Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	November 19, 2010
To:	Janet Woodcock, MD Director, CDER
	John Jenkins, MD Director, Office of New Drugs
From:	Gerald J. Dal Pan, MD, MHS Director, Office of Surveillance and Epidemiology
Subject:	Updated Epidemiological Review of Propoxyphene Safety
Drug Name(s):	Propoxyphene Products
Application Type/Number:	Multiple NDAs and ANDAs
Applicant/sponsor:	Xanodyne (NDA Sponsor) and Multiple ANDA Sponsors

Note: This version corrects erroneous footnote numbering in the version signed on 18 November 2010.

I. INTRODUCTION

This document provides a summary of a review completed in January 2010 by the Office of Surveillance and Epidemiology/Division of Epidemiology (OSE/DEPI) of epidemiological data relating to the safety of propoxyphene drug products. The OSE staff involved in the review included Fatmatta Kuyateh, MD, MS, Medical Officer; Catherine Dormitzer, PhD, MPH, Epidemiologist; Sigal Kaplan, PhD, Team Leader; Cynthia Kornegay, PhD, Team Leader; and Solomon Iyasu, MD, MPH, Director. The review was conducted as part of FDA's ongoing safety surveillance of propoxyphene drug products following the July 7, 2009 denial of a Citizen Petition filed by Public Citizen in 2006 (the 2006 Petition), which asked the agency to withdraw propoxyphene drug products from the U.S. market on grounds that their risks outweigh their relatively weak benefits as an analgesic.

Based on a comprehensive review of the available evidence, including an advisory committee meeting held in January 2009 (2009 AC), FDA concluded that there was insufficient evidence to support withdrawing propoxyphene from the market at that time, and the 2006 Petition was denied.[1] In particular, epidemiological evidence relied on in the 2006 Petition was found to be suggestive, but not conclusive, with regard to the Petition's assertion that propoxyphene has been associated with substantial numbers of non-intentional and intentional deaths.

Following the denial of the 2006 Petition, OSE was asked to review whether certain data sources relied on in the Petition could be re-analyzed, supplemented, and/or expanded to provide further certainty on this point. OSE also was asked to review information in several articles published both before and after FDA's denial of the 2006 Petition. In January 2010, the OSE reviewers determined that the updated epidemiological evidence favored removal of propoxyphene from the market. The findings of that review are described below.

After consideration by a CDER-wide working group and the Drug Safety Board, CDER management decided that, although the updated evidence and analysis strengthened concern regarding propoxyphene,the available data did not provide sufficient evidence to conclude that propoxyphene, at recommended doses, was responsible for the observed findings. Further work was undertaken, including a review of clinical pharmacology and animal toxicology data by Dr. Mark Avigan in OSE, and a final decision was deferred pending review of new clinical evidence from an ongoing study of potential cardiac risks (TQT study), which, at that time, was being conducted by the NDA sponsor, Xanodyne Pharmaceuticals Inc. FDA has now reviewed the results of Xanodyne's preliminary pharmacokinetic study, conducted to determine appropriate dosing for the TQT study, and has concluded that the data demonstrate a clear, dose-related effect on cardiac electrophysiology. The results of the new TQT study provide evidence that propoxyphene can have an adverse cardiotoxic effect at therapeutic doses. The postmarket signals, including expanded epidemiological analyses, and the findings of Dr. Avigan's review, are consistent with this conclusion.

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[1] Docket No. FDA-2006-P-0270/PDN (July 7, 2009)

This memorandum describes the epidemiological review that was conducted prior to the receipt of the new clinical evidence from the TQT study.

After review of the data in this memorandum, a review of clinical pharmacology data and animal toxicology data conducted by Dr. Mark Avigan of OSE, and the electrocardiographic results from the above-referenced TQT study, I conclude that propoxyphene and propoxyphene-containing products should no longer be marketed.

II. DISCUSSION

This memorandum describes our re-evaluation and updated analyses of epidemiological data and information. These include:

- Florida Medical Examiner Data
- Data from the Drug Abuse Warning Network (DAWN), including data on emergency department visits (DAWN-ED) and reports of fatalities received from medical examiners or coroners (DAWN-ME/C
- Suicide Data from England and Wales
- 1984 Case Study of Severe Propoxyphene Self-Poisoning
- 1987 Study of Effects of Governmental Warnings
- Comparative Study of Fatality Rates for Propoxyphene vs. Other Analgesics
- Case Study of Effects of UK Propoxyphene Withdrawal on Suicide Deaths
- Additional Information Reviewed by OSE

A. Florida Medical Examiner Data

At the 2009 Advisory Committee meeting, Dr. Sidney Wolfe presented a report titled "Drugs Identified in Deceased Persons by Florida Medical Examiners" produced by the Florida Department of Law Enforcement (FDLE). He showed a graph of propoxyphene-related deaths ranging from 328 to 368 for the period of 2003 to 2007. He pointed out that in 2007, 85 (25%) of the 341 propoxyphene-related deaths were caused by propoxyphene.

The FDLE releases reports annually titled "Drugs Identified by Florida Medical Examiners". Through toxicology reports submitted to Florida medical examiners, the FDLE identifies drug-related deaths for which the drug was determined to be the cause of death, or present in the body at the time of death but not causal. A drug is only indicated as the cause of death when, after examining all evidence and the autopsy and toxicology results, the medical examiner determines the drug played a causal role in the death. Multiple drugs can be listed as the cause of death.[2] The mortality data presented by Dr. Wolfe were notable but warranted further investigation since these numbers were not to

[2] *2008 Medical Examiners Commission Drug Report: http://www.fdle.state.fl.us/Content/getdoc/a37959db-85e0-42f9-b6d6-cdef532f22f8/2008DrugReport.aspx*

be put into the context of use, and could not be directly compared to other mortality associated with other opioids.

OSE/DEPI requested and received similar drug-related mortality data from the FDLE (Table 1). Because the numbers reported at the Advisory Committee meeting were not placed in the context of drug exposure or availability, we could not compare the numbers of deaths to those of other opioids. As a result, OSE/DEPI conducted a more comprehensive analysis of the FDLE data. Information on total prescriptions dispensed was obtained for use as a measure of estimated exposure in Florida. The frequency of deaths was then adjusted for potential exposure by using the number of prescriptions dispensed as the denominator. Two comparator analgesics, tramadol and hydrocodone, were analyzed using the same methods to examine if similar trends of drug-related deaths were found. Tramadol was selected because it has a similar indication to propoxyphene and is currently not a scheduled opioid, so it has a similar level of control to propoxyphene, which is a C-IV level of scheduling. Hydrocodone combination products are scheduled as a C-III, and consequently expected to have more toxicity and higher levels of drug abuse than propoxyphene. Hydrocodone therefore served as a positive control. Hydrocodone also has large sales volume resulting in estimates that are more precise. In addition, tramadol and hydrocodone have been considered possible alternatives to propoxyphene.

Table 1 shows, for each drug, the total number of deaths for which the drug was present at time of death, and the number of deaths for which the drug was determined by the medical examiner to be the cause of the death. The number in parentheses is the percentage of the total deaths for which the drug was determined by the medical examiner to be the cause of death.

There were 1,740 deaths reported by the Florida Medical Examiners Office where propoxyphene products was either present or causal, 670 deaths for tramadol and 2,963 deaths for hydrocodone products for the years 2003 through 2007. Over this five-year period, propoxyphene was determined to be causal in 26% of the propoxyphene-related deaths. Tramadol was causal in 21% of tramadol-related deaths and hydrocodone in 34% of hydrocodone-related deaths. From 2003 – 2007, there were approximately 11 million prescriptions for propoxyphene, 34 million for hydrocodone and 6.6 million for tramadol. The number of prescriptions dispensed serves as a proxy for the amount of drugs available (or exposure) in the community. Over the five-year period, the number of drug-related deaths adjusted for drug utilization was approximately 16 deaths per 100,000 prescriptions for propoxyphene, 10 deaths per 100,000 prescriptions for tramadol and 9 deaths per 100,000 prescriptions for hydrocodone, the positive control. The number of deaths per 100,000 prescriptions was consistently higher for propoxyphene than the comparator drugs through all five years of data particularly when considered as causal. The two-fold difference in number of drug-caused deaths per 100,000 prescriptions for propoxyphene, compared to tramadol and hydrocodone is noteworthy. The increased ratio of deaths per 100,000 prescriptions associated with propoxyphene strongly suggests greater toxicity when compared to tramadol and hydrocodone. These results provide evidence to support withdrawing propoxyphene from the market.

Table 1: FDLE: Number of Drug Related Deaths Reported by Florida Medical Examiners, and Dispensed Prescriptions for Propoxyphene, Tramadol and Hydrocodone 2003 -2007, Florida

	Propoxyphene	**Tramadol**	**Hydrocodone**
Number of drug-related deaths	1,740	670	2,963
Present[a]	1280	527	1964
Causal[b]	460 (26%)	143 (21%)	910 (33%)
Number of Prescriptions Dispensed in Florida	10,931,158	6,608,176	33,987,828
Number of Total Deaths[c] per 100,000 prescriptions	**15.9**	**10.1**	**8.7**
Number of Causally-Related Deaths per 100,000 prescriptions	**4.2**	**2.2**	**2.9**

Source: Florida Department of Law Enforcement and SDI: Vector One ® National, Extracted 11/09
[a]Present = drug present in the body at the time of death
[b]Causal = medical examiner determines the drug played a causal role in the death via autopsy and toxicology results
[c]Total deaths = deaths for which drug was present + deaths for which drug was causal

B. Data From DAWN

The Drug Abuse Warning Network (DAWN) provides two sets of data: emergency department visits (DAWN-ED) and deaths from medical examiners or coroners (DAWN-ME/C).

Epidemiological data from DAWN were presented at the 2009 AC meeting by Captain Kathy Poneleit, from the Office of Applied Studies at the Substance Abuse and Mental Health Services Administration (SAMHSA). Captain Poneleit began by presenting data from the DAWN-ED, a stratified probability sample of hospitals that provides national estimates of drug-related ED visits by drug. She compared adverse reactions associated with propoxyphene, propoxyphene acetaminophen, and codeine combinations in 2007. The number of ED visits for adverse reactions in 2007 was lower for single-ingredient propoxyphene (796) than for propoxyphene-acetaminophen combinations (8910) or codeine (14,775). When information for single ingredient propoxyphene and propoxyphene-acetaminophen were combined, adverse reactions accounted for 46 percent of all propoxyphene-related ED visits. For codeine, adverse events accounted for 71 percent of all visits. No deaths were found in the ED data.

Captain Poneleit also presented data from the DAWN-ME/C database, which collects data on drug-related deaths reviewed by medical examiners and coroners in selected metropolitan areas of the United States and selected States. The jurisdictions that

participate in DAWN's death investigations do not constitute a statistical sample, and the metropolitan statistical areas (MSA) and jurisdictions that participate in this effort varies by year. As a result, extrapolation of drug-related deaths to the nation as a whole is not possible. One hundred and sixty eight jurisdictions participated in DAWN in 2007 and reported 503 deaths in which propoxyphene was detected. Of these deaths, 92% involved multiple drug use and 7% involved only propoxyphene or propoxyphene-acetaminophen. The number of propoxyphene-related deaths were much lower (503) than deaths related to oxycodone, hydrocodone, and methadone (2097, 1731, and 2887 deaths, respectively).

The data presented by Captain Poneleit included only the number of ED visits and do not take into account the extent of drug use or availability in the community. OSE/DEPI has examined similar ED data obtained from DAWN, using the nationally projected number of prescriptions as a proxy for drug exposure in these communities. The results show that, although the number of ED visits for single ingredient propoxyphene is low, the number of ED visits per 100,000 prescriptions is notably higher than for propoxyphene-acetaminophen or for codeine products (Table 2). The reasons for this marked difference are unknown. When combined, the number of all propoxyphene-related emergency department visits per 100,000 prescriptions is lower than for codeine. Previous studies[3] have shown that people who overdose on propoxyphene frequently do not make it to the hospital before death. As a result, emergency department visit data are not as informative as medical examiner data for ascertaining propoxyphene-related death.

[3] Whittigton RM. Dextropropoxyphene deaths: coroner's report. Hum Toxicol. 1984;3 Suppl: 175s -185s.

Table 2: National Estimates of ED Visits Reported in DAWN and Number of ED Visits per 100,000 Prescriptions for Propoxyphene, Single, APAP Combination and Codeine Products -- 2007

National Estimates of ED Cases: 2007*	
Propoxyphene	3,154
Propoxyphene-acetaminophen	17,544
Codeine	20,741
National Estimates of Prescriptions Dispensed: 2007**	
Propoxyphene	556,926
Propoxyphene-acetaminophen	21,770,334
Codeine	15,745,566
ED Visits per 100,000 Prescriptions: 2007	
Propoxyphene	566
Propoxyphene-acetaminophen	81
Propoxyphene + propoxyphene-acetaminophen	93
Codeine	132

*Office of Applied Studies, SAMHSA, Drug Abuse Warning Network
**Source: SDI: Vector One ® National, Extracted 11/09

DAWN Medical Examiner Data: OSE requested and received medical examiner data from SAMHSA for the metropolitan statistical areas (MSA) and 8 states with consistent participation between the years 2004 and 2007. The data provided include drug-related deaths, reported by medical examiners, for which propoxyphene or the comparator drugs tramadol or hydrocodone were present. Due to confidentiality concerns, DAWN suppresses counts of deaths less than four. Since an occurrence of no event is reported as "0", we have imputed the value for a suppressed cell by inserting the average count of "2" to lower the likelihood of an undercount. Tramadol and hydrocodone, the two comparator analgesics used for the FDLE medical examiner data analyses, were selected to examine trends of drug-related deaths. Reasons for choosing these two drugs as comparators have been previously described in section discussing the FDLE data.

Table 3 summarizes the counts of drug-related deaths that were collected by the MSAs and eight states for 2004 – 2007. The medical examiners reported whether the drug was the only one found at autopsy (single-drug involvement) or whether multiple drugs were found at autopsy (multiple-drug involvement). For all three drugs, there were more deaths for which multiple-drugs were found at autopsy. For the state data and MSA data, there were more drug-related deaths for hydrocodone than propoxyphene or tramadol. The counts for the states are lower than many of the counts found for the MSAs because, for

the most part, the states are not the highly populated whereas the MSAs include areas that are densely populated.

Table 3. Counts of Drug-Related Deaths for Participating MSAs and States for Propoxyphene, Tramadol, and Hydrocodone, by Multiple or Single Drug Involvement, DAWN ME 2004 – 2007

	Propoxyphene	**Tramadol**	**Hydrocodone**
Metropolitan Statistical Areas (MSA)			
Single Drug Involvement	132	89	232
Multiple Drugs Involvement	1,516	844	4,461
Total drug-related deaths	**1,611**	**911**	**4,665**
States			
Single Drug Involvement	34	39	51
Multiple Drugs Involvement	302	263	850
Total drug-related deaths	**336**	**292**	**895**

Source: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network

To parallel the analysis done with the FDLE data, drug utilization data were obtained for use as a measure of estimated exposure in the MSAs and eight states. The number of drug-related deaths were adjusted for drug exposure by using the number of prescriptions dispensed as the denominator. After adjusting for the number of prescriptions in each of the eight states, the number of drug-related deaths per 100,000 prescriptions is higher for propoxyphene than for tramadol or hydrocodone (the positive control) in all but one state (Table 4).

Table 4: Count Summary of Drug Involved Deaths reported to DAWN Medical Examiners in Eight States 2004 - 2007

(All ages/ single & multiple drugs)

	Propoxyphene			Tramadol			Hydrocodone		
States	Death	Prescriptions	Death/ 100,000 Rx†	Death	Prescriptions	Death/ 100,000 Rx†	Death	Prescriptions	Death/ 100,000 Rx†
Maine	19	320,256	5.9	8	243,131	3.3	44	206,3404	2.1
Maryland	67	811,537	8.3	78	1,411,053	5.5	70	4,050,544	1.7
Massachusetts*	54	759,150	7.1	43	158,11,54	2.7	71	3,641,037	1.9
New Hampshire	8	235,123	3.4	12	268,375	4.5	27	1,286,565	2.1
New Mexico	63	445,968	14.1	20	340,293	5.9	119	2,033,420	5.9
Oklahoma*	59	1,258,642	4.7	33	1,322,475	2.5	251	6,025,333	4.2
Utah	50	272,417	18.4	92	792,108	11.6	287	4,475,714	6.4
Vermont	16	95,719	16.7	6	164,754	3.6	26	570,690	4.6

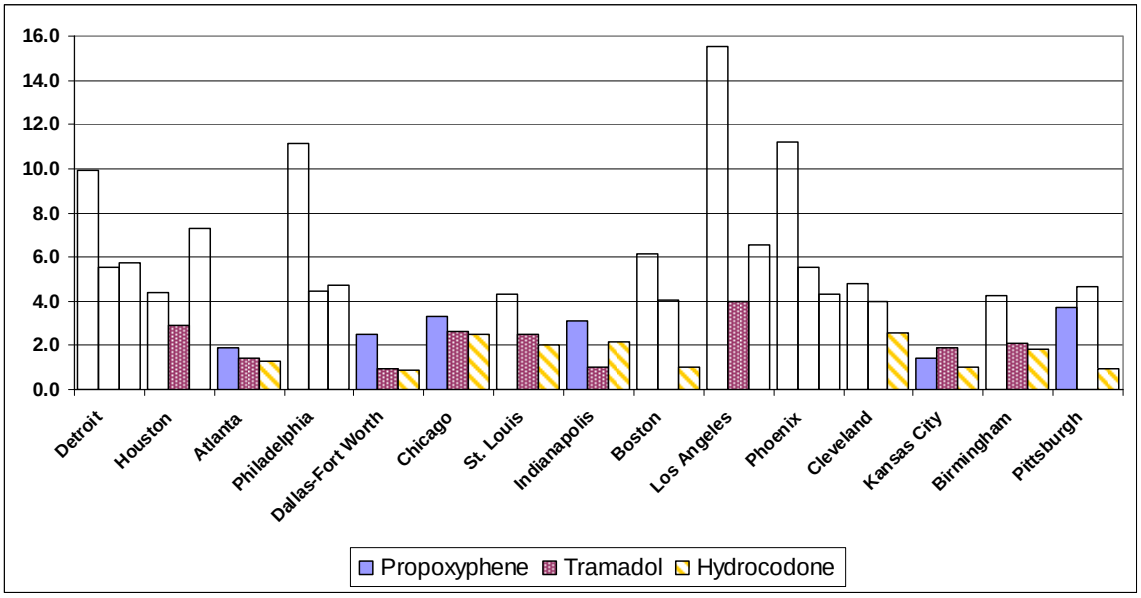
* death data sere not collected for Massachusetts and Oklahoma in 2004

†Rx = prescriptions

Source: SDI: Vector One ® National, Extracted 11/09 and Office of Applied Studies, SAMHSA, Drug Abuse Warning Network

Similar trends were observed with the MSA data. Figure 1 provides a graphic depiction of the number of drug related deaths per 100,000 prescriptions in the years 2004 – 2007 for the fifteen MSAs with the highest number of propoxyphene prescriptions The number of propoxyphene-related deaths per 100,000 prescriptions is consistently higher for propoxyphene than that for tramadol and hydrocodone except for Houston, Kansas City and Pittsburgh. More importantly, this trend is observed for a majority of the MSAs for which data are available, suggesting a greater likelihood of death when propoxyphene is present at autopsy. Results for all MSAs are displayed in Appendix Table A4.

Figure 1: Number of Deaths reported to DAWN Medical Examiners per 100,000 Prescriptions by Drug for the Fifteen MSAs with the Highest Number of Propoxyphene Prescriptions, 2004 – 2007



Source: Wolters Kluwer, Extracted 11/09 and Office of Applied Studies, SAMHSA, Drug Abuse Warning Network

For the period of interest, our analysis of the Florida Department of Law Enforcement Medical Examiners Reports, and DAWN-ME/C state and MSA data consistently show an excess of propoxyphene-related deaths compared to tramadol and the positive control, hydrocodone. These consistent results provide evidence to support the citizen's petition to withdraw propoxyphene from the market.

C. Suicide Data from England and Wales

OSE has reviewed a study by Hawton et al. which was published in the British Journal of Medicine on June 18, 2009, and was not addressed in FDA's July 7, 2009 denial of the 2006 Citizen Petition.[4]

1. Study Description

The goal of this study was to investigate the possible effect of the withdrawal of co-proxamol (propoxyphene-acetaminophen) and the Committee on Safety of Medicines (CSM) announcement on prescribing and mortality involving co-proxamol and other analgesics in England and Wales. In January 2005, CSM recommended that co-proxamol be withdrawn from the UK market. The Medicines and Healthcare products Regulatory Agency (MHRA) announced a phased withdrawal on January 31, 2005 requesting that no new patients be prescribed the medication, and that current patients on co-proxamol be

[4] Hawton K., Bergen H, Simkin S, et al, Effect of withdrawal of co-proxamol on prescribing and deaths from drug poisoning in England and Wales: time series analysis, BMJ 338:2270-75

changed to a suitable alternative before the cancellation of all co-proxamol production licenses on December 31, 2007. The investigators obtained quarterly prescription data from the Information Centre for Health and Social Care's prescription statistics department in England and the Prescribing Unit of Health Solutions in Wales. Death data (suicides and deaths of undetermined intent, and accidental poisoning involving co-proxamol, co-codamol [codeine-acetaminophen], codeine, co-dyhydramol [dihydrocodeine-acetaminophen], dihydrocodeine, NSAIDs, paracetamol [acetaminophen], and tramadol) were provided by the Office for National Statistics for the period of 1998-2007 in England and Wales. Only deaths involving single drugs or single drugs and alcohol were analyzed. The authors used interrupted time series analysis to estimate changes and levels in trends in prescribing as well as trends in deaths from poisoning after the withdrawal of co-proxamol was put into effect in 2004. Segmented regression analysis was used to control for baseline levels and trends observed before the withdrawal of co-proxamol.

Figure 1 of the article (shown below) shows the number of prescriptions per quarter across the years 1998 - 2007. The results showed a steep and immediate decline in prescriptions for co-proxamol for the first and second quarters of 2005, the period immediately following intervention, and further reduction afterward.

The number of co-proxamol prescriptions decreased overall by about 59%, [Mean = 859,000 per quarter, 95% CI (653000; 1065000)] in the period following the announcement of co-proxamol withdrawal from 2005-2007. Significant overall decreases in prescriptions for NSAIDs (19%) and dihydrocodeine (6%) were also observed for the same period. Corresponding overall increases in prescriptions for paracetamol, co-codamol, codeine, and tramadol were observed. However the increase for tramadol was not found to be statistically significant [Mean = 64,000 per quarter; 95% CI (-5000, 133000).

Figure 2 of the article (shown below) shows a subset of the mortality data findings. A steep reduction in suicide and deaths of undetermined intent (open verdicts) involving co-proxamol was observed in the first quarter of 2005, with a reduction continuing through the duration of the study period. Suicides and open verdict deaths involving co-proxamol decreased overall by 295 deaths [95% CI (251, 338)] in the period 2005 to 2007. The observed reduction was larger when accidental deaths were included in the analysis [Total change = -349, 95% CI (-306, -392)]. No statistically significant corresponding change was observed for deaths involving the other analgesics (combined).

The authors observed a reduction in suicide and open verdict deaths involving all drugs [Mean quarterly change = -31; 95%CI (-66, 3)] from 2005 to 2007, as well as a decrease in suicides and open verdict deaths due to any cause [Mean quarterly change = -22; 95%CI (-89, 45)]. However, neither of those decreases was statistically significant.

The authors concluded that the withdrawal of co-proxamol from the market was associated with a decrease in prescriptions for co-proxamol, which in turn was associated

with 349 fewer suicides and accidental deaths involving co-proxamol between 2005 and 2007.

2. OSE/DEPI Comments

The key strengths of this study are 1) inclusion of deaths involving only a single drug thus increasing the likelihood of measuring the association between the drug and related-death, and 2) the use of interrupted time series autoregression to control for any expected baseline changes in level and trend of deaths over time. Based on findings from the study, regulatory action/withdrawal of propoxyphene from the market strongly suggests a public health benefit. Although the analysis of the data are based on an ecological and not a casual association between drug withdrawal and drug-related death (since there may be other underlying factors that could account for the decrease in both prescriptions and death), the fact that deaths involving co-proxamol were reduced beyond expected after the regulatory action restricting propoxyphene prescribing are compelling.

These data, in conjunction with the Scottish and UK data[5,6] that were described in a previous DEPI review[7], support the withdrawal of propoxyphene from the market.

[5] 2009 Report from Medicines and Healthcare Products Regulatory Agency (not published)

[6] Afshari R, Good AM, Maxwell SRJ, Bateman DN. Co-proxamol overdose is associated with a 10-fold excess mortality compared with other paracetamol combination analgesics. Br J Clin Pharmacol 2005; 60:444-447.

[7] OSE/DEPI review dated February 27, 2009, OSE RCM# 2008-1517

Fig 1 | Prescriptions for analgesics dispensed in England and Wales, 1998-2007.

Fig 2 | Mortality in England and Wales from analgesic poisoning (suicide and open verdicts), 1998-2007, for people aged 10 years and over (substances taken alone, with or without alcohol)

D. 1984 Case Study of Severe Propoxyphene Self-Poisoning

1. Study Description

The objective of this study[8] was to describe the course of severe propoxyphene self-poisoning in patients admitted to an intensive care unit (ICU) in Copenhagen, Denmark. The authors described a case series of 222 consecutive patients admitted to the ICU for propoxyphene overdose from 1975 to 1981. Patients had to have met one of the following inclusion criteria, which according to the authors "should be directly related to intake of an overdose of propoxyphene":

- respiratory failure
- circulatory failure
- ECG abnormality
- ingestion of more than 1000 mg of propoxyphene

The authors observed that 98 (44%) of all the study patients had ingested only propoxyphene. The remaining 56% had ingested propoxyphene in combination with alcohol, barbiturates, antidepressants, or benzodiazepines, although the authors note that propoxyphene was the main toxic substance in all the patients.

Impaired circulation was observed in 107 patients (48%) upon admission, of which 33 (15%) exhibited compensatory tachycardia which the authors attributed to a negative chronotropic effect of propoxyphene. ECG abnormalities including widened QRS complex and first degree A-V block, were observed in 91 patients (41%). In addition, the authors hypothesize that negative chronotropic effects of propoxyphene (previously observed in pigs that were given intravenous propoxyphene) may be responsible for the vasodilatory and hypotensive effects observed in the study patients.

Seventeen patients died, eight (47%) of whom had ingested propoxyphene alone. Cardiac failure was the cause of death for 53% of the patients. Five of the six (83%) patients 65 years and older who died, had cardiac failure listed as cause of death. Of the four brain damage cases, three (75%) were less than 65 years old.

2. OSE/DEPI Comments

The authors' use of the term "consecutive cases", as interpreted from the study methods, refers to the approach of including all patients who were admitted to the ICU during the study period and met the inclusion criteria.

This study contributes valuable information to the literature in describing cases of overdose in which propoxyphene is implicated. Within this case series, the majority of deaths (53%) observed were due to cardiac failure. Only six out of 17 fatal cases (35%)

[8] Sloth Masden P et al. Acute Propoxyphene Self-Poisoning in 222 Consecutive Patients. Acta Anaesthesiol, Scand., 1984:28:661-665

were aged 65 years or older; all six died of cardiac failure. Electrocardiogram or blood pressure abnormalities were observed in 13 of the fatal cases (76%), but not all (only 11 out of 13 or 78%) had a cardiovascular event listed as the cause of death.

The authors claim that propoxyphene is responsible for the fact that only a few patients exhibited compensatory tachycardia. Although we would expect compensatory tachycardia to be the usual physiologic response to severe hypotension or shock, the authors cannot claim propoxyphene caused this lack of usual response because there was no control group to put the study results into context and shed light on whether similar results would be observed in a comparable population who did not ingest propoxyphene. While these results could serve as basis for several hypotheses about the effects of propoxyphene, well designed trials or epidemiology studies with appropriate control groups are necessary to strengthen the evidence for a causal association. The FDA is requiring that the propoxyphene NDA holder conduct a clinical trial to assess the risk of QT prolongation associated with propoxyphene. These results should provide confirming evidence for or against a causal association in healthy individuals between propoxyphene and cardiovascular impairment, but may not inform us about the cardiovascular risks in individuals with predisposing health issues. However, they are not expected to be available until mid to late 2010.

Thus this evidence, by itself, does not support withdrawal of propoxyphene from the market.

E. 1987 Study of Effects of Governmental Warnings

OSE reviewed a study titled *Effect of government and commercial warnings on reducing prescription misuse: the case of propoxyphene*, Soumerai S.B., Avorn J, Gortmaker S., Hawley S, Am. J. Public Health, Dec. 1987, 77(12):1518-23.

1. Study Description

The data from this interrupted time series analysis depict trends in the use and prescribing of propoxyphene before, during, and after an educational campaign aimed at physicians and pharmacists. The campaign activities, implemented by FDA and Eli Lilly (the major manufacturer of propoxyphene at that time), were conducted between 1978 and 1980, and included drug label revisions, mail distribution of educational materials, and publications in the FDA Bulletin.

Yearly national prescription data for propoxyphene and NSAIDs were obtained from IMS America's National Prescription Audit (NPA) (provided by FDA) for the period 1974 – 1983. These data included the total number of new versus refill prescriptions by quarter from late 1978 to early 1981 and dose per prescription. Overdose death data were obtained from the Drug Abuse Warning Network (DAWN) from July 1977 to June 1983, and from another study by Finkle, which identified overdose cases within a population of 56.5 million. The authors used time series regression models to detect differences in trends before and after the campaigns.

The figures below show the study results. A downward trend in propoxyphene prescriptions of about 8% per year per million population was observed before the campaign period, but remained unchanged during the campaign period. The authors concluded that this downward trend might be partially explained by the vigorous promotion of NSAIDs at the time. The downward trend flattened out in the post-campaign period. The authors noted that analysis of prescriptions dispensed may not have been sensitive enough to measure the effects of the campaign warnings, which addressed specific uses of propoxyphene but did not intend to eliminate the use altogether. The time-series did not detect any change in the number of refills before and after the campaign, nor did they detect a difference in the average dose per prescription. In addition, the DAWN data showed no change in trend of overdose deaths related to propoxyphene, although the Finkle study detected a sharp downward trend before 1979 that flattened out thereafter.

The authors concluded that the warning campaign had little impact on reducing the way propoxyphene was prescribed or on the risk of overdose deaths.

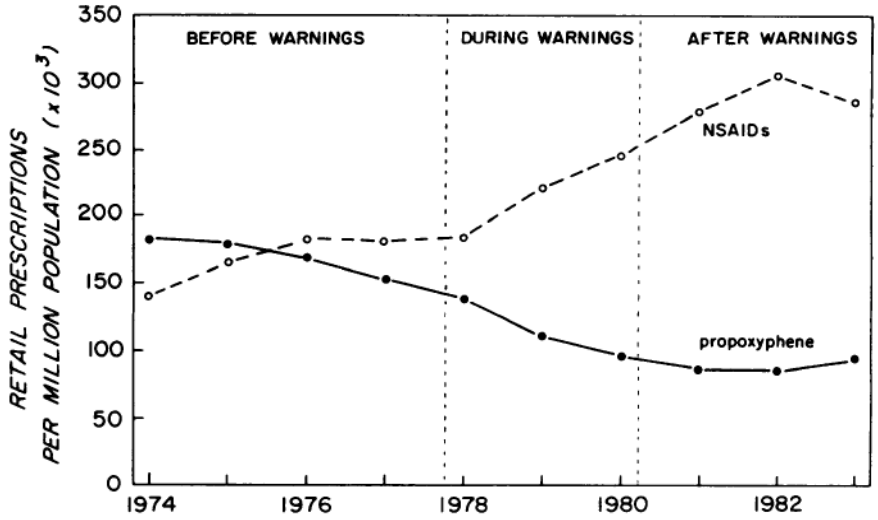


FIGURE 1—Prescriptions for Propoxyphene-containing Products versus Non-steroidal Anti-inflammatory Drugs (NSAIDs) Dispensed by Retail Pharmacies in the US from 1974–1983
Data provided from US FDA, based on National Prescription Audit.[25,26] Slope of regression line before warnings was −15,704 propoxyphene prescriptions per million population per year (SE = 2,542); change in slope during warnings (NS) was −404 (SE = 3,995); change in slope during 1981–83 was +12,499 (SE = 4,681).

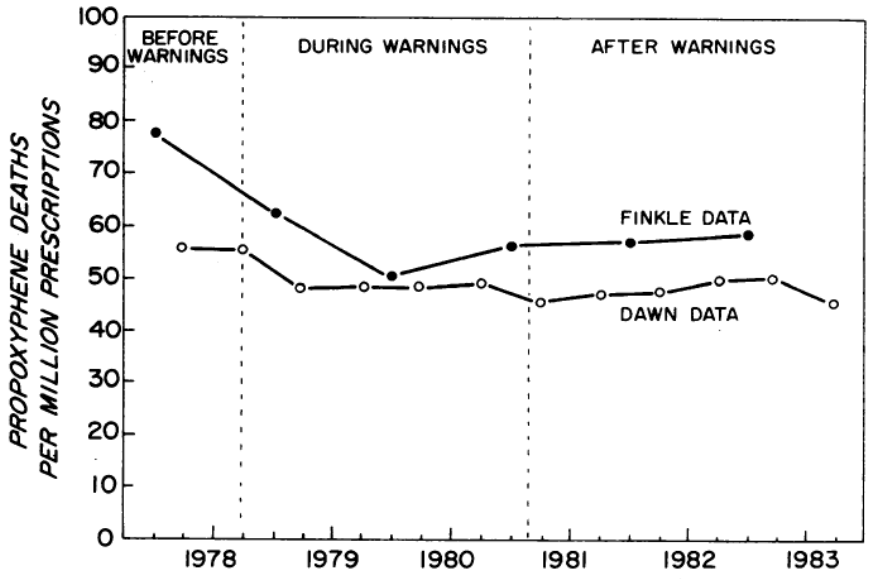


FIGURE 3—Trend in Propoxyphene-related Deaths per Million Propoxyphene Prescriptions Dispensed by Half-year Periods among 22 consistently Reporting SMSAs in the Drug Abuse Warning Network (July 1977–June 1983); and by Year in Finkle's 26 Study Sites (1977–1982)[34]
The denominator of propoxyphene prescriptions dispensed is based on IMS data for the nation as a whole,[26] adjusted to reflect the proportion of the US population covered by the study sites (23%, and 26%, respectively).

2. OSE/DEPI Comments

The fact that there was no overall observed change in trends of deaths and prescribing suggests that the previous changes in labeling and the educational campaign implemented in the US had little or no effect on propoxyphene overdose deaths and prescribing. However public health campaigns have evolved over the years to incorporate the use of technologies and methods that were scarce or non-existent in the past and may be more effective in today's environment. As such, this evidence by itself does not support the withdrawal of propoxyphene from the market.

F. Comparative Study of Fatality Rates for Propoxyphene vs. Other Analgesics

OSE reviewed a study titled *ECG abnormalities in co-proxamol (paracetamol/ dextropropoxyphene) poisoning*, Afshari R., Maxwell S., Dawson A., Bateman D.N., Clin Toxicol (Phila), 2005, 43(4):255-9 (Tab 17).

1. Study Description

This article describes two studies in which ECG changes were investigated following co-proxamol overdose. Those results were presented at the January 30, 2009 Advisory Committee meeting, and are discussed in detail in the OSE Background Package prepared for that meeting.

2. OSE/DEPI Comments

The study results did not provide evidence of a "markedly elevated fatality rate". Other studies of propoxyphene-related fatalities were cited in the discussion section as supporting evidence that sodium channel blockade is a significant factor contributing to death in cases of co-proxamol poisoning.

G. Case Study of Effects of UK Propoxyphene Withdrawal on Suicide Deaths

OSE reviewed a study titled *Effect of withdrawal of co-proxamol on prescribing and deaths from drug poisoning in England and Wales: time series analysis*, Hawton K., Bergen H., Simkin S., Brock A., Griffith C., Romeri E., Smith K.L., Dapur N., Gunnell D., BMJ 2009, 338:b2270. This study is addressed above in section C.

H. Additional Information Reviewed by OSE

OSE/DEPI has included additional information relating to propoxyphene which may not have been previously addressed. The additional information reviewed includes:

- A report by the Office for National Statistics on drug-related poisonings in England and Wales
- A review of a Letter to the Editor published in Clinical Toxicology in September 2009
- A description of results of studies cited by Afshari et al. in support of high propoxyphene-related fatality

1. Office for National Statistics Report – Deaths Related to Drug Poisoning in England and Wales, 2008[9]

This report, which describes deaths related to drug poisoning in England and Wales for the period 2004 to 2008, supports the Hawton et al. article discussed above and provides more evidence in support of withdrawing of propoxyphene from the market. The data, which were obtained from the UK Office of National Statistics database for 2004 to 2008, are based on registration of deaths within each calendar year. The figures reported for 2008 are provisional, and are calculated using the population projections for 2008.

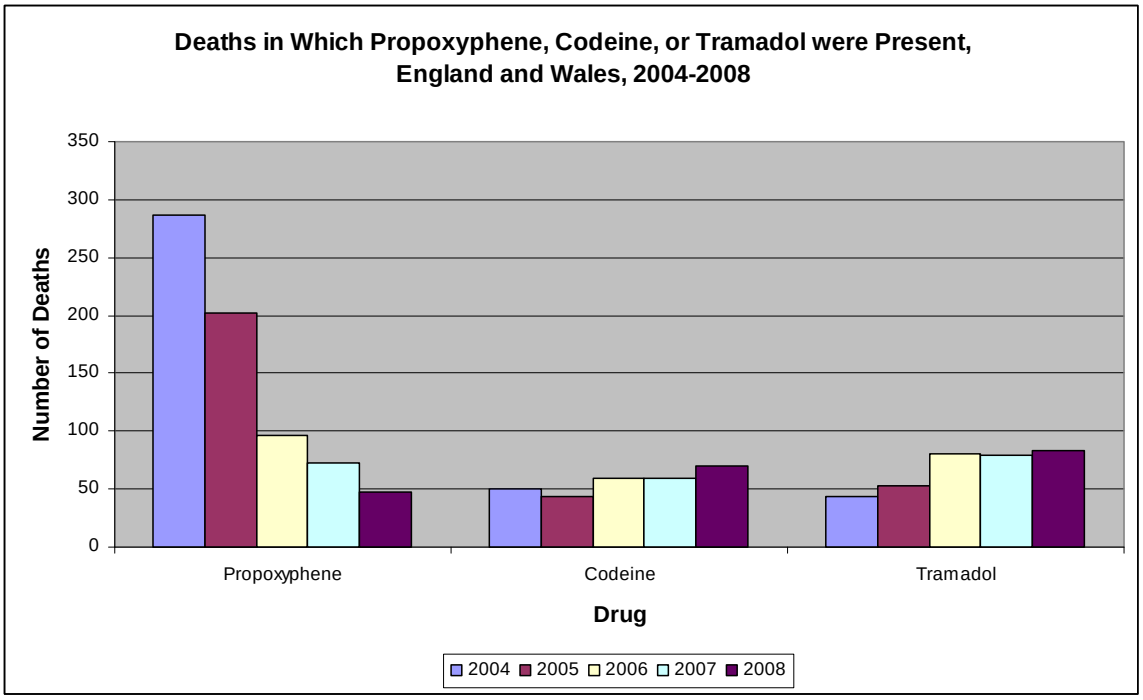
The results reveal an increase in the overall number of deaths related to all drug poisoning from 2007 to 2008. Deaths involving paracetamol and its compounds (including propoxyphene) increased slightly between 2007 and 2008 from 242 to 260. However, there was an overall decline in paracetamol deaths within the four year period largely due to deaths involving co-proxamol, for which there was an 83% decrease from 287 to 48 deaths. A corresponding decrease in age-standardized mortality rate was

[9] Office for National Statistics. Deaths related to drug poisoning in England and Wales, 2008. Statistical Bulletin. 26 August 2009.

observed for paracetamol and its compounds, which stabilized in 2006 for males and in 2007 for females. There were no mentions of deaths involving co-proxamol alone.

On the other hand, all deaths involving tramadol alone or concurrently with other drugs increased over this same period from 43 to 83. Deaths for which tramadol was the only drug implicated increased slightly from 26 to 29.

The figure below depicts counts of deaths involving propoxyphene, codeine, and tramadol for the period of 2004 to 2008. Overall, the results show a decrease in co-proxamol related deaths from 2004 to 2008, and an unexplained slow increase in deaths involving codeine and tramadol during that same period.



Data Source: Office for National Statistics. Deaths related to drug poisoning in England and Wales, 2008. Statistical Bulletin. 26 August 2009.

It is pertinent to note that the counts of death are not adjusted for drug use, thus comparisons across drugs may not be accurate.

2. *Clinical Toxicology Letter to the Editor September 2009*[10]

The Letter to the Editor published in the September 2009 issue of Clinical Toxicology reports propoxyphene-related poisoning data collected within the US, obtained from the National Poison Data System [NPDS formerly Toxic Exposure Surveillance System (TESS)] from 1983 to 2007. The authors state these important data support the Advisory Committee's recommendation on January 30, 2009 to remove propoxyphene from the market. The authors criticize FDA for not considering NPDS/TESS data, which could have supplemented the FDA's 91 case reports of propoxyphene-related deaths retrieved from the Adverse Event Reporting System (AERS).

The letter reports counts of deaths and non-fatal cases with a major outcome involving propoxyphene. A major outcome is defined as overdose producing life-threatening signs or symptoms as a result of the exposure or one that results in significant residual disability of disfigurement. There were a total of 124,845 overdose cases involving propoxyphene or propoxyphene-acetaminophen products between 1983 and 2007 in the US. Of these, 564 resulted in death, and another 3,313 resulted in a major outcome. The database did not distinguish between single drug and multiple drug overdoses until 2006,

[10] Hayes B, Anderson BD. Twenty five years of poison center experience with propoxyphene overdoses the FDA could not find. Clin Tox 2009; 47:905-906.

therefore some of these cases may not have been due solely to propoxyphene. In 2006 and 2007, there were 83 major outcomes and 10 deaths out of 11,184 overdose cases involving ingestion of propoxyphene alone.

OSE/DEPI Comments: The significance of this letter lies in the fact that the authors misrepresent FDA's review of adverse events and deaths related to propoxyphene products by incorrectly stating the FDA AERS findings and criticizing the FDA for not considering NPDS/TESS data. In fact, a post-marketing safety review by the Division of Drug Risk Evaluation (DDRE) dated July 25, 2005, evaluated TESS data along with AERS, DAWN, and IMS drug use data.

Contrary to the authors' statements in the letter, the AERS review yielded 3,075 adverse event reports for propoxyphene products including 1,160 deaths. In addition, 91 death reports were identified for Darvocet, which is one of many brands of propoxyphene products currently on the market.

Although DDRE's TESS review covered less than 25 years of data (1999 to 2003), there were some important findings. DDRE's summary of 2005 TESS review is shown below.

- For the years 1999 to 2003 there was an 11% increase in propoxyphene-associated exposure calls, but the number of fatal exposures with propoxyphene products declined by about 50%.

- Unintentional calls accounted for about 30% of calls for both propoxyphene and hydrocodone; the percent of unintentional calls did not change over time for either drug.

- The majority of propoxyphene-associated exposure calls occurred in individuals who reportedly took multiple products simultaneously with suicidal intent.

- Over 60 percent of calls for both propoxyphene and hydrocodone calls were from patients that were followed-up in a healthcare facility.

- Overall, propoxyphene-associated fatalities represented about 1% of the total 1,106 fatalities that were reported in the TESS database in 2003; compared to 7% for hydrocodone-associated fatalities.

3. Data Cited in Support of Propoxyphene Fatality Rate

OSE reviewed an article by Afshari et al., *ECG abnormalities in co-proxamol (paracetamol/dextropropoxyphene) poisoning,* Afshari R., Maxwell S., Dawson A., Bateman D.N., Clin Toxicol (Phila), 2005, 43(4): 255-9. Although this article did not study deaths, in the discussion section the authors cited other studies to support their conclusion that sodium channel blockade plays a role in deaths involving co-proxamol. These studies are described below.

Study I- Description: The first study was conducted in the UK[11]. The investigator analyzed all deaths due to propoxyphene in Birmingham, UK between 1976 and 1979 and in 1983. A total of 35 deaths were considered to be due to propoxyphene from 1976 to 1979 with an annual rate rising from 4% to 14%. Most of the propoxyphene-related deaths (91%) occurred outside a hospital facility compared to 39% occurring outside a hospital for all other analgesic-related deaths. Deaths were determined to have occurred rapidly (within a few hours) after ingestion with one case occurring in less than 1 hour. In 1983, propoxyphene was mentioned in 14 fatal overdose cases, which was more than the total for all opiates, salicylates, and paracetamol together (11).

OSE/DEPI Comments: The observation of rapid death in this study was used by Afshari et al. to support the authors' conclusion that the widened QRS complexes observed on the study subjects ECGs suggest propoxyphene plays a role in sodium channel blockade, which leads to a high fatality.

In addition, these data add to existing evidence that most propoxyphene-related deaths occur outside a hospital facility where adequate treatment could occur if cases were able to reach the hospital. Although the total number of propoxyphene deaths was greater than the total number of other drugs combined, it is pertinent to keep in mind that the numerator data are not adjusted for the total number of drugs prescribed and available for use.

Study II – Description: Another study[12] cited by Afshari et al. compared the numbers of suicides with co-proxamol, paracetamol, and tricyclic antidepressants. The study also compared fatal and non-fatal self-poisonings to estimate the relative fatality of overdoses with co-proxamol, paracetamol, and tricyclic antidepressants. Mortality data were obtained from the UK Office for National Statistics on deaths in people aged 10 years and older in England and Wales for the period of 1997 to 1999. The authors observed 4,162 drug related deaths within the study period, of which 766 (18%) were due to co-proxamol alone. Comparison of ratios of fatal poisonings to non-fatal poisonings for each drug/drug category suggested the odds of fatal overdose with co-proxamol to be 28 times higher than paracetamol [95% CI (24.9, 32.9)] and 2.3 times higher than tricyclic antidepressants [95% CI (2.1 to 2.5)].

OSE/DEPI Comments: The observation of a higher lethality of co-proxamol compared to paracetamol and tricyclic antidepressants was used by Afshari et al. to highlight the markedly elevated fatality of propoxyphene.

[11] Whittington RM. Dextropropoxyphene deaths: coroner's report. Human Toxicol 1984; 3(suppl):175S – 185S.

[12] Hawton K, Simkin S, Deeks J. Co-proxamol and suicide: a study of national mortality statistics and local non-fatal self-poisonings. BMJ 2003; 326:1006-1008.

This study documents evidence that co-proxamol use in the UK was associated with a significant proportion of drug-related deaths, and supports other UK data[13] (discussed in a previous DEPI review[14]) that found propoxyphene to be more toxic in overdose compared to drugs for similar indication. These data, in conjunction with the DAWN and FDLE medical examiner data included in this review support withdrawal of propoxyphene from the market.

[13] Afshari R, Good AM, Maxwell SRJ, Bateman DN. Co-proxamol overdose is associated with a 10-fold excess mortality compared with other paracetamol combination analgesics. Br J Clin Pharmacol 2005; 60:444-447.

[14] OSE/DEPI review dated February 27, 2009, OSE RCM# 2008-1517.

APPENDIX:

Table A1: FDLE: Number of Drug Related Deaths Reported by Florida Medical Examiners, and Dispensed Prescriptions for Propoxyphene, Tramadol and Hydrocodone 2003 -2007, Florida

Drug	Year	2003	2004	2005	2006	2007	Total
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of Drug Related Deaths (% of total deaths) *							
Propoxyphene	Causal	108 (30%)	96 (28%)	100 (27%)	71 (22%)	85 (25%)	460 (26%)
	Present	248 (70%)	251 (72%)	268 (73%)	257 (78%)	256 (75%)	1280 (74%)
	Total	356	347	368	328	341	1,740
Tramadol	Causal	21 (20%)	22 (18%)	31 (21%)	34 (24%)	35 (22%)	143 (22%)
	Present	85 (80%)	98 (82%)	116 (79%)	106 (76%)	122 (78%)	527 (78%)
	Total	106	120	147	140	157	670
Hydrocodone	Causal	180 (32%)	228 (36%)	221 (34%)	236 (32%)	45 (35%)	910 (33%)
	Present	392 (68%)	404 (64%)	427 (66%)	495 (68%)	85 (65%)	1803 (67%)
	Total	572	632	648	731	130	2,713
Number of Prescriptions Dispensed in the State of Florida							
Propoxyphene		2,200,984	2,396,757	2,558,994	1,846,491	1,927,932	10,931,158
Tramadol		994,546	1,157,767	1,482,214	1,335,548	1,638,101	6,608,176
Hydrocodone		5,466,519	6,176,808	7,567,414	7,579,078	7,198,009	33,987,828
Number of Total (Causal and Present) Deaths per 100,000 prescriptions							
Propoxyphene	Total	16.2	14.5	14.4	17.8	17.7	15.9
Tramadol	Total	10.7	10.4	9.9	10.5	9.6	10.1
Hydrocodone	Total	10.5	10.2	8.6	9.6	1.8	8.0
Number of Causally-Related Deaths per 100,000 prescriptions							
Propoxyphene	Causal	4.9	4.0	3.9	3.8	4.4	4.2
Tramadol	Causal	2.1	1.9	2.1	2.5	2.1	2.2
Hydrocodone	Causal	1.6	1.6	1.5	1.4	1.7	1.6

Source: Florida Department of Law Enforcement and SDI: Vector One ® National, Extracted 11/09
*Present = drug present in the body at the time of death.
Causal = medical examiner determines the drug played a causal role in the death via autopsy and toxicology results
Total deaths = deaths for which drug was present + deaths for which drug was causal

Table A2: Counts of Drug Involved Deaths in a Consistent Panel of 63 MSAs* reported to Medical Examiners in DAWN for Years 2004 – 2007 by Age Group and Type of Drug

Age groups	# of drugs	Propoxyphene	Tramadol	Hydrocodone
All ages	Total	1,611	911	4,665
	Single Drug	132	89	232
	Multiple Drugs	1,516	844	4,461
<18	Total	12	4	52
	Single Drug	0	0	4
	Multiple Drugs	12	4	52
18-44	Total	765	449	2,433
	Single Drug	58	46	115
	Multiple Drugs	729	427	2,345
45-64	Total	806	455	2,090
	Single Drug	78	50	137
	Multiple Drugs	760	424	1,982
65-74	Total	78	22	117
	Single Drug	10	2	12
	Multiple Drugs	68	20	110
75+	Total	54	30	64
	Single Drug	6	4	2
	Multiple Drugs	48	26	62

* MSA=metropolitan statistical area
Suppressed death less than 4 was substituted with "2"
Source: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network

Table A3: Counts of Drug Involved Deaths in Eight States reported to Medical Examiners in DAWN for Years 2004 – 2007 by Age Group and Type of Drug

Age groups	# of drugs	Propoxyphene	Tramadol	Hydrocodone
All ages	Total	336	292	895
	Single Drug	34	39	51
	Multiple Drugs	302	263	850
<18	Total	4	2	17
	Single Drug	0	0	4
	Multiple Drug	4	2	14
18-44	Total	162	155	493
	Single Drug	18	20	22
	Multiple Drugs	155	139	475
45-64	Total	152	138	364
	Single Drug	26	20	35
	Multiple Drugs	132	120	338
65-74	Total	18	4	26
	Single Drug	4	0	0
	Multiple Drugs	16	4	26
75+	Total	14	4	8
	Single Drug	4	2	0
	Multiple Drugs	12	4	8

Suppressed death less than 4 was substituted with "2"
Source: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network

Table A4: Count Summary of Drug Involved Deaths reported to DAWN Medical Examiners in a Consistent Panel of Metropolitan Areas and Number of Deaths per 100,000 prescriptions by Drug 2004 – 2007 (All ages/ single & multiple drugs)

	Propoxyphene			Tramadol			Hydrocodone		
MSA	Death	Prescription	Death/ 100,000 prescription	Death	Prescription	Death/ 100,000 prescription	Death	Prescription	Death/ 100,000 prescription
Albuquerque, NM Metropolitan Statistical Area	19	104,193	18.2	10	113,855	8.8	40	840,151	4.8
Atlanta	22	1,152,402	1.9	14	999,336	1.4	75	5,980,351	1.3
Baltimore	30	289,377	10.4	34	559,861	6.1	38	1,714,394	2.2
Bangor, ME Metropolitan Statistical Area	0	55,885	0.0	4	43,625	9.2	4	206,786	1.9
Barnstable Town, MA Metropolitan Statistical Area a	2	14,007	14.3	4	27,747	14.4	4	117,842	3.4
Bend, OR Metropolitan Statistical Area a, b	0								
Birmingham	22	516,456	4.3	8	382,359	2.1	54	3,001,696	1.8
Blacksburg-Christiansburg-Radford, VA Metropolitan a, b	2		2						
Boston	38	616,208	6.2	38	935,836	4.1	41	4,082,704	1.0
Bristol, VA Metropolitan Statistical Area a, b	0		2			2			
Buffalo	20	382,939	5.2	6	138,564	4.3	40	1,524,049	2.6
Burlington-South Burlington, VT MSA	4	21,160	18.9	0	59,913	2 0.0	6	207,971	2.9
Charlottesville, VA Metropolitan Statistical Area a	2	10,879	0 18.4	0	23,276	4 0.0	2	81,856	2.4
Chicago	28	843,111	3.3	23	863,826	2.7	131	5,210,762	2.5

	Propoxyphene			Tramadol			Hydrocodone		
MSA	Death	Prescription	Death/ 100,000 prescription	Death	Prescription	Death/ 100,000 prescription	Death	Prescription	Death/ 100,000 prescription
Cleveland	28	586,553	4.8	24	604,505	4.0	49	1,909,617	2.6
Cumberland, MD-WV Metropolitan Statistical Area a	0	31,478	0.0	4	28,113	14.2	2	71,460	2.8
Dallas-Fort Worth	25	988,231	2.5	8	832,681	1.0	54	6,357,624	0.8
Danville, VA Metropolitan Statistical Area a	0	14,088	0.0	0	13,468	0.0	2	40,268	5.0
Denver	23	227,985	10.1	30	344,678	8.7	71	2,027,461	3.5
Detroit	148	1,486,865	10.0	38	683,829	5.6	346	6,058,699	5.7
Eugene-Springfield, OR MSA a	2	23,680	8.4	2	23,495	8.5	2	232,911	0.9
Fargo, ND-MN Metropolitan Statistical Area a	4	17,688	22.6	0	18,773	0.0	6	64,421	9.3
Farmington, NM Metropolitan Statistical Area b	2								
Fort Smith, AR-OK Metropolitan Statistical Area	4	119,596	3.3	2	107,669	1.9	4	579,605	0.7
Harrisonburg, VA Metropolitan Statistical Area a, b	0		2						
Hagerstown-Martinsburg, MD-WV MSA a	2	25,915	7.7	2	22,188	6 9.0	2	61,427	3.3
Houston	56	1,266,834	4.4 2	26	896,345	2.9	513	7,036,109	7.3
Indianapolis	19	616,646	3.1	4	407,030	1.0	74	3,386,658	2.2
Kansas City	8	569,701	1.4	9	482,037	2 1.9	26	2,563,557	1.0
Kingsport-bristol, TN-VA MSA	0			0					

MSA	Propoxyphene			Tramadol			Hydrocodone		
	Death	Prescription	Death/ 100,000 prescription	Death	Prescription	Death/ 100,000 prescription	Death	Prescription	Death/ 100,000 prescription
a, b									
Las Cruces, NM Metropolitan Statistical Area	4	45,835	8.7	4	28,836	13.9	11	141,044	7.8
Lawton, OK Metropolitan Statistical Area	2	28,193	7.1	2	31,577	6.3	4	188,839	2.1
Lewiston-Auburn, ME Metropolitan Statistical Area	2	41,215	4.9	2	31,496	6.4	6	153,971	3.9
Logan, UT-ID Metropolitan Statistical Area b	4								
Los Angeles - Los Angeles Division, Orange County Division a, c	92	593,703	15.5	34	852,277	4.0	340	5,200,865	6.5
Louisville	21	452,247	4.6	8	342,817	2.3	51	2,667,724	1.9
Lynchburg, VA Metropolitan Statistical Area a	2	25,231	7.9	2	30,363	6.6	2	111,182	1.8
Manchester-Nashua, NH MSA b	2								
Medford, OR Metropolitan Statistical Area a	0	16,243	0.0	0	14,056	0.0	5	152,058	3.3
Miami - Dade County Division, Fort Lauderdale Division a, c	18	234,159	7.7	12	194,149	6.2	56	570,785	9.8
Milwaukee-Waukesha-West Allis, WI MSA	24	329,716	7.3	13	321,564	4.0	40	1,691,530	2.4
Minneapolis	8	320,836	2.5	13	488,308	2.7	27	2,169,883	1.2

	Propoxyphene			Tramadol			Hydrocodone		
MSA	Death	Prescription	Death/ 100,000 prescription	Death	Prescription	Death/ 100,000 prescription	Death	Prescription	Death/ 100,000 prescription
New Orleans	19	351,494	5.4	8	326,411	2.5	114	2,486,000	4.6
New York - 5 Boroughs Division, NY Suburban Division , Newark Division a,c	28	396,393	7.1	36	931,238	3.9	139	2,963,487	4.7
Ogden-Clearfield, UT Metropolitan Statistical Area b	4								
Oklahoma City, OK Metropolitan Statistical Area	14	414,432	3.4	9	422,831	2.1	61	2,774,295	2.2
Philadelphia	116	1,041,004	11.1	42	943,956	4.4	156	3,288,018	4.7
Phoenix	66	588,348	11.2	31	562,458	5.5	175	4,066,570	4.3
Pittsburgh a	18	483,328	3.7	13	279,055	4.7	20	2,141,645	0.9
Pittsfield, MA Metropolitan Statistical Area a	2	4,902	40.8	2	16,363	12.2	2	45,987	4.3
Portland, OR	14	182,620	7.7	10	248,879	4.0	51	3,026,738	1.7
Portland-South Portland, ME MSA	6	83,070	7.2	2	65,820	3.0	10	392,413	2.5
Providence	6	105,585	5.7	4	163,934	2.4	9	1,330,863	0.7
Provo-Orem, UT Metropolitan Statistical Area	6	37,339	16.1	9	110,192	8.2	25	706,186	3.5
Richmond, VA Metropolitan Statistical Area a	2	103,692	1.9	2	91,138	2.2	5	387,660	1.3
Roanoke, VA Metropolitan Statistical Area a	0	35,548	0.0	2	39,732	5.0	4	189,652	2.1
Salem, OR Metropolitan Statistical Area a	4	15,622	25.6	2	14,047	14.2	2	149,236	1.3

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MSA	Propoxyphene			Tramadol			Hydrocodone		
	Death	Prescription	Death/ 100,000 prescription	Death	Prescription	Death/ 100,000 prescription	Death	Prescription	Death/ 100,000 prescription
Salisbury, MD MSA a, b	4								
Salt Lake City	21	154,900	13.6	33	380,447	8.7	105	2,475,051	4.2
San Diego	33	314,711	10.5	24	341,678	7.0	110	2,782,546	4.0
San Francisco - San Francisco Division, Oakland Division a, c	7	40,078	17.5	2	56,074	3.6	43	583,317	7.4
Santa Fe, NM Metropolitan Statistical Area	2	18,220	11.0	0	21,837	0.0	8	198,704	4.0
Seattle	18	186,446	9.7	28	375,332	7.5	120	3,259,774	3.7
Sioux Falls, SD Metropolitan Statistical Area	6	104,267	5.8	0	62,741	0.0	2	195,991	1.0
Springfield, MA Metropolitan Statistical Area	2	41,692	4.8	2	127,328	1.6	6	312,182	1.9
St. George, UT Metropolitan Statistical Area	2	49,147	4.1	6	63,968	9.4	6	248,299	2.4
St. Louis	31	716,312	4.3	13	522,332	2.5	40	1,993,501	2.0
Tulsa, OK Metropolitan Statistical Area	17	328,908	5.2	11	342,054	3.2	110	2,300,240	4.8
Virginia Beach-Norfolk-Newport News, VA-NC MSA a, b	2								
Washington, DC	17	398,808	4.3	23	712,393	3.2	43	3,095,044	1.4

Source: Wolters Kluwer, Extracted 11/09 and Office of Applied Studies, SAMHSA, Drug Abuse Warning Network

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GERALD J DALPAN

11/19/2010

This memo documents my concurrence with Dr. Mark Avigan's memo of 19 April 2010 recommending withdrawal of propoxyphene from the market.