TABLE 6.—DEATHS ASSOCIATED WITH PROPOXYPHENE (DPX)

Category	Source of data						
	Baselt et al.[1]	Hine et al.[2]	Finkle et al.[3]	FDA reports of accidental deaths[4]	DAWN medical examiner reports of accidental or unexpected deaths[5]		
					1975	1976	1977
Total cases	29	72	1,022	48	229	187	179
Years involved	1973–74	1971–75	1972–75	1969–77	1975	1976	1977
Mean age	38	35	25	30			
Percent male	58	56	45	40			
Due to DPX alone:							
Number	8	14	244	15	56	27	29
Percent of total	28	19.6	24	27	24	12	16
Due to DPX and ethyl alcohol:							
Number	5	23	238	15	36	40	29
Percent of total	17	32	23	31	16	21	16
Due to DPX and other drug only:							
Number	8	17	349	10	101	87	79
Percent of total	28	23.6	34	21	44	47	44
Due to DPX and ethyl alcohol plus other drug(s):							
Number	8	18	191	6	32	26	28
Percent of total	28	25	18	12	14	14	16

[1] Reference 16.
[2] Reference 18.
[3] Reference 17.
[4] FDA spontaneous adverse reaction reporting program.
[5] Drug Enforcement Administration, Drug abuse Warning Network.

3. At present there is no clear evidence of deaths attributed to DPX products alone when taken in recommended doses and without alcohol or tranquilizers also being involved. There are, however, several "accidental" deaths that have occurred apparently as a result of the consumption of DPX in quantities only slightly in excess of recommended therapeutic dosage, usually combined with alcohol or tranquilizers or both. Dr. Larry Lewman, Multnomah County (Oregon) Medical Examiner, in testimony before the Senate Subcommittee cited previously in this notice, presented data in support of this possibility (Ref. 11). While reports such as this are very infrequent, given the wide availability of DPX, they raise concern that death of persons taking the drug at or near the recommended doses may be more common than is currently appreciated.

4. The mechanism of death in cases of DPX overdose is commonly attributed to respiratory depression, a typical action of narcotics. This theory is substantiated by a large number of case reports from a wide variety of sources. However, the possibility of a specific and primary cardiotoxic effect, independent of respiratory depression has been raised. The demonstration of dose-related progressive condition block appears clear in experimental animals, and in some patients with acutely toxic overdoses there are reported electrocardiographic (ECG) changes. This is not unexpected in view of the local anesthetic activity of both DPX and its primary metabolite norpropoxyphene. It has been postulated that, with chronic dosing, DPX accumulates to near toxic levels and adversely affects myocardial conduction, but this has not been the experience in heroin addicts on long-term, high-dose DPX napsylate maintenance. Moreover, when there are ECG changes in DPX overdoses and the CNS depressant effects are reversed by naloxone, the ECG changes rapidly revert to normal when respiration returns (or is mechanically supported) and acidosis is corrected. Therefore; the cardiac changes are most likely secondary to hypoxia rather than norpropoxyphene toxicity, which would take at least several hours to be reversible. Moreover, as shown in Table 5, only a small percentage of the deaths are in the over 60 age group which accounts for 35 percent of the reported prescribing. This population would be presumably more sensitive to any cardiovascular toxicity associated with DPX, but the paucity of deaths in this age group is notable. Cardiotoxicity at a therapeutic dose has not been observed.

5. DPX can produce psychological and physical dependence of the opiate type when taken for an extended period of time. It will substitute for other opiates in addicted persons, but only to a limited extent. Because of the abuse potential of DPX, it was placed in Schedule IV of the Controlled Substances Act. The