Public Citizen 35 YEARS
Protecting Health, Safety & Democracy
Congress Watch • Critical Mass • Global Trade Watch • Health Research Group • Litigation Group
Joan Claybrook, President

2692 6 FEB 28 A8:10

February 28, 2006

Andrew Von Eschenbach, M.D., Acting Commissioner
U.S. Food and Drug Administration
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Von Eschenbach:

Public Citizen, representing 160,000 consumers nationwide, hereby petitions the Food and Drug Administration (FDA) pursuant to the Federal Food, Drug and Cosmetic Act 21, U.S.C. Section 355(e)(3), and 21 C.F.R. 10.30 to immediately begin the phased removal from the market of propoxyphene (Darvon) and all propoxyphene-containing products such as Darvocet (propoxyphene and acetaminophen). Propoxyphene (now sold mainly as a generic drug), which has a cardiotoxic metabolite, has been associated with 2110 reported accidental deaths in the U.S. from 1981 through 1999. It is a narcotic that induces the classic triad of psychological dependence, physical dependence, and tolerance, and has repeatedly been shown in controlled clinical trials to be a relatively weak painkiller. The phased withdrawal in the U.K of these products was announced one year ago when the British government stated that the efficacy of this product "is poorly established and the risk of toxicity in overdose, both accidental and deliberate, is unacceptable." They further said that "It has not been possible to identify any patient group in whom the risk-benefit [ratio] may be positive." (http://www.mhra.gov.uk/home/groups/pl-a/documents/drugsafetymessage/ con019461.pdf) A phased withdrawal, instead of an immediate one, is necessary because of the addicting properties of the drug and the need to switch patients to other painkillers.

Overview

Explaining the background for removing propoxyphene products from the market, the British Committee on the Safety of Medicines pointed out, in January 2005, that "Each year there are 300-400 fatalities following deliberate or accidental drug overdose involving co-proxamol [propoxyphene/acetaminophen] in England and Wales alone. Approximately one-fifth of these deaths [60-80] are considered to be accidental." Thus in those two countries alone, with a population of 53 million people---approximately 18% of the size of the U.S.-- there were an estimated 60 to 80 accidental deaths a year from co-proxamol or propoxyphene/ acetaminophen.

Because it continues to be so widely prescribed in the U.S. (the 12th highest-selling generic drug in 2004 with 23 million prescriptions filled and sales that year of $291 million[1]) and

2006P-0090 CP1

because toxicity develops at only slightly above the recommended daily dose – especially in combination with alcohol and other central nervous system depressants – propoxyphene is consistently mentioned as one of the top 10 drugs found in the subject's system during autopsies.[2] Medical examiners note its presence in more deaths each year than most other prescription drugs. Data from the Drug Abuse Warning Network (DAWN), which provides autopsy information from medical examiners nationwide, has implicated propoxyphene in 5.6% of all drug-related deaths (including prescription, over-the-counter, and illicit drugs) in just over 19 years (1981-1999). This amounts to 7,109 total reported U.S. deaths since 1981 merely for the counties covered by DAWN, which account for only approximately one-third of the population of the country.

Propoxyphene is implicated in a high proportion of accidental deaths each year, because the majority of the drug is converted into a metabolite that is even more toxic and has a longer half-life than its parent compound. From 1981 to 1999, DAWN reported 2,110 accidental propoxyphene-related deaths, or 38.6% of the total number of propoxyphene-related deaths. (DAWN no longer details manner of death but the total number of propoxyphene-related deaths has remained relatively the same since data collection on manner of death stopped in 1999—see Figure 1 for total death data through 2002). Because DAWN reports data only from medical examiners in counties whose total population makes up one-third of the country, it is reasonable to conclude that the true number of accidental propoxyphene-related deaths since from 1981 through 1999 may be three times greater than the 2,110 deaths actually reported.

Beers et al. put propoxyphene among the drugs that are inappropriate for use in the elderly due to its lack of significant efficacy and high incidence of adverse effects.[3] Nevertheless, propoxyphene is the most prevalent of all drugs considered inappropriate by Beers that are used by the elderly.[4] Further, the elderly account for a large proportion of propoxyphene use. As Li Wan Po, et al. conclude in a systematic review of the efficacy of propoxyphene as an analgesic: "on the basis of data on analgesic efficacy and acute safety...there is little objective evidence to support prescribing a combination of paracetamol [acetaminophen as in Tylenol] and dextropropoxyphene in preference to paracetamol alone in moderate pain such as that after surgery."[5]

Among community-dwelling elderly patients, 6.6 percent were using propoxyphene in 1999, translating into more than two million community-dwelling Medicare beneficiaries.[6] In a study involving 157,000 elderly HMO members, the rate of use of propoxyphene was seven percent, making it the most commonly used of the list of 33 medicines deemed inappropriate for the elderly.[7] In a nationwide study of emergency departments, propoxyphene, was the third most commonly prescribed drug on the inappropriate list, being prescribed 3.3 million times to the elderly during emergency room visits from 1992-2000.[8] In nursing homes, the inappropriate use of propoxyphene was even higher than in the community, with use by 15.5 percent of institutionalized elderly Medicare beneficiaries.[9] In a recent study in nursing homes, the first study to measure the adverse health impact of inappropriate prescribing, the authors calculated the increased risk of serious adverse health outcomes (hospitalizations, emergency department visits or death) for various inappropriately prescribed drugs. Those using propoxyphene were almost 2.4 times more likely to require hospitalization or emergency department visits or to die.[10]

History of Propoxyphene Restriction Efforts

In November 1978, the Health Research Group (HRG) of Public Citizen proposed significantly altering propoxyphene's regulatory status in either of two ways: HRG petitioned the

Department of Health, Education and Welfare (HEW) to ban the drug as an "imminent hazard." As an alternative, HRG asked HEW to tighten restrictions on the drug's use by placing it in Schedule II of the Controlled Substances Act. A key factor in the HEW decision to reject the HRG proposals was Eli Lilly's commitment to an "educational program" intended to sensitize prescribers and patients to the hazards of propoxyphene products. In a 1978 HEW appraisal of Lilly's efforts, the following was reported: "Lilly has not conducted its campaign to prescribers as FDA had expected. Detail persons visiting physicians failed to emphasize the user warnings in the majority of visits, left samples of Darvon in 50-75 percent of visits, and on the average spent less than half of the time on Darvon during the visits."[11] It appears that Eli Lilly converted its education program into a marketing initiative.

According to a DEA compliance survey regarding propoxyphene: "abuse of propoxyphene appears to be directly related to the relative ease with which this drug is obtained from physicians."[12] Yet as FDA's Dr. Louis Morris wrote "the Darvon educational campaign has not been shown to have had an important impact into physician decision-making."[13]

In fact, even though Lilly no longer manufactures these drugs, having sold the rights to Darvon/Darvocet to aaiPharma several years ago, propoxyphene-containing compounds, mostly generic versions, remain among the top-selling drugs on the market.[14] This high level of prescribing persists despite propoxyphene's eventual placement in Schedule IV of the Controlled Substances Act (which includes drugs with limited potential for dependence such as diazepam [Valium] as opposed to Schedule II, which includes drugs with a high potential for dependence such as codeine). Lilly's half-hearted attempts to comply with the weak restrictions enacted the last time the government considered the dangers of propoxyphene have clearly allowed this drug to remain as a viable analgesic in the minds of doctors throughout the nation, despite its inappropriateness for treating pain and the serious dangers it presents to patients.

Weak Analgesic Properties

Many studies have shown the relative ineffectiveness of propoxyphene as a painkiller. In a recent comprehensive review of randomized clinical trials, Collins, et al., found that for most kinds of pain (e.g., post-operative pain), ibuprofen is more effective than propoxyphene/acetaminophen (the latter, the ingredient in Tylenol). Further, codeine/acetaminophen was found to be more effective than propoxyphene/acetaminophen, although that difference was not statistically significant. Ibuprofen, however, was a significantly stronger analgesic than the propoxyphene compound, requiring that fewer patients be treated at the standard dose for at least one of those patients to achieve 50% pain relief.[15]

The similarity of the efficacy of the acetaminophen-containing preparations of propoxyphene and codeine appears to be deceptive, as evidence suggests that much of the analgesic properties of propoxyphene /acetaminophen are due to the acetaminophen alone. Hopkinson, et al., for example, compared the analgesic effect of two combinations of drugs: 1) 1000 mg. acetaminophen alone and 2) 650 mg. acetaminophen plus 100 mg. propoxyphene. They found that the acetaminophen only treatment was significantly more effective than the propoxyphene/acetaminophen combination in the relief of pain (63% vs. 42% achieving effective pain relief), indicating that propoxyphene adds no analgesic properties to acetaminophen.[16]

Propoxyphene alone has been shown to be no more effective than two aspirin for relief of most kinds of pain, such as post-operative pain.[17] Further, in a comprehensive survey of the published literature up to 1970, Miller, et al., examined 243 articles on propoxyphene and found few hard data on its therapeutic value compared with other analgesics. Seven of the 16

reviewed studies comparing propoxyphene with placebo — 4 of which used the manufacturer's suggested dose of 65 mg. — showed that propoxyphene was not superior to placebo. The authors concluded that "propoxyphene is no more effective than aspirin or codeine, and may even be inferior to these analgesics."[18] A more recent systematic review by Li Wan Po et al. of 26 randomized trials comprising 2231 patients with post-operative pain (including some of the data mentioned earlier) found that in head to head and indirect comparisons of acetaminophen with the combination of propoxyphene and acetaminophen, the combination was no better than acetaminophen on its own. The authors conclude that "on the basis of data on analgesic efficacy and acute safety...there is little objective evidence to support prescribing a combination of acetaminophen and dextropropoxyphene in preference to acetaminophen alone in moderate pain such as that after surgery." The authors further "concur with Miller et al that the popularity of the acetaminophen combination does not lie in improved efficacy" over other analgesics.[19]

Although some have claimed that propoxyphene may be effective in chronic pain such as that from cancer,[20] there exist no randomized controlled trials that indicate any such effect. Dr. Charles Moertel, a well-known former cancer specialist at the Mayo Clinic, noted that "for the treatment of severe pain, the use of Darvon either alone or in combination is grossly inadequate treatment and is really inhumane to the patient." Dr. Moertel also stated that "it is possible to maintain good medical practice without the use of Darvon."[21] Further, even were propoxyphene shown to be effective for this kind of pain, chronic usage increases the likelihood of adverse events due to buildup of the cardiotoxic propoxyphene metabolite, norpropoxyphene.

Beyond the questionable wisdom of prescribing a drug with severe adverse effects that provides little benefit, the relative ineffectiveness of propoxyphene translates into an additional kind of increased danger to patients. When the recommended dose fails to alleviate their pain, patients may choose to take additional pills, exceeding the recommended daily dose. It does not require much additional drug beyond the daily dose to generate either dependency or toxicity, as the following section demonstrates.

Toxicity: Extremely Low Margin of Safety

Propoxyphene, a potent cardiotoxic agent, can cause severe cardiovascular effects with overdose or even when used as directed. Upon metabolism, the majority of propoxyphene is converted into norpropoxyphene (NPX), which is particularly dangerous as it is 2.5 times more potent than its parent compound in producing cardiac depression and has a half-life (time before ½ of the substance is cleared from the body) of approximately 36 hours, three times longer than that of propoxyphene. Adverse cardiovascular events are marked by prolongation of the QRS complex on an electrocardiogram (which can increase the risk for an abnormal cardiac rhythm) and include bundle branch block (interruption of cardiac conduction), bradycardia (slowed heartbeat), asystole (absence of contractions), diminished myocardial contractility (ability of the heart to contract), and hypotension. These events are not reversed by opiate antagonists such as naloxone and up to 76% of deaths from propoxyphene overdose are a result of cardiac toxicity.[22] This high toxicity accounts for the finding that only 30-40% of propoxyphene-related deaths are attributed to suicidal overdoses; over 40% have been found to be accidental.[23]

The fact that norpropoxyphene is cleared from the body more slowly than its parent compound and thus reaches considerably higher blood levels and is more cardiotoxic, explains the high risk of accidental overdose.[24] According to Dr. Randall Baselt, FDA expert toxicology witness at the April 6, 1979 hearings on Darvon: "This accumulation of drug sets the stage for accidental overdosage; one or two additional depressant drugs, such as alcohol or diazepam,

may be sufficient even in normally used amounts [of alcohol or diazepam] to cause death in susceptible persons."[25]

Henry, et al., report that the cardiac toxicity of propoxyphene may derive from membrane stabilization, the depression of excitability in nerve and heart tissue.[26] Whitcomb et al. similarly found that propoxyphene acts as a potent sodium channel blocker, which depresses the action potential of myocytes.[27] There is a significant relationship between the dose of propoxyphene and prolongation of the QRS complex, representing an increase in the time required for the ventricles to depolarize. This relationship is not seen with other opioids.[28] The prolongation of the QRS complex associated with sodium channel blockade can be a precursor to ventricular arrhythmia, which is often fatal.

Table 1 below, constructed from published and unpublished data on blood levels of propoxyphene and norpropoxyphene in individual users illustrates the propensity of norpropoxyphene to accumulate over time to amounts far in excess of propoxyphene even when the recommended doses are being used. For example, in the four people using propoxyphene chronically at levels up to 6 pills per day, the recommended daily dose, blood levels of propoxyphene of 0.24-0.85 µg/g and blood levels of norpropoxyphene of 0.6-3.0 µg/g were noted. In the six people using between one and two times the recommended dose (7-12 pills) blood levels of propoxyphene of 0.42-0.87 µg/g but norpropoxyphene levels of 1.8-5.1 µg/g were noted. In these six subjects, the average blood level of propoxyphene was 0.61 µg/g, but the average level of norpropoxyphene was 3.7 µg/g – more than six times higher than the propoxyphene level.[29,30,31]

Pills/day[a]	Type of Subject[b]	Duration of Drug Use	Maximum Blood Concentration (µg/g)[c]		Reference
			DXP	NPX	
3 (HCl)	Cancer patient	60 days	0.746 (2)	3.01 (2)	29
3 (HCl)	Cancer patient	14 days	0.275 (2)	0.75 (2)	29
3 (HCl)	Normal vol.	4 days	0.241 (2)	0.6 (4)	29
6 (HCl)	Normal vol.	4 days	0.849 (2)	1.24 (6)	29
9 (N)	Addict	28 days	0.519 (3)	3.83 (6)	30
11 (N)	Addict	42 days	0.567 (3)	4.94 (9)	30
11 (N)	Addict	84 days	0.513 (6)	5.07 (6)	30
12 (N)	Addict	84 days	0.424 (6)	1.83 (6)	30
12 (HCl)	Cancer patient	365 days	0.866 (2)	3.23 (4)	31

Table 1: Blood propoxyphene and norpropoxyphene levels in individual regular users of propoxyphene products

a: The recommended daily dose is 1 pill every 4 hours or 6 pills per day
HCl = propoxyphene hydrochloride N = norpropoxyphene napsylate
b: The subjects included normal volunteers, cancer patients using propoxyphene products for pain relief, and former addicts involved in addiction maintenance experiments.
c: The number in parentheses represents the hours after the last dose when the maximum blood levels of propoxyphene and norpropoxyphene were attained.

The fact that people using propoxyphene products at or slightly above the recommended dose can get norpropoxyphene blood levels above 1 µg/g is particularly alarming in view of the findings that in many cases of accidental death due to propoxyphene products, the blood

norpropoxyphene levels are in the same range as those found in chronic users of the drug, such as those listed in Table 1.[32] This suggests that chronic users of propoxyphene are at high risk for accidental overdose. Furthermore, comparable blood levels (above 1 µg/g) of norpropoxyphene in animals can cause significant blockage of conduction through the heart – a toxicity which can lead to arrhythmias and death.[33]

The margin of safety of propoxyphene, the ratio between the dose that contains 99% of the effectiveness of the drug and that which kills 1% of those who use it,[34] is extremely low, especially given its relative inefficacy as an analgesic. The dose of propoxyphene necessary for cardiac toxicity to occur overlaps significantly with the increased dose which a user, dissatisfied with the analgesic effects and still in pain, may ingest. The margin of safety is even worse when other drugs are involved, especially alcohol. The recommended dose for both chronic and acute pain is one pill every four hours, or six pills per day. Young, et al., found that death can occur with 20 pills while Whittington found that as few as 6-15 pills can cause death.[35,36] The lower number reflects the ability of alcohol to potentiate the toxicity of propoxyphene. Similarly, Obafunwa, et al., found that as little as 0.168% blood alcohol content (BAC) can potentiate lethality within the propoxyphene limit of toxicity of 0.75 µg/g.[37] A study analyzing over 1000 fatal intoxications (both intentional and accidental) due to alcohol, a single drug, or both, found that the median post-mortem blood alcohol concentrations -sufficient to cause death - were much lower when propoxyphene was found in combination with alcohol (3.3 parts per thousand BAC without propoxyphene, 1.7 parts per thousand with propoxyphene).[38] Thus, propoxyphene is particularly dangerous when combined with alcohol.

A Swedish study further highlights the dangers and prevalence of propoxyphene and alcohol consumption. Jonasson, et al., identified 766 propoxyphene-related suicides in Sweden from 1992-1996 and an additional 1,016 non-suicide deaths. Alcohol was present in 425 of those non-suicides and of those, 220 were classified as having been caused directly by propoxyphene. Among the fatally intoxicated, the mean blood propoxyphene concentration was only 2 µg/g – less than three times the blood level typically found after the recommended, therapeutic dose. Further, the authors concluded that the majority of those who died from an accidental poisoning were not part of the "drug addict population."[39] The same team of authors concluded in a separate study that suicides were generally over-reported in propoxyphene-related deaths and that accidents were under-reported.[40] The authors concluded that "probably more than 40 individuals die from accidental poisonings due to a combination of propoxyphene and alcohol each year" in Sweden alone[41] – and since accidents are under-reported, this may not even reflect the true dangers of accidental poisoning from propoxyphene.

The high numbers of some of these deaths are due to the lethality of a propoxyphene overdose. Propoxyphene is rapidly absorbed from the gastrointestinal tract, leading to early cardiac risk following an overdose and death within an hour. In a study of 222 patients treated for propoxyphene overdose, both accidental and suicidal, the mortality rate was 7.7%, over three times that of tricyclic antidepressants in the same medical center.[42] A recent study by Hawton, et al., looking at suicide found that an overdose of propoxyphene /acetaminophen is more fatal than an overdose of either tricyclic antidepressents or acetaminophen. Of 4162 drug-related suicides in England from 1997-1999, 18% involved only propoxyphene /acetaminophen, while tricyclic antidepressants accounted for 22% and 9% involved acetaminophen alone. This yields 766 deaths in England over three years due only to one mode of propoxyphene-related death: suicide via poisoning with / propoxyphene acetaminophen alone. There were an additional 171 deaths in which propoxyphene /acetaminophen was used with another drug.[43]

Propoxyphene's deadly nature is revealed by the fact that among those who attempted suicide via overdose, as described in the Hawton study, an overdose with propoxyphene was 2.3 times more likely to be fatal than one with tricyclic antidepressants and 28.1 times more likely to be fatal than one with acetaminophen alone. The study's authors conclude that "Given earlier concerns about deaths from poisoning with co-proxamol (propoxyphene/acetaminophen), the absence of specific initiatives to try to reduce them is surprising and should now be addressed...availability of co-proxamol should be restricted".[44]

Data from Sweden, where propoxyphene was not required to be prescribed on a special prescription form like other narcotic drugs in the country until 2001, suggest that the drug is one of the deadliest of all those heavily prescribed. Jonsson et al. determined the number of deaths from fatal intoxications found during autopsy from 1992-2002 at the Department of Forensic Chemistry in Lingkoping, which has complete national coverage of Sweden's population of 8.9 million. Out of 6998 fatal intoxications, propoxyphene was found in 1863 – 27% - of cases, second only to ethanol. Toxic levels of propoxyphene (defined by the authors based on Druid, et al.,[45] as 0.8 µg/g) were found in 1370– 74% of the 1863–more than any other prescription drug.

The study also measured the fatality ratio, which relates the number of fatal intoxications with toxic concentrations of the substance to the number of defined daily doses per 1000 inhabitants of the country per day. Thus, a drug with a fatality ratio of 1 would cause one fatal intoxication per dose per 1000 inhabitants per day. Using this measure of the lethality of a drug, the authors determined a fatality ratio of 10.8 for propoxyphene, almost five times as high as that for acetaminophen (2.3), the drug with the next highest number of absolute deaths. In other words, for a given number of prescriptions, propoxyphene was involved in almost five times as many deaths as acetaminophen.[46] This study highlights the deadliness of the combination of high lethality and massive prescribing that characterizes propoxyphene.

The Rising U.S. Death Toll

Propoxyphene and combinations including it constitute one of the most prescribed prescription drugs in the country. In 2004, propoxyphene was the 12th most prescribed generic drug with over 23 million prescriptions sold.[47] Over the past 47 years, it has also been one of the deadliest drugs on the market, being associated with well over 10,000 confirmed deaths in the United States alone.

In the United States, DAWN collects data from medical examiners and emergency rooms in approximately 40 metropolitan areas. As of 2002, 94 million people lived in counties that reported to DAWN. Given a 2000 US population of 293 million, this means that the network represents approximately 1/3 of the total population. Although data from DAWN cannot be directly extrapolated, multiplying its results by three gives a general idea of the enormity of the damage this relatively ineffective yet dangerous drug has wrought.

Data regarding propoxyphene-related deaths for the past 20 years of DAWN are presented in figure 1.[48] While these numbers do not necessarily implicate propoxyphene as the direct or sole cause of death, since other drugs were found with it in 93.3% of the 459 cases in 1999, its toxicity makes causation likely. Furthermore, a large proportion of deaths involving propoxyphene involved alcohol and/or acetaminophen as having been used in combination. Alcohol was one of the drugs involved in 33.8% of propoxyphene deaths involving two or more drugs and acetaminophen was in 19.6%. Alcohol is not particularly lethally toxic on its own, but has been shown to potentiate propoxyphene lethality. When we originally petitioned the FDA to

ban propoxyphene in 1978, the Chief Coroner of San Francisco, Dr. Boyd Stevens, told Public Citizen that, based on autopsy findings, "if you double the Darvon dosage and take just one or two [bar] drinks, you can get into the toxic or lethal range." In some cases, acetaminophen was likely found in autopsies due to its presence in propoxyphene/acetaminophen preparations. Since propoxyphene has been shown to have a fatality ratio almost five times as great as that for acetaminophen[49], it can be concluded that propoxyphene represents the cause of death in a significant proportion of these cases.

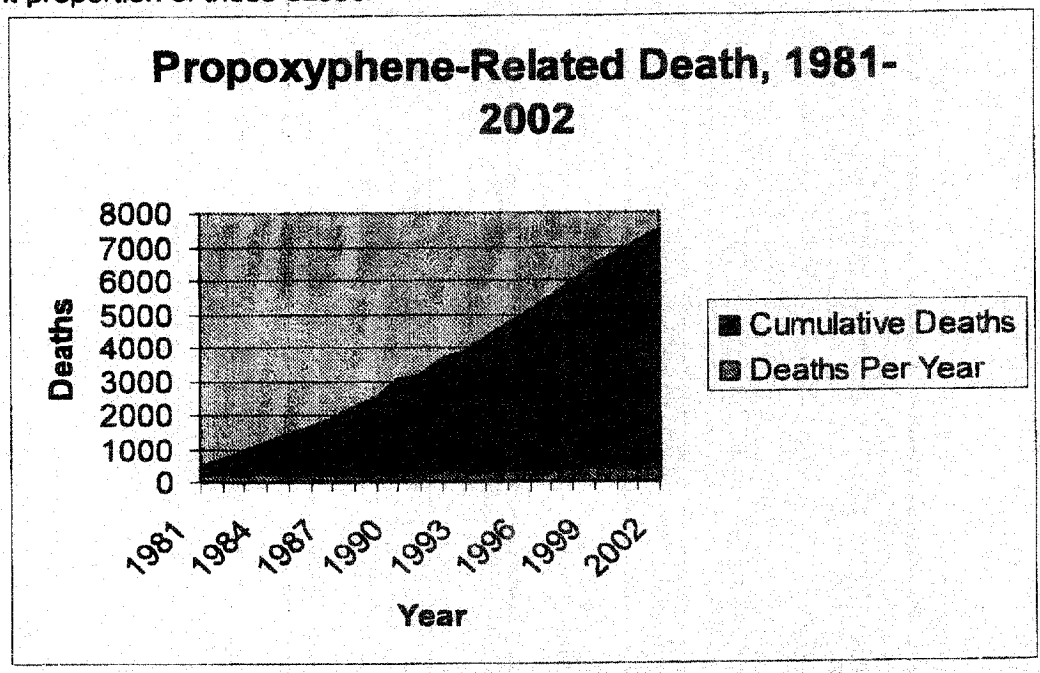

Figure 1: The DAWN system has tabulated 7,109 deaths involving propoxyphene in the period from 1981-2002.

The number of deaths involving propoxyphene in the US alone is striking. Although in 1981, propoxyphene was implicated in over 8% of drug deaths mentioned in DAWN, that number has declined to around 4% as of 1999. Nevertheless, the actual number of propoxyphene-associated deaths in absolute terms has been creeping steadily upwards since 1981. Whereas 227 deaths were reported in 1981, a high of 459 was reported in 1999. The cumulative deaths since 1981 have, at last count, reached 7,109 through 2002. As propoxyphene has been on the market since 1957, there are many more deaths, occurring before 1981 and after 2002 that have not even been calculated. Further, these numbers represent only those cases in which an autopsy was performed.

Accidental Propoxyphene-related Deaths

From 1981 to 1999, the Drug Abuse Warning Network reported 2,110 propoxyphene-related accidental deaths, 38.6% of the total number of 5,462 deaths involving propoxyphene. There has been a slight trend towards an increasing number of accidental deaths reported, such that in the five years from 1995-1999, an average of 40.3% of the deaths were accidental. Although DAWN did not release the breakdown for manner of death in 2000-2002, assuming 199 accidental deaths (as there were in 1999) yearly during this time period yields 2,707

propoxyphene-related accidental deaths for the period from 1981-2002 out of a total of 7,109 propoxyphene-related deaths.

There are several reasons why the actual number of deaths involving propoxyphene in which that person did not intend to die (accidental deaths) is certainly much higher. First, because of the nature of Federal reporting, there are no data categorized by accidental deaths either for the first two decades of propoxyphene use prior to 1981 or for the years since 1999. Second, DAWN reports data only from medical examiners in counties whose total population makes up only about 1/3 of the country. Thus, the true number of accidental propoxyphene-related deaths may be three times greater than 2,110 cases actually reported. Third, Jonasson et al. concluded, based on a review of the criteria used to assign manner of death in fatal propoxyphene poisonings in Sweden, that propoxyphene-related accidental deaths were under-reported and suicides over-reported. This suggests that a greater proportion of the 7,109 confirmed U.S. propoxyphene-related deaths since 1981 may be accidental than has been reported as such.

Lastly, these data represent only deaths in which the index of suspicion was high enough that the case was sent to a medical examiner. Cases in which an autopsy was performed in a hospital are not reported. Further, the autopsy rate in the US has been declining steadily since the 1950s from around 50% to between 5-10% today.[50,51] Since autopsies are now much less likely to be routinely performed, the true number of accidental propoxyphene poisonings is almost certainly much higher than the 2,110 confirmed cases from medical examiners' offices in the past twenty years alone.

Related to the above issue of autopsies, under-reporting of accidental deaths may be an especially significant problem in the elderly. Autopsies are performed at particularly low rates in nursing homes – Katz, et al., found an autopsy rate of only 0.8% from 1980-1984.[52] Propoxyphene is widely prescribed in the elderly, making up over 18% of prescribed analgesics in nursing homes[53], and the highly cardiotoxic and long-lasting propoxyphene metabolite norpropoxyphene is extremely prone to building up to high levels in the elderly. Since high levels of norpropoxyphene can occur at low doses of propoxyphene (as mentioned earlier, Inturrisi reports a case where a norpropoxyphene level of 5.07 µg/g was found where the propoxyphene level was only 0.513 µg/g – significantly under the level considered lethally toxic[54]), such a death from a ventricular arrhythmia in an infirm elderly decedent is unlikely to raise an index of suspicion sufficient to perform an autopsy. All this evidence points to a significantly higher number of accidental deaths related to propoxyphene than that reported by DAWN.

Propoxyphene-related Suicides

Although a large proportion of propoxyphene-related deaths have been accidental, due to the narrow margin of safety of the drug, especially when co-consumed with alcohol, for many years propoxyphene has been an important method of suicide. Since 1981, there appears to be a trend towards a somewhat lower proportion of propoxyphene-related deaths being determined to be suicides by the medical examiners included in DAWN (figure 2). Furthermore, Jonasson et al. conclude that suicides involving propoxyphene are generally over-reported and accidents under-reported.

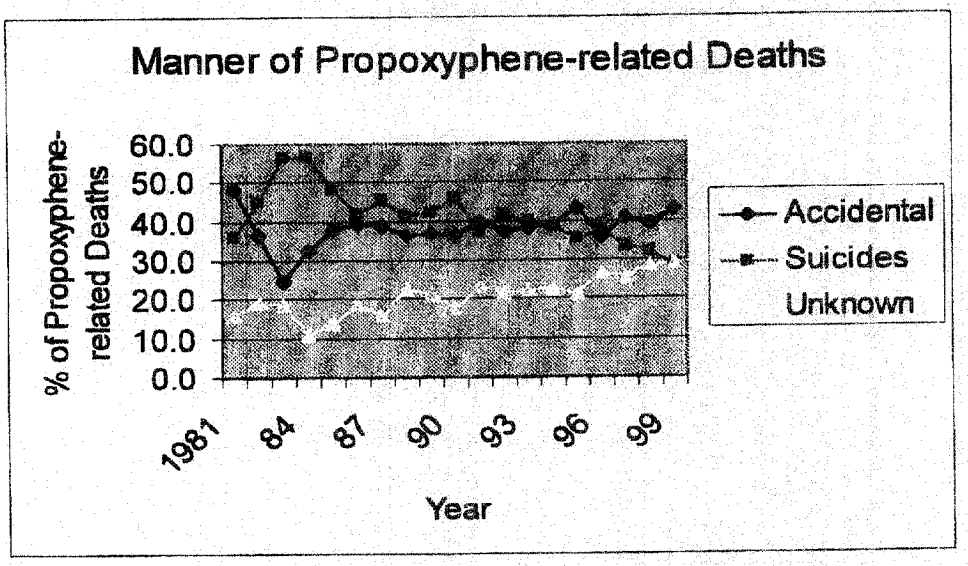

Figure 2: Proportion of deaths involving propoxyphene classified by DAWN as accidental, suicide, or unknown, on a yearly basis.

Nevertheless, in the most recent five years with such information, DAWN has reported that approximately one-third of deaths involving propoxyphene have been suicides (see figure 2 above). It could be argued that banning propoxyphene would have no effect on these deaths – those intent on suicide will choose another route and no net benefit will be produced. Indeed, a Lilly representative stated in 1980 that transferring propoxyphene to Schedule II, a less stringent restriction than our proposed complete banning of the drug, would have "negligible impact on the suicide rate" since abusers would merely "move to another drug."[55] However, the restriction of several drugs typically involved in suicides demonstrates this not to be the case. For example, figure 3 shows that restricting the availability of barbiturates by imposing Schedule II controls had a marked positive effect on reducing the number of barbiturate suicides.[56] Although the number of total drug suicides did not drop as steeply as the number of barbiturate suicides, indicating that there was some substitution of other drugs for barbiturates, this substitution was clearly not 100%. Note that the steep drop in prescriptions and suicides began in 1970 when Congressional hearings regarding barbiturates began and dropped again in 1975, when the drugs were controlled in Schedule II. The graph shows that people intending to commit suicides did not completely turn to other drugs for suicides, as the total number of drug suicides decreased along with the number of barbiturate suicides. Given that we propose removing propoxyphene from the market rather than merely restricting its use by placing it in Schedule II, the resulting drop in total suicides would be predicted to be even more significant.

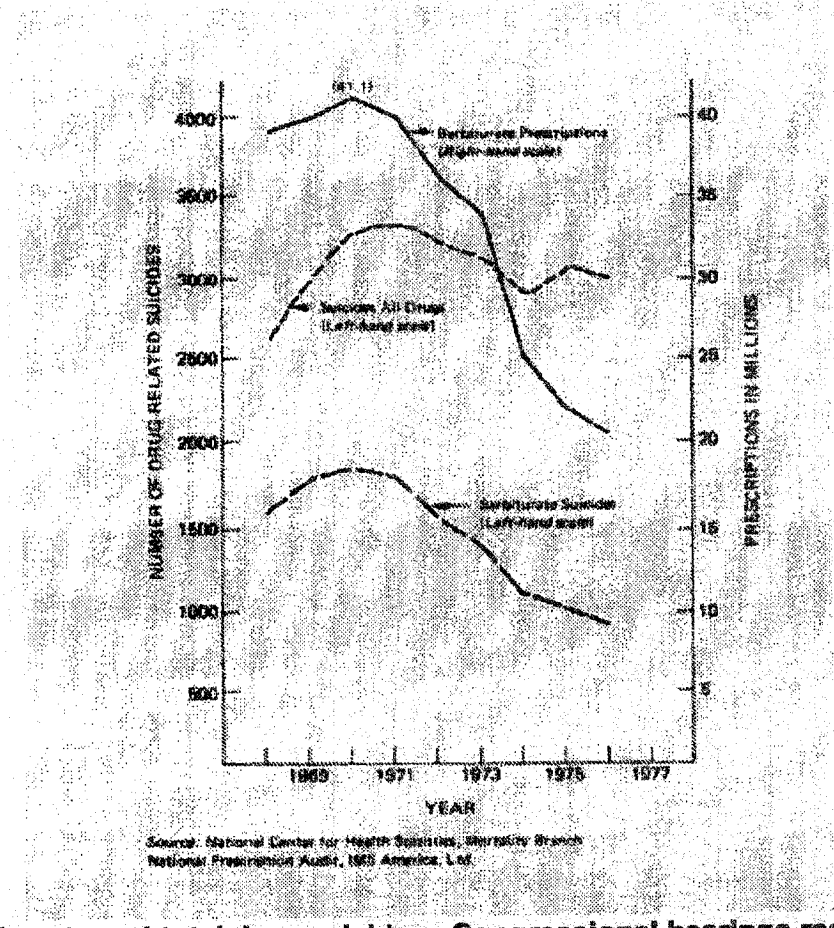

Figure 3: Barbiturate and total drug suicides. Congressional hearings regarding the restriction of barbiturates began in 1970 and barbiturates were controlled in Schedule II in 1975. Note the reductions in both barbiturate and total drug suicides at these points.

Further, many suicides are cries for help, not truly wishes for death. However, with the low margins of safety of propoxyphene due to its high toxicity, these attention-seeking attempts—often called suicidal gestures—are more likely to be "successful" when this drug is used. Thus, as a drug implicated in a large number of suicides yearly and one with few redeeming benefits, the ban of propoxyphene will likely result in a significant reduction in the total number of drug-related suicides.

Propoxyphene and the Elderly

The misuse of propoxyphene of greatest magnitude is caused by its over-prescription in the elderly. The elimination half-lives of both propoxyphene and its even more potent metabolite, norpropoxyphene, are prolonged in healthy elderly subjects relative to young controls due to decreased renal and hepatic function. In young people, propoxyphene had a 13.2 day half-life, as compared to a 23.7 day half-life in the elderly group; norpropoxyphene pharmacokinetics showed a similar trend. With repeated dosing, at the recommended doses, the elderly subjects were thus exposed to a much higher dose of the drug for longer periods of time, increasing their risk of adverse reactions.[57]

In addition to the toxic effects on the heart, the central nervous system-related adverse effects of propoxyphene use may increase the likelihood of falls and hence fall-related fractures in the elderly. Propoxyphene is thus a drug inappropriate for prescription to the elderly as defined by the criteria described by Beers et al.[58] Kamal-Bahl, et al., showed that propoxyphene use is widespread in the institutionalized population, the population of elderly that is most vulnerable and in which propoxyphene use is most inappropriate. The rate of propoxyphene use, at 15.5%, was more than twice as high in this population as in community-dwelling elderly. Further, propoxyphene use was 1.48 and 1.45 times more likely in those elderly with a history of osteoporosis and hip fracture respectively, conditions that, according to Beers, et al., should explicitly contraindicate propoxyphene.[59] Won, et al., found a similar rate of propoxyphene prescribing in nursing homes at 18.2% of prescriptions, the 2nd most prescribed analgesic behind only acetaminophen.[60]

Addiction

Evidence of dependence on propoxyphene is well-documented in the literature. Clinical trials and published case histories illustrate that propoxyphene can produce physical addiction, as manifested by withdrawal symptoms, strong psychological dependence, and tolerance. Reports on propoxyphene dosage suggest addiction can occur at less than the maximum recommended daily dose of 390 mg. and unequivocally confirm addiction at just twice the recommended daily dose. Particularly for the elderly, the long-term use consequent to addiction can have devastating consequences because of the greater build-up of the cardio-toxic metabolite, norpropoxyphene in older people.

In a well-controlled, double-blind study performed at Harvard Medical School, patients with pain were given 65 mg. of Darvon 4 times daily. (The maximum recommended daily dose is one 65 mg. pill taken 6 times daily.) Three out of 19 patients taking this dose for 3 months developed withdrawal symptoms "suggesting addiction" compared to 4 out of 16 developing withdrawal symptoms after discontinuation of 32 mg. codeine per day. None of the 14 patients using a non-narcotic analgesic ethoheptazine (Zactane) instead of propoxyphene had symptoms of addiction.[61]

In Lilly's own case reports, which they submitted to the Justice Department in 1970, is a description of a patient who took 8 Darvon tablets daily (1 1/3 the recommended dose) and was said to have "psychic dependence." Another case report describes physical addiction in a man using 10 capsules per day (1 2/3 the recommended dose) for one year.[62]

Additionally, Fraser et al. reported that propoxyphene has addiction liability, demonstrating several hallmarks of addiction caused by the drug. These include propoxyphene's abilty to partially suppress the symptoms of morphine abstinence after 800 mg. (twice the recommended daily dose) is administered within one 24-hour period. It can also induce patients to experience effects similar to those from marijuana, heroin, morphine, and cocaine after oral administration in single doses of 355-650 mg. or 6-10 pills.[63] (The maximum recommended daily dose is one 65 mg. pill six times daily.)

Given its euphoria and addiction causing properties, propoxyphene is a drug with high potential for abuse. Between September 1976 and March 1977, the National Youth Polydrug Study surveyed 2,750 teenagers, 18 or younger. 488 subjects (17.7%) indicated that they had used Darvon or Darvon-N in their lifetimes, making propoxyphene the most frequently mentioned opiate drug. When ranked in terms of prevalence of "regular use" (i.e. at least once a week), Darvon/Darvon-N was second only to heroin.[64] In a 1976 study of a stratified

probability sample (by region, race, income, etc.) of 3,024 19-30 year old men, whose names were obtained from selective service records, it was found that 14.9% had used propoxyphene for non-medical purposes. Projected to the total US male population at that time, this suggests that 3 million American men in this age group (19-30) had used propoxyphene for non-therapeutic purposes.[65]

A more recent study by Ng, et al., reports that propoxyphene is a drug of primary abuse. Of the records of 73 propoxyphene abusers from a detoxification unit, 67% revealed that propoxyphene was the first opiate ever abused. The authors concluded that propoxyphene abuse is not secondary to heroin dependence.[66] Thus, propoxyphene poses a serious addiction risk.

Emergency Room Visits

Propoxyphene is still a major drug of abuse, as can be seen by the yearly number of emergency room visits reported by the Drug Abuse Warning Network (DAWN). Data from 1994-2002 indicate approximately 5,000 emergency room visits related to propoxyphene each year. In 2002, 1680 out of 4676 or 36% of people with an emergency room visit related to propoxyphene indicated that either psychic effects or dependence on propoxyphene were the reason for the emergency room visit.[67] Thus, propoxyphene abuse remains a major problem.

Conclusion

The Health Research Group urges, by this petition, the immediate implementation of a phased withdrawal from the U.S. prescription drug market of all propoxyphene-containing products. This should be initiated immediately because this drug has considerable human toxicity, addiction potential, abuse liability, but very limited therapeutic usefulness. That this drug, which has been associated with at least 7109 reported deaths including 2110 in which the death was accidental and many times more emergency room visits since September 1972, is a serious public health problem is not disputable. Only by banning propoxyphene can this danger be eliminated.

We agree with the January 2005 decision of the U.K. to phase out this dangerous drug because efficacy of this product "is poorly established and the risk of toxicity in overdose, both accidental and deliberate, is unacceptable" and find it inexcusable that the U.S. FDA is lagging so far behind in taking this important, life-saving public health regulatory action.

Sidney M. Wolfe, M.D.
Director

Dan Suzman,
Research Associate

Public Citizen's Health Research Group

Ulf Jonasson
Doctor of Public Health,
Nordic School of Public Health, Gothenburg, Sweden
ulf.jonasson@wtnord.se

Birgitta Jonasson PhD,
Department of Forensic Medicine,
University of Uppsala, Sweden

ENDNOTES

[1] The top 200 generic drugs in 2004 (by units and by retail dollars). Drugtopics.com [online]. Using IMS data from December 2005, four companies (Teva, Mylan, Mallinckrodt, and QLT) out of a total of 13 selling propoxyphene-containing products, sold 91% of the 2.15 million prescriptions that month, with two, Teva and QLT accounting for 54% of the 2.15 million prescriptions filled that month.
[2] Substance Abuse and Mental Health Services Administration: Office of Applied Studies. Drug Abuse Warning Network Annual Medical Data 1999.
[3] Beers MH, Ouslander JG, Rollingher I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining potentially inappropriate medication use by the elderly. Arch Intern Med Jul 1997;151:1531-36.
[4] Won AB, Lapane KL, Vallow S, Schein J, Morris JN, Lipsitz LA. Persistent nonmalignant pain and analgesic prescribing patterns in elderly nursing home residents. J Am Geriatr Soc. 2004 Jun;52(6):867-74.
[5] Li Wan Po A, Zhang WY. Systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to acetaminophen. BMJ. 1997 Dec 13;315(7122):1565-71.
[6] Kamal-Bahl S, Stuart BC, Beers MH. National Trends and Predictors of Propoxyphene Use in Community-Dwelling Elderly. Am J Geriatr Pharmacother 2005;3:186-95.
[7] Simon SR, Chan KA, Soumerai SB, Wagner AK, Andrade SE, Feldstein AC, Lafata JE, Davis RL, Gurwitz JH. Potentially inappropriate medication use by elderly persons in U.S. Health Maintenance Organizations, 2000-2001. Am Geriatr Soc. 2005 Feb;53(2):227-32.
[8] Caterino JM, Emond JA, Camargo CA Jr. Inappropriate medication administration to the acutely ill elderly: a nationwide emergency department study, 1992-2000. J Am Geriatr Soc. 2004 Nov;52(11):1847-55.
[9] Kamal-Bahl SJ, Doshi JA, Stuart BC, Briesacher BA. Propoxyphene use by community-dwelling and institutionalized elderly Medicare beneficiaries. J Am Geriatr Soc. 2003 Aug;51(8):1099-104.
[10] Perri M 3rd, Menon AM, Deshpande AD, Shinde SB, Jiang R, Cooper JW, Cook CL, Griffin SC, Lorys RA. Adverse outcomes associated with inappropriate drug use in nursing homes. Ann Pharmacother. 2005 Mar;39(3):405-11.
[11] HEW Quarterly Report on Propoxyphene, Third Quarter 1978 – Fourth Quarter 1979, p. 2.
[12] DEA, Compliance Survey Regarding Propoxyphene," to the FDA, US Department of Justice, Washington DC, March 20, 1979, p. 5.
[13] Morris L. Memorandum on the Lilly Quarterly Report on Darvon, to the Director of the Division of Drug Experience. February 5, 1980.
[14] The top 200 generic drugs in 2004 (by units). Drugtopics.com [online]. Mar 22, 2003.

[15] Collins SL, Edwards JE, Moore RA, McQuay HJ. Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain. Cochrane Database Syst Rev. 2000;(2):CD001440.
[16] Hopkinson JH 3rd, Blatt G, Cooper M. Effective pain relief: comparative results with acetaminophen in a new dose formulation, propoxyphene napsylate-acetaminophen combination, and placebo. Curr Ther Res Clin Exp. 1976 Jun; 19(6): 622-630.
[17] Miller RR, et al.. Propoxyphene hydrochloride: a critical review. JAMA. 1970; 213(6): 996-1006.
[18] Miller RR, et al.. Propoxyphene hydrochloride: a critical review. JAMA. 1970; 213(6): 996-1006.
[19] Li Wan Po A, Zhang WY. Systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to paracetamol. BMJ. 1997 Dec 13;315(7122):1565-71.
[20] Hanks GW, Forbes K. Co-proxamol is effective in chronic pain. BMJ. 1998; Jun 27;316(7149):1980.
[21] Moertel CG. Testimony before the Select Committee on Small Business, U.S. Senate, in Competitive Problems in the Drug Industry, Part 34, U.S. Government, Washington DC, 1979, pp. 16641 and 16642.
[22] Whitcomb DC, Gilliam FR 3rd, Starmer CF, Grant AO. Marked QRS complex abnormalities and sodium channel blockade by propoxyphene reversed with lidocaine. J. Clin. Invest. 1989; 84: 1629-36.
[23] Mortality data from the Drug Abuse Warning Network. 1981-2002.
[24] Verebeley K, Inturrisi CE. The simultaneous determination of propoxyphene and norpropoxyphene in human biofluids using gas liquid chromatography. J of Chrom. 1973; 75: 195-205.
[25] Baselt RC. Forensic toxicology of propoxyphene fatalities. Testimony before FDA, April 6, 1979, p. 4.
[26] Henry JA, Cassidy SL. Membrane stabilizing activity: a major cause of fatal poisoning. Lancet. 1986, i: 1414-7.
[27] Whitcomb DC, Gilliam FR 3rd, Starmer CF, Grant AO. Marked QRS complex abnormalities and sodium channel blockade by propoxyphene reversed with lidocaine. J. Clin. Invest. 1989; 84: 1629-36.
[28] Afshari R, Bateman DN. ECG abnormalities in co-proxamol (paracetamol / dextropropoxyphene) poisoning. Journal of Toxicology: Clinical Toxicology. 2003; 41: 560.
[29] Inturrisi CE. Personal communication to Dr. Sidney M. Wolfe. January 29, 1979.
[30] Gorodetsky C. Personal communication to Dr. Sidney M. Wolfe. February 8, 1979.
[31] Verebeley K, Inturrisi CE. The simultaneous determination of propoxyphene and norpropoxyphene in human biofluids using gas liquid chromatography. J of Chrom. 1973; 75: 195-205.
[32] Christensen H. Dextropropoxyphene and norpropoxyphene in blood, muscle, liver, and urine in fatal poisoning. Acta Permacol et Toxicol. 1977; 40: 298-209.
[33] Lund-Jacobsen H. Cardio-respiratory toxicity of propoxyphene and norpropoxyphene in conscious rabbits. Acta Pharmacol et Toxicol. 1978; 42: 171-178.
[34] Toxicology Tutor I: Glossary. http://www.sis.nlm.nih.gov/ToxTutor/Tox1/glossm.htm [online].
[35] Young RJ, Lawson AAH. Distalgesic poisoning: cause for concern. BMJ. 1980. 280: 1045-7.
[36] Whittington RM. Dextropropoxyphene deaths: coroner's report. Hum Toxicol. 1984: 3(suppl): 1755-85S
[37] Obafunwa JO, Busuttil A, al-Oqleh AM. Dextropropoxyphene-related deaths--a problem that persists? Int J Legal Med. 1994;106(6):315-8.
[38] Koski A, Ojanpera I, Vuori E. Interactions of alcohol and drugs in fatal poisonings. Hum Exp Toxicol. 2003; 22(5): 281-287
[39] Jonasson U, Jonasson B, Saldeen T. Middle-aged men – a risk category regarding fatal poisoning due to dextropropoxyphene and alcohol in combination. Preventive Medicine. 2000 Aug;31(2 Pt 1):103-6.
[40] Jonasson B, Jonasson U, Saldeen T. Suicides may be overreported and accidents underreported among fatalities due to dextropropoxyphene. J Forensic Sci. 1999 Mar;44(2):334-8.
[41] Jonasson U, Jonasson B, Saldeen T. Middle-aged men – a risk category regarding fatal poisoning due to dextropropoxyphene and alcohol in combination. Preventive Medicine. 2000 Aug;31(2 Pt 1):103-6.
[42] Jaffe JH, Martin WR. 1980. Opioid agonists and antagonists. *In* The Pharmacological Basis of Therapeutics. AG Gilman LS Goodman and A Gilman, editors. McMillan Publishing Co., Inc., New York. 479-534.
[43] Hawton K, Simkin S, Deeks J. Co-proxamol and suicide: a study of national mortality statistics and local non-fatal self poisonings. BMJ. 2003 May 10;326(7397):1006-8.
[44] Hawton K, Simkin S, Deeks J. Co-proxamol and suicide: a study of national mortality statistics and local non-fatal self poisonings. BMJ. 2003 May 10;326(7397):1006-8.
[45] Druid H, Holmgren. A complilation of fatal and control concentrations of drugs in postmortem femoral blood. J Forensic Sci. 1997; 42: 79-87.

[46] Jonsson A, Holmgren P, Ahlner J. Fatal intoxications in a Swedish forensic autopsy material during 1992-2002. Forensic Sci Int. 2004 Jun 30;143(1):53-9.
[47] The top 200 generic drugs in 2004 (by units). Drugtopics.com [online]. Mar 22, 2003.
[48] Mortality data from the Drug Abuse Warning Network. 1981-2002.
[49] Jonsson A, Holmgren P, Ahlner J. Fatal intoxications in a Swedish forensic autopsy material during 1992-2002. Forensic Sci Int. 2004 Jun 30;143(1):53-9.
[50] Welsh TS, Kaplan J. The Role of post-mortem examination in medical education. 1998 Aug;73(8): 802-805.
[51] Sinard JH. Factors affecting autopsy rates, autopsy request rates, and autopsy findings at a large academic medical center. Exp Mol Pathol. 2001 Jun;70(3):333-43.
[52] Katz PR, Seidel G. Nursing home autopsies. Survey of physician attitudes and practice patterns. Arch Pathol Lab Med. 1990 Feb;114(2):145-7.
[53] Won AB, Lapane KL, Vallow S, Schein J, Morris JN, Lipsitz LA. Persistent nonmalignant pain and analgesic prescribing patterns in elderly nursing home residents. J Am Geriatr Soc. 2004 Jun;52(6):867-74.
[54] Inturrisi CE. Personal communication to Dr. Sidney M. Wolfe. January 29, 1979.
[55] Furman RH, in response to a question by Congressman Leland during Congressional hearings on Darvon, May 21, 1980.
[56] Reproduced from the Institute of Medicine Report of a Study: Sleeping Pills, Insomnia, and Medical Practice. NAS 1979, p. 66.
[57] Flanagan RJ, Johnston A, White AS, Crome P. Pharmacokinetics of dextropropoxyphene and nordextropropoxyphene in young and elderly volunteers after single and multiple dextropropoxyphene dosage. Br J Clin Pharmacol. 1989 Oct;28(4):463-9.
[58] Beers MH, Ouslander JG, Rollingher I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining potentially inappropriate medication use by the elderly. Arch Intern Med Jul 1997;151:1531-36.
[59] Kamal-Bahl SJ, Doshi JA, Stuart BC, Briesacher BA. Propoxyphene use by community-dwelling and institutionalized eldlerly medicare beneficiaries. J Am Geriatr Soc. 2003; Aug 51(8):1099-1104.
[60] Won AB, Lapane KL, Vallow S, Schein J, Morris JN, Lipsitz LA. Persistent nonmalignant pain and analgesic prescribing patterns in elderly nursing home residents. J Am Geriatr Soc. 2004; Jun;52(6):867-74.
[61] Cass LJ et al. Physical Dependence Potentiality of Analgesics. Curr. Ther. Res. Clin. Exp. 1961; 3:289-299.
[62] US Justice Department. A study of the abuse potential of dextropropoxyphene with control recommendations. January 1976, pp. 57-64.
[63] Fraser HF, Isbell H. Pharmacology and Addiction Liability of dl- and d-propoxyphene. Bull Narc. 1960; 12: 9-14.
[64] Farley EC, Santo Y. The Abuse of Darvon in a National Sample of Adolescents Admitted to Drug Abuse Treatment Programs. Philadelphia Psychiatric Center, unpublished.
[65] O'Donnell JA et al. Young men and drugs: a nation-wide survey. NIDA, 1976.
[66] Ng B, Alvear M. Dextropropoxyphene addiction--a drug of primary abuse. Am J Drug Alcohol Abuse. 1993;19(2):153-8.
[67] Trends in Drug-Related Emergency Department Visits, 1994-2002 At a Glance. Drug Abuse Warning Network (DAWN). November 2003

Jaffe, Lyle D

From: Sidney Wolfe [swolfe@citizen.org]
Sent: Tuesday, February 28, 2006 11:32 AM
To: Jaffe, Lyle D
Subject: amendment to today's petition to ban propoxyphene

ENVIRONMENTAL IMPACT STATEMENT

Nothing requested in this petition will have an impact on the environment.

CERTIFICATION

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sidney M.Wolfe M.D.
Director, Public Citizen's Health Research Group
1600 20th St. NW, Washington, DC. 20009
202 588-7735 fax 588-7796
e-mail swolfe@citizen.org
Web sites: www.citizen.org/hrg
www.worstpills.org