
	New Orleans	9	1.094	8.2

These are the 23 metropolitan areas which have been under surveillance by the DAWN Network for at least 2 1/2 years.

DPX-Related Deaths(except San Diego) are from Information Systems Section of Drug Enforcement Agency, Department of Justice. Included are all deaths where drug is a contributing factor or in which a toxic level is found (or suspected because of ingestion history).

Deaths for San Diego are from San Diego coroner's office since San Diego did not become part of the DAWN System until mid-1975. (San Diego includes only 1974-1977.)

Populations of metropolitan areas are from DAWN (Department of Justice) Quarterly Report (July-September 1977).

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For example, Phoenix, the leading U.S. metropolitan area-- as far as DPX-associated death rates--had 81 deaths during that interval. With an area population of 1.218 million the rate was found to be 81 divided by 1.218 or 66.5 deaths per million.

At the other end of the list of metropolitan areas is New Orleans. Its DPX-death rate is 8.2 per million or less than 1/8 that of Phoenix.

① Although DPX was placed in Schedule IV by DEA in March, 1977, this appears to have had little effect on its prescribing or abuse, as has been the case with other drugs placed in Schedule IV. (Schedule IV allows a prescription to be called in over the phone and as many as 5 refills each 6 months. Schedule II would place production quotas on the manufacture of DPX, disallow oral prescriptions and not allow any refills.)

In 1977, there were 33.5 million prescriptions filled for DPX drugs, down only 9.5% from 37 million in 1976. In 1977, during the last 9 months of which DPX was in Schedule IV, there were 589 DPX-related deaths, up from 445 in 1976, before Schedule IV "controls" were imposed.

② According to a 1976 Department of Justice Report on the abuse of DPX, DPX-related fatalities outranked all prescription drugs in death-rate even when the number of prescriptions written were adjusted for. By dividing the number of drug-related deaths by the number of prescriptions, DPX (in this instance plain propoxyphene sold as Darvon by Lilly) was well ahead of all drugs including phenobarbital and valium.

In addition to evidence that DPX (mostly Lilly's Darvon products) is doing more damage than the wares of dope-pushers in many U.S. cities, it is important to analyze why doctors have made DPX so popular.

#### DOCTORS MISLED ON DPX EFFECTIVENESS

Originally introduced as a "non-narcotic" by Lilly in 1957, Darvon(DPX) was said by the company, to be "equal to codeine... milligram for milligram" in its pain-killing properties. At present the preponderance of properly-controlled studies fail to show that DPX is any more effective than aspirin and many show it to be less effective than aspirin, or, in some cases, no more effective than a placebo. It is clearly less effective than codeine. The other attractive feature of this "non-narcotic" was that doctors didn't need a narcotic prescription to use it. The American Medical Association book on Drug Evaluation (1st Edition, 1971) stated, of DPX, that "its popularity is probably due to the fact that it does not require a

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narcotic prescription, rather than to its effectiveness as an analgesic...."

#### DOCTORS ALSO MISLED ON DPX DANGER

Lilly also claimed DPX had "fewer side effects than codeine" but by 1970, the respected source of drug information, The Medical Letter wrote "many physicians are not sufficiently aware that coma, circulatory and respiratory depression, convulsion and death can result from overdose with propoxyphene, that the clinical picture is similar to that seen with narcotic drugs...."

A recent survey (1977) of U.S. physicians shows that most continue to think DPX is a much less dangerous drug than other drugs, which, in fact, are involved in far fewer drug deaths than DPX.<sup>1</sup>

#### A FINE LINE BETWEEN USE AND ABUSE

In larger than recommended doses DPX produces a euphoria or "high" which makes it attractive as a drug of abuse. It is generally agreed that DPX can be addicting--albeit less so than morphine--and one study concluded that "addiction can occur under the usual circumstances of medical prescribing."<sup>2</sup>

The 2nd Edition of Clinical Pharmacology (1978) by Melmon and Morelli stated that "the most prominent effects (of DPX) may be its addictive quality."

The Department of Justice DAWN (Drug Abuse Warning Network) data show that among patients in emergency rooms whose source of drugs could be ascertained, over 90% obtained their DPX with legal prescriptions.<sup>3</sup>

#### NATURE OF DPX DEATHS

In a May 4, 1978 letter to FDA, Oregon Deputy State Medical Examiner Dr. Larry Lewman wrote that "propoxyphene is by far the most common cause of fatal drug overdose in Oregon."

- 1 International Journal of Addiction 12, 43, 1977.
- 2 International Journal of Addiction 9, 775, 1974.
- 3 DAWN Quarterly Report, July-September 1977.

2 Oregon data

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He went on to say that although some DPX overdose deaths were, in fact, attempted suicides, "accidental overdoses of DPX" was the category "into which most of the DPX overdoses in Oregon appear to fall." In other words, the margin between the doses which achieve the desired euphoria and those which are harmful or even fatal is extremely narrow.

Dr. Lewman did not believe that education of physicians was adequate and suggested, in the same letter to FDA, that DPX be moved into Schedule II. (On November 7, 1978, Oregon Public Health Officer, Dr. Edward Press, redirected this request to reschedule DPX in Schedule II in a petition to the Department of Justice, Drug Enforcement Administration.)

In summary, DPX is the deadliest prescription drug in the U.S., has been related to the deaths of thousands of people in the U.S. (and elsewhere) and is even outdoing morphine and heroin in 14 U.S. cities in its relationship to drug deaths.

In my view, there are two possible courses of action:

1. Invoke the Imminent Hazard Section of the Food, Drug and Cosmetic Act, 21 U.S.C. §355(e), and immediately suspend the New Drug Application (and marketing) of DPX. If you determine that there is no legitimate use for DPX as a pain-killer or that the risks of DPX outweigh any benefits even as a pain-killer, and that the drug should therefore be eventually removed from the market, the magnitude of DPX deaths during the 2-3 years that would transpire before the "slow" banning procedures mandate use of the imminent hazard provision. The evidence of DPX-caused deaths is more than sufficient to prove that this drug is "posing a significant threat of danger to public health."

In the British Medical Journal, an editorial on the "Dangers of Dextropropoxyphene"<sup>1</sup> queried, "How good is the case for using the drug at all?" After discussing the lack of "hard data on its therapeutic value...compared with other analgesics", the Journal goes on to say that "any doctor prescribing the drug rather than a simple, less expensive and potentially less toxic preparation should be aware of the hazards and able to justify his choice."

<sup>1</sup> British Medical Journal 1, p. 668, 1977.

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The one use, now under investigation, for which the benefits of DPX may outweigh its risks is in the treatment of narcotic addiction. Because DPX is a narcotic, it has been used to withdraw addicts from other narcotics, such as methadone, its close relative. Since there is in existence an Investigational New Drug (IND) approval for DPX, this use would not be altered by declaring it an imminent hazard and stopping its marketing as an analgesic.

2. Reschedule DPX in Schedule II. If you believe there is a legitimate use for DPX as a pain-killer--despite its relative ineffectiveness for this indication--it could be placed in Schedule II for those people for whom both aspirin and acetaminophen and other less dangerous analgesics were not effective or not tolerated. I do not know how large a group, if any, this might be but I would estimate that it is less than 1% of those currently using DPX. The enclosed petition to the Drug Enforcement Administration seeks this rescheduling under the Controlled Substances Act, 21 U.S.C. §811(a). This act requires that the Secretary of HEW submit an opinion to the Department of Justice concerning any proposed scheduling or re-scheduling of drugs.

Although I favor the imminent hazard route and this letter constitutes our petition to ban DPX as an imminent hazard to the public health, you must decide how best to protect the American public from this deadly drug which--in addition--is wasting more than 140 million dollars a year of health care resources.

I look forward to a prompt reply.

Sincerely,

Sidney M. Wolfe, M.D.  
Director Health Research Group

SMW:pm

Enclosure

NOTE: Legal and/or scientific research for the petition was contributed by Ellis Gordon, Michael Lipsett, an attorney now attending University of California, San Diego Medical School; and Deborah Schechter, staff associate of the Health Research Group. Staff researchers at the Department of Justice, Drug Enforcement Agency, were also helpful in providing data not otherwise available.

Sidney M. Wolfe, M.D. and )  
Public Citizen Health )  
Research Group )

Petitioners

TO: Honorable Griffin Bell  
Attorney General of the United States; and  
Honorable Peter Bensinger, Administrator  
Drug Enforcement Administration, Department of Justice

PETITION REQUESTING TRANSFER OF THE NARCOTIC DEXTROPROPOXYPHENE  
(DARVON) AND ITS SALTS FROM CONTROLLED SUBSTANCES SCHEDULE  
IV TO SCHEDULE II.

I. PETITIONERS

Petitioner Sidney Wolfe is a medical doctor licensed to practice in Washington, DC.

Petitioner Public Citizen Health Research Group is a Washington-based, non-profit organization engaged in public interest research on health issues, including drug abuse.

II. AUTHORITY FOR PETITIONERS

Petitioners' authority to submit this petition derives from the Controlled Substances Act, 21 U.S.C. § 811(a), and the Administrative Procedure Act, 5 U.S.C. § 553(e).

III. THE CASE

In 1977 the Administrator of the Drug Enforcement Administration (DEA) found that the widespread abuse of dextropropoxyphene (Darvon) justified its inclusion in Schedule IV of the Controlled Substances Act. Despite the restrictions which Schedule IV places on the prescription of dextropropoxyphene, this drug continues to be widely prescribed and abused. Petitioners contend that in order to curb such abuse dextropropoxyphene must be subjected to the stringent controls of Schedule II.

Under the Controlled Substances Act, the Attorney General may by rule transfer a drug into Schedule II if he finds that: (1) the drug has a high potential for abuse; (2) the drug has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions, and (3) abuse of the drug may lead to severe psychological or physical dependence. 21 U.S.C. §§811, 812 (b)(2). There is substantial evidence that dextropropoxyphene (Darvon) fulfills these three criteria of Schedule II.

In addition, there is reliable medical evidence that this drug is relatively ineffective as an analgesic, the primary purpose for which it is prescribed. From a therapeutic standpoint, nothing would be lost by restricting the availability of this drug through the imposition of Schedule II controls.

Sidney M. Wolfe, M.D. and )  
Public Citizen Health )  
Research Group )

Petitioners

TO: Honorable Griffin Bell  
Attorney General of the United States; and  
Honorable Peter Bensinger, Administrator  
Drug Enforcement Administration, Department of Justice

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IV. INTRODUCTION

Dextropropoxyphene (hereafter DPX) is structurally related to methadone, a synthetic narcotic; its effects are qualitatively similar to those of narcotics. In 1956, a year before DPX was first marketed as Darvon by Eli Lilly and Company, it was reported that this drug could produce narcotic-like effects of respiratory depression, pupil constriction, and euphoria, and could reduce the severity of withdrawal from morphine.<sup>1</sup> Nevertheless, this narcotic analogue was introduced to physicians as a non-narcotic analgesic, equal, milligram for milligram to codeine, but without the potential for addiction and abuse of the latter.<sup>2</sup> As a result of DPX's being promoted as a potent non-narcotic analgesic, DPX gained such popularity that it has become one of the most commonly prescribed drugs in the United States.<sup>3</sup>

Despite promotional efforts of the Lilly Company to the contrary, DPX remains a narcotic, more harmful and less effective than originally believed. In larger than recommended doses it produces a euphoric "high", which makes it attractive as a drug of abuse. Side effects of DPX, such as dizziness, constipation, nausea and vomiting are typical of narcotics. High doses of DPX produce the characteristic quartet of narcotic overdose--respiratory depression, pinpoint pupils, coma, and circulatory collapse--as well as convulsions, cardiac arrhythmias and pulmonary edema.<sup>4</sup> The respiratory depression produced by DPX overdose can be reversed by naloxone, which is used to treat narcotic overdose.<sup>5,6,7</sup> Physical and psychological dependence on DPX can occur, although this dependence is not so severe as that caused by morphine.<sup>8</sup>

Like the narcotics heroin and morphine, DPX is deadly. From April 1975 to June 1977, (the most recent date for which reliable published comparative statistics are available), it was the second most frequently implicated drug (2nd only to heroin and morphine) in coroners' reports of drug-related deaths in large American metropolitan areas.<sup>9</sup>

Even the Eli Lilly Company has had to modify its public posture. By 1972, it had conceded that "propoxyphene's general pharmacologic properties are those of the narcotics as a group."<sup>10</sup>

Placing DPX in Schedule IV has not significantly affected the sales or abuse of this dangerous narcotic. The value of Lilly's sales (revenue to manufacturer) of 7 DPX products increased from \$82,001,000 in 1976 to \$82,878,000 in 1977.<sup>11</sup> Considering that the retail drug markup is often close to 70%<sup>12</sup>, Americans spent nearly \$140,000,000 during 1977 on Lilly-produced Darvon and Darvon combinations, even though there was a slight decrease in the total number of prescriptions. This does not include the products of the other 32 companies licensed to produce DPX. While reported abuse of DPX has not significantly increased since March 1977, neither has it declined as will be seen in the next section. This is due in large part to the ready availability of DPX--the vast majority of DPX abusers obtain the drug with legal prescriptions. This petition will show that the more stringent controls of Schedule II should be imposed on DPX in order to restrict its availability.

#### V. Criterion 1 - High Potential For Abuse

In determining that a drug should be included in Schedule II, it must be established that the drug has a high potential for abuse<sup>13</sup> 21 U.S.C. §812 (b)(2)(A). A drug's potential for abuse can be estimated in clinical tests such as those for opiate narcotics.

"Assessing Abuse Potential....A drug is considered to be nonopioid with respect to abuse liability (1) if it does not suppress the opioid withdrawal syndrome when tested in subjects physically dependent on morphine, (2) if it does not produce morphine-like physical dependence when given chronically, and (3) if postaddicts neither consistently identify it as "dope" (morphine-like) nor repeatedly request it when offered the opportunity to do so. On the other hand, if a compound is found to share these key characteristics with morphine, it is considered to have a high abuse liability."<sup>13</sup>

As used herein, "abuse" refers to intentional non-therapeutic use of a drug. This included taking a drug for any of the following reasons: (1) dependence (addiction); (2) psychic effects; (3) attempted or successful suicide. See section on Legal Analysis, below, for discussion of legislative interpretation of the term.

According to clinical trials using these criteria, DPX's abuse liability is lower than that of morphine and codeine. However, ultimately the abuse liability of a drug must be evaluated in light of the prevalence of its abuse. Indeed, in determining the proper scheduling for a drug, the Attorney General is directed to consider a drug's "actual or relative potential for abuse." 21 U.S.C. § 811 (c)(1). Looking for evidence of DPX abuse, one discovers an embarrassment of riches. Prior to the inclusion of DPX in Schedule IV in 1977, there was extensive medical and statistical documentation that this drug, alone and in combination with alcohol and other drugs, was subject to both oral and intravenous abuse which resulted in over a thousand deaths between 1969 and 1975. 14-26

Reviewing the medical literature and nation-wide drug abuse statistics, a study commissioned by the Justice Department found in 1976 that:

1. Dextropropoxyphene is a centrally active narcotic analgesic (pain-killer) 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.

In summary, DPX's narcotic-like pharmacologic properties have made it a highly abuseable drug.

#### OLDER DPX DEATH STUDIES

In a huge Lilly-sponsored study involving medical examiners with a jurisdiction covering 52 million people, it was reported that DPX had been implicated in at least 1,022 deaths by the middle of 1975.<sup>28</sup> The authors found that, "the number of deaths involving propoxyphene is increasing each year, and at a faster rate than total drug deaths." They also found that "65.9% of all the cases had the word propoxyphene in the 'cause of death' statement on the death certificate." and that "in 34.1% of the cases the cause of death was officially attributed to something other than propoxyphene alone." In Detroit, the number of drug deaths involving DPX tripled from 1973 to 1975.<sup>29</sup> A similar pattern was observed in North Carolina, with 21 such deaths in 1973, 30 in 1974, and 16 during just the first three months of 1975.<sup>30</sup>

\* Although the easily separable DPX pellet is no longer found in Lilly DPX capsules, at least a few other pharmaceutical companies still produce DPX in this highly abuseable preparation. See FDC Reports, December 12, 1977.

The aforementioned study commissioned by the Justice Department provided an analysis of drug-associated fatalities reported in the DAWN system<sup>31</sup> from July 1973 to September 1975. This analysis showed that DPX was involved in 1,221 deaths, second only to heroin. Furthermore, DPX displayed the greatest relative toxicity of all the drugs reported in the DAWN system. One measure of toxicity utilized was deaths per 1000 emergency room mentions of the drug in the DAWN statistics as compiled in a Department of Justice study on DPX abuse.<sup>31</sup> Reports from coroner's offices of drug-related deaths divided by the number of mentions for the same drug in the DAWN emergency room network showed that DPX was the highest of any drug with 113 coroner-reported deaths for every 1000 emergency room mentions. It ranked ahead of heroin/morphine(98) diazepam (valium)(18) and phenobarbital (104).

Another index of its fatal toxicity as a function of how often it is prescribed can be found by dividing the number of deaths by the number of prescriptions for the drug. Again, DPX outranked all prescription drugs(including diazepam) in the same study.<sup>32</sup>

Why is DPX so toxic? As with other narcotics, it can cause pulmonary edema (fluid accumulation in the lungs) and respiratory depression which can frequently result in fatal respiratory arrest.<sup>33-36</sup> In addition, DPX and its metabolites can depress electrical conduction in heart muscles which can result in arrhythmias and cardiac arrest.<sup>37-48</sup> Fatalities among those using the drug for its psychic effects are due to the small margin of safety between toxic doses and those required to achieve euphoria.<sup>49,50</sup>

<sup>31</sup> Drug Abuse Warning Network, a Drug Enforcement Administration program then operating in 46 states. The statistics cover reports from hospital emergency rooms and from medical examiners (i.e. coroners), who had submitted reports at least 90% of possible reporting days during the life of the DAWN program.

<sup>32</sup> Specifically atrioventricular nodal conduction. The implication of this important finding is that persons with underlying cardiac disease who take DPX even at prescribed doses may inadvertently trigger an arrhythmia culminating in cardiac arrest.

RECENT DPX DEATH DATA

From April 1975 to June 1977, DPX remained the second most commonly mentioned drug in DAWN coroners' reports after a combined category of heroin (Schedule I) and morphine (Schedule II).<sup>51</sup>

Most recently, as heroin has become somewhat better controlled-- at least as reflected by a reduction in deaths from its use--DPX-related deaths have surpassed heroin(and morphine) related deaths in many cities. According to the latest DAWN report published by the Drug Enforcement Agency,<sup>52</sup> in 14 of the 23 cities (61%) for which data comparing DPX-associated deaths with heroin/morphine deaths were available, DPX was associated with more deaths than heroin/morphine in the first half of 1977.\*

These cities were: BOSTON, BUFFALO, CLEVELAND, DALLAS, DENVER, INDIANAPOLIS, MIAMI, MINNEAPOLIS, NEW YORK, OKLAHOMA CITY, PHILADELPHIA, PHOENIX, SAN ANTONIO, SEATTLE.

The DAWN statistics also demonstrate that DPX has been abused much more frequently than several Schedule II drugs. The following table shows the number of mentions that DPX, methaqualone (Quaalude), amphetamines, and secobarbital received in the total DAWN system during the last full year for which comparative data were available.

TABLE I

PROPOXYPHENE(DPX) RELATED DEATHS  
(JULY 1976 - JUNE 1977)  
CORONERS' REPORTS

<u>DRUG</u>	<u># CORONERS' REPORTS</u>	
Dextropropoxyphene(DPX)	491	
Diazepam(Valium)	388	
Meprobamate(Miltown)	316	SCHEDULE IV
Chlordiazepoxide(Librium)	70	
Flurazepam(Dalmane)	66	
Amphetamines	27	
Methaqualone(Quaaludes)	57	SCHEDULE II
Secobarbital(Seconal)	222	

Similarly, as also shown in the table, the DAWN statistics show that DPX is more frequently abused than the reported Schedule IV drugs.

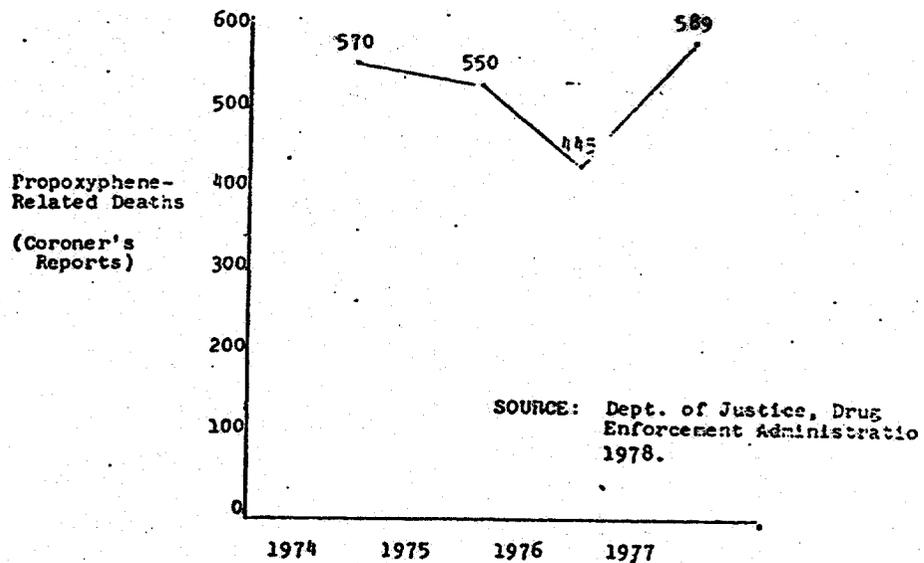
\* The most recent time period for which data are available.

In relation to reported Schedule IV drugs, DPX is involved in more coroners' reports than the three others.

Although these comparative data include just 3 months during which DPX had become subject to Schedule IV restrictions, more recent data\* including all of 1977 reveal that the control requirements of Schedule IV have failed to significantly alter the prevalence of DPX abuse. Figure 1A shows the time trend for the past four years for DPX-related deaths.

FIGURE 1A

TIME TREND FOR DPX-RELATED DEATHS



(Each point represents the total at the end of the year.)

DPX Into Schedule IV

It can be seen that deaths involving DPX declined somewhat between 1975 and 1976, due, perhaps in part, to the warnings then appearing in the medical and lay press.<sup>53,54</sup>

\* Obtained from the Section of Information Systems, Drug Enforcement Administration, Washington, DC.

However, by the time DPX was added to Schedule IV (March 1977), these drug-related deaths were once again on the increase. The total number of DPX-related deaths in the U.S. for the last 4 years is 2,154. Recent reports of DPX-related deaths from abroad indicate that this crescendo of abuse is not limited to the United States.<sup>55-59</sup>

DPX-RELATED-DEATHS

As mentioned previously, in about 2/3 of cases, DPX is mentioned on the death certificates as "cause of death" whereas in 1/3 of cases the death is attributed to "something other than DPX alone."<sup>60</sup>

In this Lilly-sponsored study<sup>61</sup> in 24% of the DPX-related deaths, DPX was the only drug involved and in an additional 18% DPX and alcohol were involved. In other cases, even though additional drugs were involved, DPX was mentioned on the death certificate in the "cause of death" statement.

More recent data show an increase in the percentage of cases in which DPX was the only drug involved. By 1977 (See Figure 1A) there were 589 DPX-related deaths of which 190 or 32% involved only DPX. (Up from 24% in the Lilly study and 23.3% in 1976.)

DPX DEATH RATES IN U.S. CITIES

In order to compare various U.S. metropolitan areas in terms of DPX-related deaths, the number of such deaths for each area between July 1973 and December 1977 was divided by population (in millions) of that area. These results can be seen in Table 2.

TABLE 2

PROPOXYPHENE(DPX-AS IN DAWN) DEATH RATES  
FOR U.S. METROPOLITAN AREAS<sup>a</sup>

Rank	Area	DPX-Related Deaths (7/73-12/77) <sup>b</sup>	Population <sup>d</sup> (in Millions)	Deaths/Million People
1	Phoenix	81	1.218	66.5
2	San Francisco	189	3.129	60.4
3	San Diego	95 <sup>c</sup>	1.588	59.8
4	Dallas	80	1.690	47.3
5	Denver	61	1.387	44.0
6	Los Angeles	276	6.945	39.7
7	Cleveland	78	1.975	39.5
8	San Antonio	37	.949	39.0
9	Miami	52	1.439	35.1
10	Buffalo	46	1.327	34.7
11	Detroit	132	4.174	31.6
12	Oklahoma City	21	.683	30.7
13	Philadelphia	133	4.797	27.7
14	Boston	72	2.731	26.8
15	New York City	274	11.316	24.2
16	Chicago	151	6.983	21.6
17	Atlanta	32	1.532	20.9
18	Washington, DC	60	2.935	20.4
19	Indianapolis	15	1.147	13.1
20	Minneapolis	20	1.845	10.8
21	Seattle	14	1.411	9.9
22	Kansas City	11	1.268	8.7
23	New Orleans	9	1.094	8.2

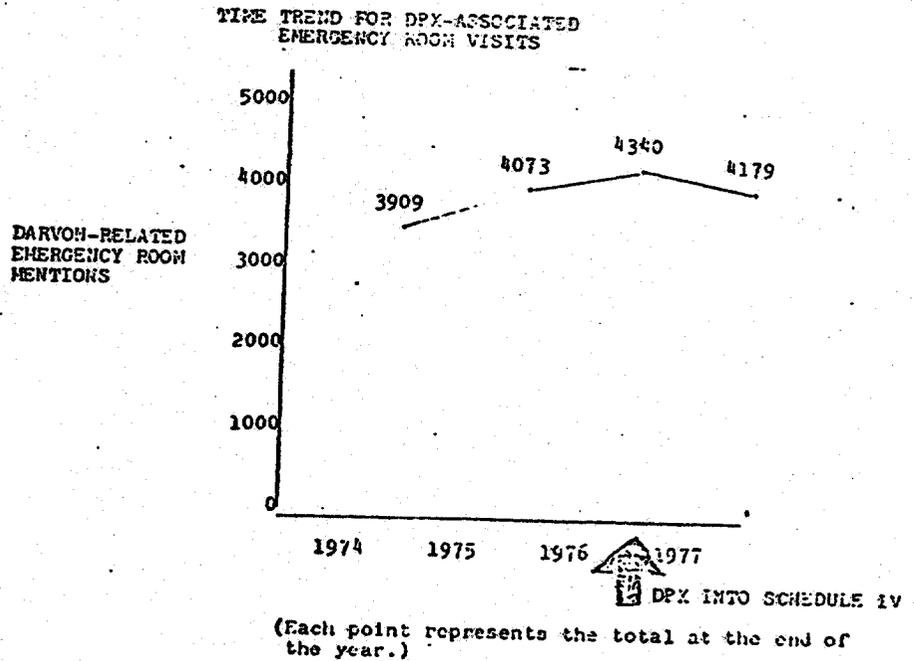
- a. These are the 23 metropolitan areas which have been under surveillance by the DAWN Network for at least 2 1/2 years.
- b. DPX-Related Deaths (except San Diego) are from Information Systems Section of Drug Enforcement Agency, Department of Justice. Included are all deaths where drug is a contributing factor or in which a toxic level is found (or suspected because of ingestion history).
- c. Deaths for San Diego are from San Diego coroner's office since San Diego did not become part of the DAWN System until mid-1975. (San Diego includes only 1974-1977.)
- d. Populations of metropolitan areas are from DAWN (Department of Justice) Quarterly Report (July-September 1977).

For example, Phoenix, the leading U.S. metropolitan area-- as far as DPX-associated death rates--had 81 deaths during that interval. With an area population of 1.218 million the rate was found to be 81 divided by 1.218 or 66.5 deaths per million.

At the other end of the list of metropolitan areas is New Orleans. Its DPX-death rate is 8.2 per million or less than 1/8 that of Phoenix.

Inspection of the time-trend of DAWN emergency room reports, as seen in Figure 1B, reveals that there has also been no remarkable decline since Schedule IV controls were imposed early in 1977.<sup>62</sup>

FIGURE 1B



Clearly the controls of Schedule IV have not significantly diminished the reported abuse of this drug. Moreover, since the DAWN statistics only account for approximately 30% of U.S. population with 582 emergency rooms and 103 medical examiners (coroners)

included in the system, the above data, represent only a partial picture of DPX abuse.<sup>63</sup>

As can be seen in Table 3, within a year after amphetamines, methaqualone and secobarbital were placed in Schedule II, there were decreases of 50%, 52.4%, and 47.6% respectively, in the number of prescriptions. Within 4 years, all had decreased substantially more so that prescriptions for each were about 25% of what they had been before Schedule II was imposed. Placing drugs in Schedule IV, however, has much less effect on the number of prescriptions. For diazepam (valium) Schedule IV caused only a 6.9% decrease in prescriptions the first year.

TABLE 3  
EFFECT ON THE NUMBER OF PRESCRIPTIONS  
OF PLACING DRUGS IN SCHEDULE IV OR SCHEDULE II

	Drug	Annual Number of Prescriptions (Millions)		% Change In Prescriptions
		Before Scheduling	1 Year After	
Schedule IV	Diazepam (Valium)	58 Million	54 Million	-6.9%
	Flurazepam (Dalmane)	11.5 Million	12.75 Million	+10.9%
	Propoxyphene (Darvon)	37 Million	33.5 Million	-9.5%
Schedule II	Amphetamines	16 Million	8 Million	-50.0%
	Methaqualone (Quaaludes)	42 Million	20 Million	-52.4%
	Secobarbital (Seconal)	8 Million	4.3 Million	-47.6%

Flurazepam, already on the rise when placed in Schedule IV, rose an additional 10.9% during the first year.

Thus, placing DPX in Schedule IV has predictably had little effect on the number of prescriptions, availability or abuse (See Figure 1A, p 7, as measured by annual DPX-deaths). Since there is continuing evidence even relative to the Schedule II drugs for its abuse (See Table 1, p 6), DRA should transfer DPX to Schedule II.

VI. Criterion 2 - Accepted Medical Use

A second finding that must be made if a drug is to be included in Schedule II is that it have an "accepted" medical use or an accepted medical use with severe restrictions. 21 U.S.C. § 812(b)(2). Over thirty million prescriptions for DPX preparations were issued and refilled in 1977,<sup>64</sup> providing evidence that DPX is still widely "accepted" in the medical community, despite considerable evidence that at best DPX is no more effective an analgesic than aspirin.<sup>65</sup> Physicians' misconceptions about the effectiveness and the abuse potential of this drug have led to overprescribing and abuse.

Among patients whose source of drugs could be ascertained in DAWN emergency rooms, over 90% had obtained their DPX with legal prescriptions.<sup>66</sup> In a recent survey of physicians' attitudes towards various drugs, DPX was rated as one of the most innocuous, while other controlled substances which are less lethal than DPX (e.g. Librium, Seconal, Methadrine and Phenobarbital), were considered to be more dangerous.<sup>67</sup> Thus the abundant prescribing of DPX could be more accurately characterized as an "accepted medical mis-use."

However, DPX Napsylate (DPX-Nap) does have a medical use in the detoxification and maintenance of narcotic addicts,<sup>68-70</sup> although the use of DPX for the purpose is presently under the Investigational New Drug Provision of the Food, Drug and Cosmetic Act. In high doses DPX-Nap exerts significant morphine-like effects, and can suppress symptoms of withdrawal from other narcotics.<sup>71</sup> The literature suggests that DPX-Nap may be most beneficial in assisting withdrawal from methadone.<sup>72-73</sup> DPX-Nap is physically less addictive than methadone, which has made it attractive as an agent to detoxify narcotic addicts. However, because such high doses are required to suppress symptoms of narcotic withdrawal and because DPX has such a high potential for abuse, detoxification must be carefully supervised and access to DPX-Nap strictly controlled.

Other than narcotic detoxification, not yet an "approved" indication for use of the drug, its use as a pain-killer or analgesic is clearly an accepted medical use even though, as discussed above, it has led to widespread abuse and, as will be seen, is much less effective than generally believed.

We would agree with the statement in the January 3, 1970 Medical Letter that "65 mg dose of DPX has mild analgesic effect and can be tried in patients in whom the usual doses of analgesics such as aspirin or acetaminophen (as in Tylenol or Datril) are not effective or not tolerated."

We would add, however, that the number of such people is extremely small and were the use of DPX limited to this population, the number of prescriptions would be more like 300,000 per year than 30 million (1/100 as much use as now).

VII. Criterion 3 - Dependence (Addiction)

The last finding that must be made regarding DPX is that its abuse may lead to severe psychological or physical dependence.<sup>74</sup> 21 U.S.C. § 812(b)(2)(c). This disjunctive language of the Controlled Substances Act indicates that a finding of either severe psychological or physical dependence resulting from DPX abuse will justify its inclusion in Schedule II. There is substantial evidence that DPX can produce strong psychological dependence and, sometimes, significant physical dependence.

Clinical trials have shown that DPX can produce physical addiction, as manifested by withdrawal symptoms. Although this apparently does not occur at recommended doses for relief of pain,<sup>74</sup> patients undergoing narcotic withdrawal using DPX-Nap have become physically addicted to the latter.<sup>75</sup> In 1956, Fraser and Isbell

<sup>74</sup> As used herein, physical dependence refers to a condition of latent central nervous system hyperexcitability induced by frequent administration of a drug. Signs and symptoms of abstinence or withdrawal appear when drug administration suddenly ceases. (In the case of opiates, a withdrawal syndrome can be precipitated by administration of narcotic antagonists such as naloxone and nalorphine.) Psychological dependence on a drug can develop along with, or in the absence of, physical dependence. A salient characteristic of psychological dependence on a drug is the tendency for the latter to provide positive reinforcement for repetitive drug use by direct action.

concluded that:

"[D-propoxyphene] has addictive liability. This is indicated by, (a) the induction of opiate-like symptoms when administered in large oral doses to former opiate-addicts, (b) its ability to partially suppress signs of abstinence from morphine, (c) the production of consistent, although very mild, signs of abstinence when the drug was abruptly discontinued after 53 or 54 days of addiction in five subjects."<sup>76</sup>

Four years later these investigators undertook controlled experiments which suggested that the addictive potential of DPX was "substantially less than that of codeine."<sup>77</sup>

Case reports tend to substantiate the claim that the physical dependence produced by DPX is generally moderate; however, psychological dependence can be significant. Elson and Domino reported a case of DPX addiction "characterized by extreme psychic craving, euphoria, and tolerance to the dextropropoxyphene hydrochloride...The patient showed definite withdrawal signs, including chills, profuse perspiration, cramping, abdominal pain, headaches, nervousness and diarrhea."<sup>78</sup> (emphasis added)

Reviewing the literature on DPX dependence in 1971 (six published reports), Salter stated:

"It is evident from these reports that propoxyphene can produce both strong psychological dependence and some degree of physical dependence, although quantitatively, less than that of morphine or codeine. Significant tolerance does occur and mild to moderate withdrawal symptoms may sometimes be elicited in a dependent person by sudden discontinuance of the propoxyphene."<sup>79</sup> (emphasis added)

Occasionally physical withdrawal symptoms may be severe.

Mattson et al. described 4 patients chronically dependent on high doses of DPX:

"Not only did the patients continue using the drug for its psychic effect, but 3 of them were unable to stop because discontinuation produced withdrawal symptoms characterized by perspiration, tremulousness, and nausea which were promptly relieved when more propoxyphene was taken. One patient developed a severe delirium lasting four days after discontinuation of the drug."<sup>80</sup>

Judging from the published literature, oral abuse usually appears to lead to dependence and psychic craving only in doses much higher than the so-called therapeutic dose for relief of pain symptoms.<sup>81</sup> Yet Salguero et al. described a case of severe psychic (but minimal physical) dependence in an individual whose average intake was only 65 mg every 2 to 4 hours, or just 1.5 to 3 times the recommended therapeutic dose.<sup>82</sup> The Justice Department study even noted cases of psychic dependence developing at the recommended therapeutic levels for pain.<sup>83</sup>

Addiction to DPX may occur in individuals with no prior psychiatric history or drug abuse. Exemplifying DPX addiction in persons innocent of prior drug abuse are cases of newborn infants, addicted in utero, who have displayed signs and symptoms of withdrawal shortly after birth.<sup>84,85,86</sup> In 1974, in a review of the literature and presentation of seven new cases, Maletsky provided convincing evidence that:

1. Addiction to propoxyphene can occur in individuals neither psychiatrically ill nor "addiction prone";
2. Addiction can occur under the usual circumstances of medical prescribing;
3. Tolerance and withdrawal can be clearly demonstrated;
4. Addiction can occur without the initial euphoria.<sup>87</sup> (emphasis added)

Considering the relative analgesic ineffectiveness of DPX at low doses, it is not difficult to understand why patients might increase their dosage in trying to achieve better pain relief, however, some patients may become inadvertently addicted.

It is clear that oral administration is sufficient to maintain addiction; intravenous injection is not necessary.<sup>88</sup> Indeed, dependence cannot be maintained for long by intravenous or subcutaneous infusion because of DPX's destructive effects on the veins and soft tissues.<sup>89</sup> Nevertheless, narcotic addicts shoot DPX intravenously when more potent narcotics are in short supply, e.g., when the addicts are incarcerated.<sup>90</sup>

In light of the foregoing evidence of psychic and physical dependence and tolerance, the Administrator of the DEA found that "Abuse of DPX may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III."<sup>91</sup> If this is true, the dependence produced by drugs and other substances in Schedule III, and a fortiori by those in Schedule II, should be considerably more severe. Yet it is not clear that certain drugs in Schedule II produce any greater degree of physical or psychologic dependence than DPX. Of amphetamines, for example, a widely-used medical textbook states that, "Physical dependence manifested as withdrawal signs is difficult to establish...The development of tolerance is also not easy to prove."<sup>92</sup> Goodman and Gilman, an authoritative pharmacology text states:

For a long time it was believed that, except for drug craving, prolonged sleep, general fatigue, lassitude, and depression, there were no withdrawal symptoms from amphetamine-like drugs and, therefore, no physical dependence...It is still considered true that abrupt discontinuation of sympathomimetic amines does not cause major, grossly observable, physiological disturbances that would necessitate the gradual withdrawal of the drug. But the prolonged sleep, lassitude, fatigue, and depression, that follow discontinuation of these drugs are difficult to attribute merely to the preceding loss of sleep and weight...Most observers now recognize the existence of a withdrawal syndrome following discontinuation of amphetamine-like drugs. Its role in perpetuating drug use or relapse is not clear.<sup>93</sup> (emphasis added)

The relation between this withdrawal syndrome, characterized by fatigue and hunger, and amphetamine use has not even been firmly established. Yet amphetamines have been included in Schedule II, despite the lack of evidence of severe physical dependence.

DPX is far more widely abused than the amphetamines and, when abused it produces a comparable degree of psychological dependence and a greater degree of physical dependence. Thus DPX represents an even stronger case for inclusion in Schedule II.

VII. Analgesic Impotence of Propoxyphene

While DPX's potential for abuse has been understated, the claims for its analgesic potency have been grossly exaggerated. No significant analgesic effect has ever been shown for DPX preparations in properly conducted\* clinical studies. In a review of the published literature undertaken in 1970, Miller et al., discovered that only 20 of 243 "studies" on DPX had been conducted double-blind.\*\*<sup>94</sup> Even among these 20 studies, several had design defects such that their results were of questionable validity. Gleaning what remained of the analgesic efficacy of DPX in relieving several kinds of pain, the authors concluded: "Propoxyphene is no more effective than aspirin or codeine and may even be inferior to these analgesics...When aspirin does not provide adequate analgesia, it is unlikely that propoxyphene will do so."

Sixteen of the studies reviewed by Miller had compared DPX with placebo. In nearly half of these (7/16), there was no significant difference in analgesia between DPX and placebo. Four of these latter studies included tests using 65 milligram (mg) doses of DPX, which remains the manufacturers' suggested dose.<sup>95</sup>

Three more recent double-blind studies have suggested that, at the manufacturer's recommended dose, DPX is no more effective in pain relief than placebo.<sup>96,97,98</sup> Moertal et al. concluded:

"The therapeutic credentials of both propoxyphene (Darvon) \$9.50 per 100 doses of 65 mg) and ethoheptazine (Zactone, \$7.40 per 100 doses of 75 mg) must be classified as very equivocal. In this study, neither showed a significant advantage over placebo, and both were significantly inferior to aspirin."<sup>97</sup>

\* I.e., including, at a minimum, randomization and double-blind observation.

\*\* A double-blind trial exists where neither patient nor observer knows which treatment the patient is receiving. This minimizes bias and preconceptions of patient and observer both, and is imperative in a study design in order to achieve meaningful results.

Although Dr. C.M. Gruber, one of Eli Lilly's medical spokesman, took exception to this conclusion,<sup>100</sup> his own published investigations have also shown that DPX is no more effective than placebo in single 65 mg doses.\* 101

In 1977 Miller reviewed 13 double blind studies\*\* of DPX's analgesic effectiveness, twelve of which had been published subsequent to his earlier review.<sup>102</sup> Five of these thirteen studies purported to evaluate the relative efficacy of DPX hydrochloride and DPX napsylate, which was introduced in 1971 by the Lilly Company just before its patent on DPX hydrochloride expired. Miller's conclusion: "The introduction of the napsylate salt PRX [i.e. dextropropoxyphene] has not provided a more effective preparation, and the napsylate has no other clinically significant advantages over the hydrochloride."

Lacking proof of superior analgesic efficacy, the popularity of DPX Napsylate products (Darvon-N, Darvocet-N, Darvon-N with ASA, etc.) attests to the superior efficacy of the Lilly Company's promotional efforts.

The other eight studies reviewed by Miller once again failed to demonstrate that DPX had any analgesic advantage over the other less expensive medications. Indeed, as noted above, three of these studies suggested that DPX was no more effective than placebo.

Miller's review also discussed all the double-blind studies comparing DPX hydrochloride and DPX napsylate combination products with other analgesics. Considering the paucity of well-designed studies comparing combination drugs with single analgesics, the fact that most analgesic preparations prescribed are combinations is surprising. Miller found only one well-designed study comparing acetaminophen (the active ingredient in Tylenol, Datril, etc.), acetaminophen plus DPX (i.e. Darvocet), DPX alone, and placebo.<sup>103</sup>

\* Dr. Gruber's conclusion in his 1977 study (note 90) that DPX in multiple doses does provide significantly greater relief than placebo is suspect because he neglected to randomize the patients in his study.

\*\* Including 2 of the 3 just discussed.

That study demonstrated that acetaminophen alone was as effective in pain relief as acetaminophen plus DPX. In other words, the analgesic property of this combination can be attributed to the acetaminophen by itself.

Similarly, in his review Miller discovered only one good study comparing aspirin with aspirin plus DPX.<sup>104</sup> The authors of that study found that propoxyphene napsylate plus aspirin was "significantly inferior to aspirin plus either codeine or oxycodone; but not significantly different from aspirin alone." In other words, here once again, the DPX combination analgesic provided no significant benefit over plain aspirin.

Finally, of only five double-blind studies on DPX and aspirin, phenacetin, and caffeine (APC) combinations, Miller found that two compared DPX and APC with APC alone. One of these two studies found that DPX Napsylate plus APC was superior to APC alone.<sup>105</sup> This alleged superiority of DPX-APC over APC alone must be interpreted in light of the above-mentioned well-designed studies where no such difference in pain relief attributable to DPX could be detected. That is, the alleged advantage of DPX plus other analgesics must be quantitatively minute since none but this particular Lilly study could discover it.

Thus Miller states: "There is little evidence that combinations of PRX [i.e. DPX] with other analgesics are superior to one analgesic alone. Aspirin or acetaminophen appears to be just as effective when given alone as when given with PRX."

In conclusion he declares:

"It is now more doubtful than ever that PRX HC<sub>1</sub> [i.e. DPX] 65 mg provides an analgesic effect equal to that of aspirin 650 mg... There is no conclusive evidence that combinations of PRX with other analgesics are more effective than PRX or other analgesics alone. In view of these findings, the continued widespread use of PRX preparations is perplexing."

It is clear that from a therapeutic standpoint, little if anything would be lost by restricting the availability of DPX. DPX is apparently no more effective in pain relief than aspirin or acetaminophen.

IX. Legal Analysis

The evidence of the actual abuse and acute toxicity of DPX summarized above demonstrates that the more stringent Schedule II controls are now warranted. DPX's abuse potential has been compared to that of other drugs which have been placed in Schedule I by DEA. As Dr. Theodore Cooper, then Assistant Secretary for Health admonished in a 1976 memorandum recommending that DPX be placed in Schedule IV:<sup>106</sup>

"As with most psychoactive drugs, abuse potential of a particular drug is usually described in terms of proto-type or 'reference' drugs. In this respect, propoxyphene has been compared to codeine, morphine and heroin. Such comparisons have included both acute physiological and psychological effects of propoxyphene and the chronic effects of high dose administration."<sup>106</sup>

Dr. Cooper acknowledges DPX's potential for abuse and acute toxicity are well recognized, and the facts of widespread actual abuse confirms Dr. Cooper's reference to the similarities between DPX and heroin and morphine. Perhaps most compelling of the evidence thus far assembled concerning the extent of DPX's actual abuse is the DAWN statistics which demonstrate that deaths involving DPX abuse in 14 major metropolitan areas occur more frequently than deaths involving heroin and morphine combined.<sup>107</sup>

Although Dr. Cooper recommended that DPX be placed in Schedule IV, it's difficult to reconcile this recommendation with his finding that DPX's potential for abuse is equivalent to substances like heroin and morphine, which have been placed in Schedule I. However, whatever reasons Dr. Cooper may have had in 1976 for not advocating more stringent controls on DPX, his recommendation was untenable in light of then existing statistics which established the unchecked actual abuse of DPX.

The effect of transferring DPX to Schedule II is that the drug will be subject to requirements that prescriptions be in writing and may not be refilled, 21 U.S.C. § 829(a), and that the drug will not be produced in excess of government-established quotas based on estimated medical and scientific need. 21 U.S.C. § 826(c). In contrast, Schedule IV allows prescriptions for DPX to be transmitted orally and refilled five times in any six month period. 21 U.S.C. § 829(b). Moreover, the penalty for violating provisions of the Act where a Schedule II drug is involved is substantially more severe than for a Schedule IV drug.<sup>108</sup>

As has been the case with amphetamines and other widely abused drugs which DEA has been forced to transfer into Schedule II to curb their abuse, DPX abuse will not subside unless the more stringent Schedule II controls are imposed.

Because of the CSA's overriding emphasis on protecting the public from hazardous drugs, Congress, in the CSA Act, requires the Attorney General to determine the schedule in which to place a particular drug on the basis of three factors; its potential for abuse, its currently accepted medical use, and the degree to which it causes physical or psychological dependence.<sup>109</sup> To provide guidance to the Attorney General, the statute further states that the Attorney General's inquiry must include an evaluation of the following factors:

1. Its actual or relative potential for abuse.
2. Scientific evidence of its pharmacological effect, if known.
3. The state of current scientific knowledge regarding the drug or other substance.
4. Its history and current pattern of abuse.
5. The scope, duration and significance of abuse.
6. What, if any, risk there is to the public health.
7. Its psychic or physiological dependence liability.
8. Whether the substance is an immediate precursor of a substance already controlled under this subchapter. [21 U.S.C. § 311(c).]

In addition to the factors listed in Section 811(c) of the Act, the Attorney General must request the recommendation of the Secretary of HEW, including the Secretary's consideration of the eight factors listed above. 21 U.S.C. § 811(b).

It is apparent from the statute that the critical inquiry in considering whether to transfer a substance to a more stringent category is its potential for abuse. Indeed, the statute requires that this factor be considered before any further proceedings are initiated. 21 U.S.C. § 811(a)(1)(A). Furthermore, four of the criteria enumerated above specifically concern the substance's potential for abuse. 21 U.S.C. §§ 811(1)(4), (5) and (6).

The statutory emphasis on the substance's potential for abuse and the Congressional intent that abuse be the principal, if not the determinative part of the inquiry is confirmed by the House Report accompanying the passage of the Act, which describes the factors influencing the Attorney General's inquiry as follows:

A key criterion for controlling a substance, and the one which will be used most often, is the substance's potential for abuse. If the Attorney General determines that the data gathered and the evaluations and recommendations of the Secretary constitute substantial evidence of potential for abuse, he may initiate control proceedings under this section. Final control by the Attorney General will also be based on his findings as to the substance's potential for abuse.<sup>110</sup>

The House Report continues with the definition of "potential for abuse", which includes factors relating to (1) the health of the drug user or the safety of the community; or (2) the extent that the drug is diverted from legitimate drug channels; or (3) the finding that individuals are taking the drugs on their own initiative rather than on the basis of medical advice.<sup>111</sup> Unquestionably, the hundreds of deaths due to DPX overdose each year illustrate that DPX's potential for abuse exceeds the requirements of each of these criteria.

In a similar vein, the House Report further provides that "misuse of a drug in suicides and attempted suicides, as well as injuries resulting from unsupervised use are regarded as indicative

of a drug's potential for abuse.<sup>112</sup> In this context, it is significant that 55% of the emergency room mentions of DPX from July-September 1977 consisted of suicide attempts, according to the DAWN statistics.<sup>113</sup> Another 18% were associated with addiction or "psychic effects."<sup>114</sup>

Furthermore, the courts which have construed the CSA have also relied almost exclusively on the substance's potential for abuse in reviewing the propriety of decisions to place a drug in a particular schedule. Indeed, in The National Organization for the Reform of Marijuana Laws (NORML) v. Drug Enforcement Administration, 559 F.2d 735(D.C.Cir. 1977), the Court of Appeals rejected DEA's claim that the lack of established medical use for cannabis, standing alone, required that it be included in Schedule I. 559 F.2d at 747. Rather the Court held that under the CSA, DEA is bound to balance medical usefulness against the other factors enumerated in the Act, which the Court summarized as the potential for abuse and the danger of dependence. cf. United States v Haidon, 355 F.Supp. 743, 748-749 n.4 (D.Conn. 1973)

In addition to evidence of DPX's overwhelming abuse, two other factors further point to the need for tighter controls on DPX's availability. First, DPX's toxicity, discussed above.<sup>115</sup> DPX is particularly dangerous because the margin between the doses necessary to achieve the euphoric state and those which are harmful and often lethal is extremely narrow. As DEA recognizes, although the statute and the legislative history are silent on the weight to be given to acute toxicity in assessing the appropriate schedule for a substance, toxicity is an extremely important consideration to weigh.<sup>116</sup> In the case of DPX, toxicity weighs heavily towards the imposition of more stringent controls.

Second, the minimal therapeutic value of DPX must also be balanced against the harm and death that this drug is causing to hundreds of individuals each year. As demonstrated above, aspirin or acetaminophen (Tylenol) appears to be at least as effective when given alone as when given with DPX.<sup>117</sup> For those who can not take aspirin, and choose to take DPX over the other analgesics, Schedule II controls will hardly present a barrier to use of DPX, which will remain available on a prescription basis.

In conclusion, the extent of DPX abuse as presented above, plainly demonstrates that the present controls are wholly inadequate. DEA is required by law to curb the abuse of this minimally effective and extremely toxic drug by transferring DPX to Schedule II and should not retreat from its legislative mandate.

FOOTNOTES

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27. Drug Control Division, *supra* note 24, at 92-93.
28. Finkle, B.S., et al., *supra* note 23.
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30. McBay, A.J., and P. Hudson, *supra* note 25.
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108. The penalty under the Act where a controlled substance under Schedule II is involved is up to 5 years imprisonment, a fine of up to \$15,000 or both. In the case of a Schedule IV Substance, the penalty is up to 3 years imprisonment, a fine of up to \$10,000 or both. 21 U.S.C. § 841(b)(1)(B) and (b)(2).
109. 21 U.S.C. § 812. The findings required for Schedules II and IV are as follows:
  - (2) Schedule II
    - (A) The drug or other substance has a high potential for abuse.
    - (B) The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions.
    - (C) Abuse of the drug or other substance may lead to severe psychological or physical dependence.
  - (4) Schedule IV
    - (A) The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule III.
    - (B) The drug or other substance has a currently accepted medical use in treatment in the United States.
    - (C) Abuse of this drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III.
110. H.R. 91-1444, 91st Congress, 2d Session pt. 7, at 34, cited in U.S. Code Cong and Admin News 1970, p 4601. [Hereinafter referred to as H.R. 91-1444]
111. The term "potential for abuse" is adopted from Section 201(v) of the Food, Drug and Cosmetic Act as defined in 21 C.F.R. 166.2(c), cited in U.S. Code Cong. and Admin. News 1970, p 4601.
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