MEMORANDUM

Department Of Health and Human Services
Food and Drugs Administration
Center for Drug Evaluation and Research

Date: June 8, 2009

From: Charles Ganley, M.D., Director
Office of Nonprescription Products

Subject: Addendum to FDA Background Package for June 29-30, 2009 Meeting
Summary of Studies Reporting on Pack Size Limits in the United Kingdom

To: Advisory Committee Members
Drug Safety and Risk Management Committee, Anesthetic and Life Support Drugs Advisory Committee and Nonprescription Drugs Advisory Committee

The purpose of this memo is to provide a brief summary of some of the data available from the United Kingdom (UK) on pack size limits for OTC paracetamol (acetaminophen). It is not meant to be comprehensive but it is representative of the studies that have been published. Two speakers will present data on this issue at June 29 – 30 advisory committee meeting. The references (bookmarked in PDF file) are provided if additional information is needed for your review.

Pack size limits for OTC paracetamol and aspirin were implemented in the United Kingdom in September 1998 in order to decrease the amount of paracetamol normally kept in the home and readily available to an individual with an impulsive self-harm intent. Pack size limits were expected to lower overdose exposure levels, therefore decreasing severity of liver injury, and possibly decrease mortality and morbidity, after intentional overdose. Paracetamol remains available as a prescription only medicine, a pharmacy medicine and general sales list medicine.

The Working Group Report in your background material suggested that the restrictions on OTC paracetamol in the United Kingdom were primarily a sales limit at each transaction and, as a consequence, this dictated the pack size. This is an error. The pack size limits implemented through legislation can be summarized as follows.

Pack Size limits for paracetamol in the United Kingdom based on 1998 legislation[1]

- The legislation did not limit the number of packs that could be sold. Retailers, however, voluntarily placed sales limits of two sixteen tablet packs at non-pharmacy stores in a single transaction.
- The legislation limited the largest pack size of OTC paracetamol containing products to sixteen 500 mg tablets for non-pharmacy stores and thirty-two 500 mg tablets at pharmacies. The same pack size limit was also placed on aspirin containing products. There is no limit on pack sizes for products distributed via prescription.
- There was no requirement for packaging in blister packs; although blister packs are commonly used.
- The government mandates a sales restriction on quantities of paracetamol totaling 100 tablets or more. Pharmacists may dispense up to 100 tablets without a prescription. For the purchase of amounts greater than 100 tablets, a prescription is required.

Tables 1 and 2 show the sales data for paracetamol before and after the 1998 pack limits were put into place.

[1] Based on communication between FDA and MHRA April 2009

Table 1: United Kingdom Total Annual Supply (in grams) of Analgesics Before and After the Pack Limits.[2]

	1998	1999	2000
Paracetamol	409,054,172	198,566,850	166,456,260
Aspirin	66,465,780	21,943,740	15,488,710
Ibuprofen	26,453,320	29,616,100	45,929,400

Table 2: Number of Packs (thousands) sold over the counter in the United Kingdom [2]

	1998	1999	2000
Paracetamol 500 mg			
≤ 16 tablets	1061.4	1935.3	1781.6
>16 and ≤ 32 tablets	4564	11283	9236.1
> 32 tablets	5633.8	0	0
Total	**11259.2**	**13218.3**	**11017.7**
Ibuprofen 200 mg			
≤ 16 tablets	4157.2	3556.8	4608.1
>16 and ≤ 32 tablets	878.6	606.2	648.6
> 32 tablets	483.1	496.9	424.2
Total	**5518.9**	**4659.9**	**5680.9**
Ibuprofen 400 mg			
≤ 16 tablets	2	1.3	69.5
>16 and ≤ 32 tablets	646.5	643.8	927.2
> 32 tablets	0.1	178.4	649.3
Total	**6167.5**	**5483.4**	**7326.9**

Table 3 summarizes the published studies that assessed the impact of the pack size restrictions. Among the studies, a number of different methods were employed to explore the impact on a variety of injury metrics. When reviewing the information in table 3, it is important to consider the following:

1) Not all paracetamol products were affected by the legislation. Only OTC paracetamol single ingredient and OTC compound (combination) paracetamol products were affected. Products containing paracetamol in combination with opioid ingredients are only available by prescription. Some studies distinguish between OTC and prescription compound paracetamol products and others do not. As such, some paracetamol data will include exposure to compound paracetamol products that were not affected by the legislation.
2) The studies do not provide data past 2004. As such, there is no data on recent trends for paracetamol poisoning.
3) Some of the studies provide data on poisonings from the ingestion of drugs other than paracetamol. This provides a point of reference that allows one to consider other societal factors that may have affected the number of self harm cases.
4) The table does not summarize the rationale for selection of the statistics used in the analyses. Instead, the articles are attached for reference if you have additional questions.
5) It is important to think about which metrics would be expected to be affected by the legislation. For example, because paracetamol accounts for a small percentage of suicide deaths, it may be unrealistic to expect a change in total suicide deaths in the U.K. as a result of the legislation. Decreasing the amount available in the home with smaller pack sizes, and therefore the dose ingested, may be more likely to impact overall injury and outcome severity.
6) The impact of the legislation appears to differ between countries (e.g. England vs. Scotland).
7) The cause of death is not specified for paracetamol deaths. For cases that involved products combined with a narcotic, the cause of death may have been related to respiratory depression and not liver toxicity. Prescription paracetamol / narcotic combination drug products were not affected by the legislation.
8) The summary of the results in the table reflect the authors' interpretation and do not reflect FDA review of the data.

[2] Pharmacoepidemiology and Drug Safety 2002; 11: 329-331.

Table 3: Publications of Pack Size Limits Reporting Outcomes

Article	Location of Study Database Used Dates of Inquiry Measures of Injury	Results
1. Lancet 2000;355:2047 – 2048. Prince et. al	Location of Study Admissions to Freeman Liver Unit, Newcastle-upon-Tyne, UK Database Used Referrals to Freeman Liver Unit; national liver transplantation request - UK Transplant Support Authority (UKTSSA) Dates of Inquiry October 1995 – December 1999 Measures of Injury Severity data at Freeman Liver Unit; referrals to UKTSSA	- median monthly number of referrals to Freeman for paracetamol hepatotoxicity decreased from 2.5 before to 1.0 after September 1998 - median monthly number of referrals to UKTSSA for paracetamol hepatotoxicity decreased from 3.5 before to 2.0 after September 1998 [had been increasing by 7.5 per year in the three years prior to September 1998 - the medium dose of paracetamol decreased from 35 grams before to 25 grams after September 1998 - severity of liver toxicity remained constant for referrals to Freeman (as measured by creatinine, prothrombin time, pH and % with encephalopathy)
2. Lancet 2000; 355:2048 – 2049. Turvill et al.	Location of Study Royal Free Hospital Database Used Audit of all overdoses presenting to Royal Free Hospital Dates of Inquiry September 1995 – August 1999 Measures of Injury Calculated the number of paracetamol overdoses; identified subset of paracetamol overdoses designated as severe	- 21% reduction in all paracetamol overdoses - 64% reduction in severe overdoses (defined as requiring administration of N-acetylcysteine using National Guidelines) - the percentage of benzodiazepine overdose remained constant during this period - authors attributed decrease in paracetamol overdoses to introduction of paracetamol blister packs [Note: blister packs were available prior to pack size limit; blister packs are not a requirement of the UK legislation]
3. BMJ 2000; 321:926-927. Robinson et al.	Location of Study Five general hospitals in Belfast Database Used Hospital records of patients presenting with acute self poisoning Dates of Inquiry January to June 1998; January to June 1999 Measures of Injury	- 590 cases of paracetamol overdose in 1998 and 594 in 1999 - 67.4% admitted and 31% given antidote in 1998 ; 63% admitted and 25% given antidote in 1999 - no reduction in the number of severe paracetamol overdoses; - no difference in liver function tests - estimated quantity ingested was 10 grams (5 – 18) in 1998 and 8 grams (5 – 14) in 1999

<table>
<tr><th>Article</th><th>Location of Study
Database Used
Dates of Inquiry
Measures of Injury</th><th>Results</th></tr>
<tr><td></td><td>Amount of paracetamol ingested; paracetamol serum concentrations; liver enzymes and international normalized ratio (INR); number of hospital admissions, deaths and transfers to special unit related to paracetamol poisoning</td><td></td></tr>
<tr><td>4. BMJ 2001;322: 1 – 7.
Hawton et al.</td><td>Location of Study
England and Wales
Database Used
Office of National Statistics (ONS), admission data to five liver units in England, 7 hospitals (1 in Oxford, 4 in Bath and Bristol, 2 in Manchester)
Dates of Inquiry
ONS: September 1996 – September 1999; Liver units: October 1996 – September 1999; Hospitals: September 1997 – September 1999
Measures of Injury
Drug related deaths, number of admissions to liver units, number of poisonings</td><td>- the number of deaths related to paracetamol ingestion decreased 21% in the year after legislation compared to the average of the two years prior to legislation (decrease of approximately 40 deaths/ year)
- the annual number of admissions to liver units related to paracetamol poisoning decreased 30% in the year after legislation compared to the average of the two years prior to legislation (decrease of approximately 100 admissions per year)
- 66% fewer patients underwent liver transplantation because of paracetamol poisoning (decreased from 25/year to 12/year)
- the presentation to the hospital for paracetamol poisoning as a proportion of all poisonings did not change</td></tr>
<tr><td>5. The Lancet 2001; 358:1612 – 1613.
Newsome et al.</td><td>Location of Study
Scotland
Database Used
Patients admitted to the Scottish Liver Transplantation Unit (referral unit in Scotland for all patients with acute liver failure)
Dates of Inquiry
December 1992 – August 1998 compared to September 1998 – March 2001
Measures of Injury
Incidence of paracetamol induced liver</td><td>- 379 patients with paracetamol induced liver injury admitted between December 1992 and March 2001; 190 developed acute liver failure
- the incidence of paracetamol induced liver failure, severity of patient’s illness and outcome did not differ between time periods

Monthly referral rates
<table>
<tr><th></th><th>1992 – 1998</th><th>1998 – 2001</th></tr>
<tr><td>Paracetamol acute liver failure</td><td>2.03
(1.8 – 2.3; N= 140)</td><td>1.67
(1.3 – 2.0; N= 50)</td></tr>
<tr><td>Paracetamol acute liver failure meeting King’s College Poor Prognosis Criteria</td><td>0.97
(0.7 – 1.2; N = 67)</td><td>1.00
(0.6 – 1.4; N= 30)</td></tr>
</table></td></tr>
</table>

Article	Location of Study Database Used Dates of Inquiry Measures of Injury	Results
	failure, severity of patients illness	
6. Suicide and Life Threatening Behavior 2002; 32(3): 223 – 229. Hawton.	Location of Study 1) Seven hospitals: 1 in Oxford, 4 in Bristol and Bath, 2 in Manchester. 2) Five out of six liver units in England. 3) Office of National Statistics (ONS) for mortality data Database Used Hospital records, mortality data national statistics Dates of Inquiry Seven hospitals - Penultimate year before legislation; post legislation year. Liver units – two years before legislation and year after ONS - two years before legislation and year after Measures of Injury Seven hospitals - Number of episodes of self-poisoning for paracetamol and salicylates; number of tablets ingested; paracetamol and salicylate blood levels. Liver units – admissions due to paracetamol poisoning, patients listed for transplant, number of transplants. OFS - Mortality Data involving paracetamol and salicylates	Only paracetamol summary data provided (note that actual data was not provided in the article; information was presented as percent reductions): - in seven hospitals, 10% reduction in the proportion of self poisoning patients who used paracetamol; 7 % decrease in the number of paracetamol tablets ingested;17% reduction in the proportion of overdoses which involved more than 32 tablets; no change in highest paracetamol levels; - Liver unit: 30% reduction in the number of patients admitted for liver damage related to paracetamol; 59% reduction in the number of patients listed for liver transplantation; - Mortality statistics: 18% reduction in the proportional incidence of fatal poisonings involving paracetamol; 21% reduction in overall incidence (calculate that there were approximately 40 fewer deaths related to paracetamol). -Unable to determine whether the legislation has had an impact on the overall mortality due to suicide, although overall suicide rates were decreasing at the time of the legislation. - sales data (provided by Intercontinental Medical Statistics) collected for penultimate year and year after legislation; mean number of tablets per pack decreased by 26% but the number of packs purchased increased by 26%
7. Br. J Clin Pharmacol 2002; 54: 430 – 432. Sheen et al.	Location of Study Scotland Database Used Annual report General Register Office for Scotland that lists all of the drugs involved in fatal poisoning throughout Scotland Dates of Inquiry 1994 - 2000	- Between 1994 and 2000, there were 3878 deaths due to poisoning in Scotland. 16.6% were due to paracetamol. - Paracetamol deaths: 1994 = 90 deaths, 1995 = 81 deaths, 1996 = 96 deaths, 1997 = 102 deaths, 1998 = 93 deaths, 1999 = 70 deaths, 2000 = 112 deaths. - The pack size limit for paracetamol had no significant effect on the number of deaths related to paracetamol poisoning.

<table>
<tr><th>Article</th><th>Location of Study
Database Used
Dates of Inquiry
Measures of Injury</th><th>Results</th></tr>
<tr><td></td><td>Measures of Injury
Deaths related to paracetamol</td><td></td></tr>
<tr><td>8. Journal of Public Health 2002; 24(3):179-183. Wilkinson et al.</td><td>Location of Study
England and Wales
Database Used
Hospital Episode Statistics database
Dates of Inquiry
1995/96 to 1999/2000
Measures of Injury
Hospital admissions for deliberate self harm (may not include patients seen in the emergency room and discharged)</td><td>- paracetamol admissions decreased from 38168 in 1997/98 to 34481 in 1999/2000 (note: 1995/96 numbers were below 1999/2000 numbers but the exact number were not provided (note: 1995/96 paracetamol admission was approximately 30000)
- paracetamol self-poisoning increased as a subsidiary diagnosis from 1995/96 to 1999/2000
- sedative hypnotic and psychotropic drugs admissions increased from 27347 in 1995/96 to 37629 in 1999/2000 (note: there was a gradual increase in number for each year)
- narcotic and hallucinogen admissions increased from 3949 admissions in 1995/96 to 6830 in 1999/2000</td></tr>
<tr><td>9. QJM 2003; 96: 125 – 132. Bateman et al.</td><td>Location of Study
Scotland
Database Used
Scottish Morbidity Record and General Register Office for Scotland
Dates of Inquiry
1990 - 1999
Measures of Injury
Discharge data for poisoning and mortality data</td><td>- paracetamol accounts for the 27.9% of discharges for poisonings in the 10 year period

Discharge Rates (per 100,000 population)
<table>
<tr><th>Drug</th><th>1990
Male/female</th><th>1997
Male/female</th><th>1998
Male/female</th><th>1999
Male/female</th></tr>
<tr><td>Paracetamol</td><td>56.5/79.1</td><td>118.9/160.2</td><td>108.8/138.5</td><td>97.2/124.4</td></tr>
<tr><td>Antidepressant</td><td>22.5/36.2</td><td>54.5/79.5</td><td>59.5/83.4</td><td>60.4/82.6</td></tr>
<tr><td>Opioid</td><td>15.2/10.4</td><td>63.0/38.5</td><td>76.5/43.5</td><td>91.3/54.1</td></tr>
</table>
Deaths from poisonings
<table>
<tr><th>Drug</th><th>1990</th><th>1997</th><th>1998</th><th>1999</th></tr>
<tr><td>Paracetamol</td><td>72</td><td>101</td><td>94</td><td>72</td></tr>
<tr><td>All</td><td>404</td><td>401</td><td>352</td><td>341</td></tr>
</table></td></tr>
<tr><td>10. J of Clinical Pharmacology and Therapeutics 2003; 28:307-310. Hughes et al.</td><td>Location of Study
University Hospitals, Birmingham (UHB), UK, Queen Elizabeth Hospital (QEH) liver unit
Database Used
Records from hospital liver units
Dates of Inquiry
April 1995 – January 2002
Measures of Injury</td><td>Admissions related to paracetamol ingestion
<table>
<tr><th>Time Period Covered</th><th>Admissions to UHB</th><th>Admissions to QEH liver unit</th></tr>
<tr><td>Apr 1995 – Mar 1996</td><td>296</td><td>72</td></tr>
<tr><td>Apr 1996 – Mar 1997</td><td>336</td><td>95</td></tr>
<tr><td>Apr 1997 – Mar 1998</td><td>449</td><td>61</td></tr>
<tr><td></td><td></td><td></td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Article</th><th>Location of Study
Database Used
Dates of Inquiry
Measures of Injury</th><th>Results</th></tr>
<tr><td></td><td>Number of patients admitted for paracetamol poisoning; admissions to the liver unit with paracetamol induced hepatotoxicity</td><td>
<table>
<tr><td>Legislation September 1998</td><td></td><td></td></tr>
<tr><td>Apr 1998 – Mar 1999</td><td>299</td><td>46</td></tr>
<tr><td>Apr 1999 – Mar 2000</td><td>263</td><td>32</td></tr>
<tr><td>Apr 2000 – Mar 2001</td><td>238</td><td>36</td></tr>
<tr><td>Apr 2001 – Jan 2002*</td><td>197*</td><td>26*</td></tr>
</table>
* Not complete time period

-the authors mentioned other factors that may have contributed to decline in admissions
1. use of standard protocols to treat poisoning more rapidly and effectively upon presentation leading to decline of mortality
2. number of admissions affected by financial and staff shortages (no further clarification provided)</td></tr>
<tr><td>11. BMJ. 2004 Nov 6; 329(7474):1076.
Hawton et al.</td><td>Location of Study
1) Five hospitals: 1 in Oxford, 2 in Derby, 2 in Manchester.
2) Six liver units in England and Scotland for hospital admission data for poisoning.
3)National Statistics for England
Database Used
Office of National Statistics mortality data, Hospital records, Intercontinental Medical Statistics (sales data)
Dates of Inquiry
Mortality data: 1993 – 2001.
Liver transplant data: 1996 – 2002
Hospital data on poisonings: 1997 - 2001
Measures of Injury
Deaths by suicidal overdose with paracetamol, salicylates, or ibuprofen; numbers of patients admitted to liver units, listed for liver transplant, and undergoing transplantations for paracetamol induced hepatotoxicity;</td><td>- deaths related to paracetamol alone decline after the legislation and the effect persisted in years 2 and 3 after the legislation
- there was only a small change in overall deaths due to poisonings

Deaths related to Paracetamol in England and Wales (from table 1 in article)
<table>
<tr><th>Drug Involved</th><th>1993 - 1996</th><th>1996 - 1998</th><th>1998 - 1999</th><th>1999 - 2001</th><th>% change 2 yrs. Before to yr. 1 after</th><th>% change 2 yrs. Before to yr. 2 and 3 after</th></tr>
<tr><td>Paracetamol alone</td><td>161</td><td>192</td><td>137</td><td>127</td><td>-29</td><td>-34</td></tr>
<tr><td>Any paracetamol*</td><td>284</td><td>327</td><td>265</td><td>260</td><td>-19</td><td>-20</td></tr>
<tr><td>All poisoning</td><td>2092</td><td>2242</td><td>2186</td><td>2086</td><td>-2</td><td>-7</td></tr>
</table>
* includes products affected and those not affect by legislation

- ibuprofen deaths were few; 11 deaths in 5 years prior to legislation and 13 deaths in the 3 years after
- there was approximately a 30% reduction in the number of admissions to liver units because of paracetamol hepatotoxicity</td></tr>
</table>

<table>
<tr><th>Article</th><th>Location of Study
Database Used
Dates of Inquiry
Measures of Injury</th><th>Results</th></tr>
<tr><td></td><td>non-fatal self poisonings with analgesics and numbers of tablets taken; and sales figures for analgesics.</td><td>Annual Number of admissions, listings for transplant and transplants for paracetamol
<table>
<tr><th>Drug Involved</th><th>Year 2:1 before legislation</th><th>Year after legislation</th><th>Year 2 after legislation</th><th>Year 3:4 after legislation</th><th>Yr. 1 + 2 after/ Yr. 1 + 2 before</th><th>Yr. 3 + 4 after/ Yr. 1 + 2 before</th></tr>
<tr><td>Admissions</td><td>369/329</td><td>271</td><td>223</td><td>217/209</td><td>.71</td><td>.61</td></tr>
<tr><td>Listing for Transplants</td><td>44/42</td><td>28</td><td>31</td><td>35/26</td><td>.69</td><td>.88</td></tr>
<tr><td>Transplants</td><td>33/31</td><td>17</td><td>24</td><td>24/21</td><td>.64</td><td>.72</td></tr>
</table>
- there was a 15% reduction in presentations to the hospital for paracetamol poisoning in the year after the legislation

Annual Number of non-fatal self poisonings to Five Hospitals for Paracetamol and Ibuprofen
<table>
<tr><th>Drug Involved</th><th>Year before legislation</th><th>Year after legislation</th><th>Year 2:3 after legislation</th><th>% change Year after to Year before</th><th>% change Yr. 2 + 3 after to year before</th></tr>
<tr><td>Paracetamol alone</td><td>825</td><td>624</td><td>757:781</td><td>-24</td><td>-7</td></tr>
<tr><td>Any paracetamol</td><td>1733</td><td>1472</td><td>1681:1686</td><td>-15</td><td>-3</td></tr>
<tr><td>Ibuprofen alone</td><td>96</td><td>113</td><td>156:133</td><td>18</td><td>51</td></tr>
<tr><td>Any ibuprofen</td><td>316</td><td>332</td><td>399:402</td><td>5</td><td>27</td></tr>
</table></td></tr>
<tr><td>12. Journal of Public Health 2005; 27(1):19-24. Morgan et al.</td><td>Location of Study
England and Wales
Database Used
Mortality data from Office of National Statistics; hospital admissions for paracetamol poisoning from Department of Health database
Dates of Inquiry</td><td>- some compound paracetamol products are not covered by the pack size limits (prescription)
- there were 5655 paracetamol related deaths between 1993 and 2002
- compound paracetamol had approximately twice as many deaths as paracetamol only products
- approximately 82% of paracetamol cases did not involve alcohol or other drugs
- 47% of deaths were intentional self poisoning and 33% were undetermined</td></tr>
</table>

<table>
<tr><th>Article</th><th>Location of Study
Database Used
Dates of Inquiry
Measures of Injury</th><th>Results</th></tr>
<tr><td></td><td>1993 - 2002
Measures of Injury
Mortality data: for paracetamol alone with or without alcohol or other drugs, compound paracetamol (paracetamol in combination with another analgesic or caffeine) without or without alcohol or other drugs
Hospital Admissions for paracetamol poisoning</td><td>Death Rates per million population
<table>
<tr><td></td><td>1997</td><td>1999</td><td>2001</td><td>2002</td></tr>
<tr><td>Paracetamol only</td><td>4.5</td><td>2.8</td><td>3.1</td><td>2.2</td></tr>
</table>
- Death rates for compound paracetamol remained relatively constant over the study period
- for all drug poisoning (excluding opiates and paracetamol), age standardized mortality rates decreased (see figure 1 in article)
- When deaths involving opioids, drugs of misuse or paracetamol were excluded, trends in age-standardized mortality from all drug poisoning displayed a similar pattern to paracetamol-related poisoning, increasing until 1997 and then declining to below 1993 levels
- there are approximately 50% more hospital admissions for females than males

Hospital Admissions for Paracetamol Poisoning and Deaths
<table>
<tr><td></td><td>Hospital Admissions</td><td>Compound paracetamol deaths</td><td>Paracetamol Deaths</td></tr>
<tr><td>1995/6</td><td>26776</td><td>345</td><td>182</td></tr>
<tr><td>1996/7</td><td>29829</td><td>361</td><td>208</td></tr>
<tr><td>1997/8</td><td>32588</td><td>418</td><td>194</td></tr>
<tr><td>1998/99</td><td>27257</td><td>378</td><td>184</td></tr>
<tr><td>1999/00</td><td>25502</td><td>382</td><td>132</td></tr>
<tr><td>2000/01</td><td>24512</td><td>357</td><td>150</td></tr>
<tr><td>2001/02</td><td>24993</td><td>367</td><td>172</td></tr>
</table>
Database will not permit breakdown of hospital admissions due to paracetamol or compound paracetamol.

- authors concluded : There was evidence of a decreasing trend in paracetamol only mortality rates and this followed overall trends for other drug poisoning excluding opioids and drugs of misuse.</td></tr>
<tr><td>13. Br J Clin Pharmacol 2006;62(5):573-581. Bateman et al.</td><td>Location of Study
Scotland
Database Used
death by poisoning data provided by the General Register Office for Scotland (GROS) for 1996–2003; overdose requiring hospitalization from Scottish Morbidity Records scheme (SMR)</td><td>- data was provided for paracetamol + ethanol, paracetamol + other drugs, Co-proxamol (dextropropoxyphene + paracetamol), and paracetamol in combination products excluding co-proxamol
- the majority of paracetamol deaths occurred outside of the hospital (327 of 929 deaths occurred in the hospital)
- deaths with reference to co-proxamol accounted for 511 of 929 deaths</td></tr>
</table>

<table>
<tr><th>Article</th><th>Location of Study
Database Used
Dates of Inquiry
Measures of Injury</th><th>Results</th></tr>
<tr><td></td><td>Dates of Inquiry
1995 - 2004
Measures of Injury
In-hospital and out-hospital deaths (paracetamol referenced on death certificate); hospital admissions for poisoning</td><td>Deaths with reference to paracetamol on death certificate
<table>
<tr><th></th><th>Paracetamol ± ethanol</th><th>Paracetamol + other drugs</th><th>Co-proxamol</th><th>Paracetamol in combinations</th><th>Total</th></tr>
<tr><td colspan="6">Out-of-hospital deaths</td></tr>
<tr><td>1995</td><td>5</td><td>13</td><td>34</td><td>0</td><td>52</td></tr>
<tr><td>1996</td><td>9</td><td>11</td><td>45</td><td>0</td><td>65</td></tr>
<tr><td>1997</td><td>7</td><td>7</td><td>49</td><td>1</td><td>64</td></tr>
<tr><td>1998</td><td>6</td><td>15</td><td>51</td><td>3</td><td>75</td></tr>
<tr><td>1999</td><td>5</td><td>9</td><td>37</td><td>1</td><td>52</td></tr>
<tr><td>2000</td><td>4</td><td>18</td><td>54</td><td>3</td><td>79</td></tr>
<tr><td>2001</td><td>7</td><td>13</td><td>53</td><td>3</td><td>81</td></tr>
<tr><td>2002</td><td>9</td><td>18</td><td>50</td><td>4</td><td>81</td></tr>
<tr><td>2003</td><td>7</td><td>9</td><td>39</td><td>3</td><td>58</td></tr>
<tr><td>Total</td><td>58</td><td>113</td><td>412</td><td>19</td><td>602</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>Paracetamol ± ethanol</td><td>Paracetamol + other drugs</td><td>Co-proxamol</td><td>Paracetamol</td><td>Total</td></tr>
<tr><td colspan="6">In-hospital deaths</td></tr>
<tr><td>1995</td><td>22</td><td>4</td><td>5</td><td>0</td><td>31</td></tr>
<tr><td>1996</td><td>19</td><td>2</td><td>6</td><td>2</td><td>29</td></tr>
<tr><td>1997</td><td>24</td><td>5</td><td>17</td><td>0</td><td>46</td></tr>
<tr><td>1998</td><td>14</td><td>2</td><td>12</td><td>1</td><td>29</td></tr>
<tr><td>1999</td><td>17</td><td>2</td><td>7</td><td>1</td><td>29</td></tr>
<tr><td>2000</td><td>28</td><td>6</td><td>9</td><td>0</td><td>43</td></tr>
<tr><td>2001</td><td>25</td><td>6</td><td>17</td><td>5</td><td>53</td></tr>
<tr><td>2002</td><td>13</td><td>4</td><td>20</td><td>3</td><td>40</td></tr>
<tr><td>2003</td><td>21</td><td>2</td><td>6</td><td>0</td><td>29</td></tr>
<tr><td>Total</td><td>183</td><td>33</td><td>99</td><td>12</td><td>327</td></tr>
<tr><td>Overall</td><td>241</td><td>146</td><td>511</td><td>31</td><td>929</td></tr>
</table>
-the proportion of deaths referencing paracetamol relative to all poisonings increased post-legislation compared to pre-legislation
-the proportion of all hospital discharges referencing paracetamol relative to all poisonings</td></tr>
</table>

<table>
<tr><th>Article</th><th>Location of Study
Database Used
Dates of Inquiry
Measures of Injury</th><th>Results</th></tr>
<tr><td></td><td></td><td>increased post legislation compared to pre-legislation
- the authors conclude that the legislation has been unsuccessful in reducing hospitalizations and deaths</td></tr>
<tr><td>14. Public Health 2007;121:45-50.
Gorman et al.</td><td>Location of Study
Scotland
Database Used
Deaths from General Register Office of Scotland; hospital discharge data from the Scottish Morbidity Records Scheme
Dates of Inquiry
1995 - 2002
Measures of Injury
Changes in mortality and overdose rates; case fatality rates due to paracetamol poisoning; data presented by deprivation quintiles (by differences in socioeconomic status)</td><td>- there was an initial reduction in hospitalizations after the legislation but hospitalizations returned to pre-legislation levels in the second year.
- the proportion of paracetamol poisonings relative to all poisonings was increased after legislation

Hospital discharges (includes deaths) involving paracetamol and other poisonings (rates per 100,000)
<table>
<tr><th></th><th>Paracetamol Poisonings</th><th>Other Poisonings</th><th>Paracetamol poisonings as proportion of all poisonings</th></tr>
<tr><td>1995</td><td>113.1</td><td>263.2</td><td>.30</td></tr>
<tr><td>1996</td><td>122.5</td><td>274.1</td><td>.31</td></tr>
<tr><td>1997</td><td>140.3</td><td>273.9</td><td>.34</td></tr>
<tr><td>1998</td><td>124.2</td><td>268.9</td><td>.32</td></tr>
<tr><td>1999</td><td>111.6</td><td>260.1</td><td>.30</td></tr>
<tr><td>2000</td><td>131.3</td><td>251.4</td><td>.34</td></tr>
<tr><td>2001</td><td>141.5</td><td>256.5</td><td>.36</td></tr>
<tr><td>2002</td><td>137.3</td><td>251.3</td><td>.35</td></tr>
</table>

- deaths rates fell in the first year after the legislation and then returned to pre-legislation levels

Deaths referencing paracetamol overdose
<table>
<tr><th></th><th>Males</th><th>Females</th><th>Total</th></tr>
<tr><td>1995</td><td>40</td><td>43</td><td>83</td></tr>
<tr><td>1996</td><td>52</td><td>42</td><td>94</td></tr>
<tr><td>1997</td><td>39</td><td>63</td><td>102</td></tr>
<tr><td>1998</td><td>52</td><td>42</td><td>94</td></tr>
<tr><td>1999</td><td>36</td><td>36</td><td>72</td></tr>
<tr><td>2000</td><td>65</td><td>48</td><td>113</td></tr>
<tr><td>2001</td><td>47</td><td>65</td><td>112</td></tr>
<tr><td>2002</td><td>53</td><td>45</td><td>98</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Article</th><th>Location of Study
Database Used
Dates of Inquiry
Measures of Injury</th><th>Results</th></tr>
<tr><td></td><td></td><td>- the most disadvantaged groups (social economic group) have the highest overdose and death rates
- fatality rates/ 100 paracetamol overdoses was 1.81 for males and 1.24 for females over the period from 1995 - 2002 (individual years data not provided)
- the authors noted that describing overdose and death for paracetamol is difficult; many overdoses involve multiple agents; cannot determine whether paracetamol alone caused any of the events</td></tr>
<tr><td>15. Plos Medicine 2007;4(4);e105. Morgan et al.</td><td>Location of Study
England and Wales
Database Used
Drug poisoning deaths from Office of National Statistics
Dates of Inquiry
1993 - 2004
Measures of Injury
Age standardized mortality rates for paracetamol and paracetamol compound ; other drugs presented as comparators</td><td>- identified deaths in which paracetamol mentioned on death certificate; if certificate mentioned paracetamol with codeine, dihydrocodeine, dextropropoxyphene, these were defined as paracetamol compound
- paracetamol poisoning deaths decreased around the time the regulation were introduced; similar trends were noted for antidepressants and nonpoisoning suicides
- the authors could not conclude the legislation resulted in greater reduction of poisoning deaths.

Age Standardized Mortality Rate per Million Population
<table>
<tr><th></th><th>Paracetamol</th><th>Paracetamol compound</th><th>Aspirin</th><th>Antidepressants</th><th>Nonpoisoning Suicides</th></tr>
<tr><td>Total deaths over 12 years</td><td>2196</td><td>4378</td><td>457</td><td>5602</td><td>43824</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>1993</td><td>8.1</td><td>11.8</td><td>2.3</td><td>17.9</td><td>150.5</td></tr>
<tr><td>1994</td><td>7.1</td><td>13.1</td><td>1.9</td><td>18.7</td><td>145.5</td></tr>
<tr><td>1995</td><td>8.0</td><td>14.8</td><td>1.7</td><td>18.9</td><td>144.0</td></tr>
<tr><td>1996</td><td>7.0</td><td>14.0</td><td>2.0</td><td>20.9</td><td>135.1</td></tr>
<tr><td>1997</td><td>8.8</td><td>16.3</td><td>1.8</td><td>20.9</td><td>134.3</td></tr>
<tr><td>1998</td><td>7.9</td><td>14.5</td><td>1.4</td><td>19.5</td><td>144.5</td></tr>
<tr><td>1999</td><td>5.5</td><td>14.7</td><td>0.9</td><td>18.8</td><td>145.0</td></tr>
<tr><td>2000</td><td>5.5</td><td>14.4</td><td>0.8</td><td>17.0</td><td>136.8</td></tr>
<tr><td>2001</td><td>6.2</td><td>13.3</td><td>0.9</td><td>15.7</td><td>128.5</td></tr>
<tr><td>2002</td><td>4.5</td><td>11.7</td><td>0.6</td><td>14.8</td><td>131.4</td></tr>
<tr><td>2003</td><td>5.7</td><td>10.7</td><td>0.7</td><td>15.8</td><td>128.4</td></tr>
<tr><td>2004</td><td>5.3</td><td>10.5</td><td>0.6</td><td>15.1</td><td>125.9</td></tr>
</table></td></tr>
</table>

Article	Location of Study Database Used Dates of Inquiry Measures of Injury	Results
		- the authors noted that when multiple drugs are listed on the death certificate it is difficult to determine which drug was contributory
16. Journal of Clinical Pharmacology 2007; 32: 449-455. Dargan et al.	Location of Study St. Guy's and Thomas' Poison Unit (London, UK) Database Used St. Guy's and Thomas' Poison Unit database Dates of Inquiry 1996 - 2004 Measures of Injury Calls to unit for all poisoning and paracetamol poisoning; number of paracetamol pills ingested	- Quantity of paracetamol ingested provided in 61% of the calls (Authors excluded paracetamol available by prescription from analysis) - median number of paracetamol pills ingested by patients decreased after the legislation for males (25 → 20) and females (20 → 16) - there appears to be a decrease in the proportion of poison calls for paracetamol compared to all calls in 1999 but the proportion reverts to pre-legislation values in 2000

References (Pack Size Studies)

The following studies are summarized in an FDA memo describing data related to pack size limits legislated in the United Kingdom on OTC paracetamol products and are provided for reference or clarification. The last study is a review study that is not part of the memo.

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15. Morgan OW, Griffiths C, Majeed A. Interrupted time-series analysis of regulations to reduce paracetamol (acetaminophen) poisoning. PLoS Med. 2007 Apr;4(4):e105.

16. Morgan O, Hawkins L, Edwards N, Dargan P. Paracetamol (acetaminophen) pack size restrictions and poisoning severity: time trends in enquiries to a UK poisons centre. J Clin Pharm Ther. 2007 Oct;32(5):449-55.

17. Hawkins LC, Edwards JN, Dargan PI. Impact of restricting paracetamol pack sizes on paracetamol poisoning in the United Kingdom: a review of the literature. Drug Saf. 2007;30(6):465-79.