Summary of Published Clinical Studies of Acetaminophen Package Size Restrictions

Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Robinson D, et al. BMJ 2000;321: 926-7. Northern Ireland[a]	1/98-6/98 vs 1/99-6/99	Assess the impact of reduced availability of APAP on the number and severity of overdoses by comparing self poisoning cases in two periods of six months before and after the change to smaller packets	• Retrospective • Examined data from patients presenting with acute APAP self poisoning at five general hospitals in the Belfast area of Northern Ireland	• 590 patients presented with APAP poisoning in 1998 and 594 patients presented in 1999 • Estimated quantity of APAP ingested was 10 g in 1998 and 8 g in 1999 (p=0.004) • Serum APAP concentration at 4-6 h was 37 mg/L in 1998 and 27 mg/L in 1999 (p=0.003) • Number of patients administered antidote was 183 in 1998 and 149 in 1999 (p=0.03) • There was no significant difference in the number of patients admitted to hospital (398 in 1998 and 374 in 1999) • Concentration of serum aspartate aminotransferase at 24-48 hours was 23.0 U/L in 1998 and 23.5 U/L in 1999 • International normalized ratio at 24-48 hours was 1.1 in 1998 and 1999	Measures to restrict the availability of APAP have reduced the amount taken in single overdoses but not the incidence of severe liver failure

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Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Sheen CL, et al. Pharmaco epidemiol Drug Safety 2002;11: 329-31. UK and Northern Ireland[a]	1998-2000	Examine the OTC supply of APAP, aspirin, and ibuprofen and the impact of the APAP pack size restrictions in 1998 on the OTC sale of these drugs	• Retrospective • Examined IMS Health UK data on drug sales for APAP 500 mg, ibuprofen 200 mg and 400 mg, and aspirin 75 mg and 300 mg tablets	• Total annual supply of OTC APAP in UK was 409,054,172 g in 1998; 198,566,850 g in 1999; and 166,456,260 g in 2000 • Total annual supply of OTC aspirin in UK was 66,465,780 g in 1998; 21,943,740 g in 1999; and 15,448,710 g in 2000 • Total annual supply of OTC ibuprofen in UK was 26,453,320 g in 1998; 29,616,100 g in 1999; and 45,929,400 g in 2000 • The total number of packs of APAP supplied for OTC use in thousands was 11259.2 in 1998, 13218.3 in 1999 and 11017.7 in 2000 • The total number of packs of aspirin 75 mg supplied for OTC use steadily increased from 1998 to 2000 and the total number of packs of aspirin 300 mg decreased • The number of packs of ibuprofen 400 mg tablets steadily increased and the number of packs of ibuprofen 200 mg fell between 1998 and 1999 but increased from 1999 to 2000	The pack size restriction has reduced the total mass of APAP and aspirin sold over-the-counter while that of ibuprofen has increased. If this reduction in over-the-counter supply of APAP was directly related to overdose, the rate reduction achieved would have been expected to be greater than that observed. The shift to using ibuprofen may lead to an increase in adverse gastrointestinal events.

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Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Bathgate AJ, et al. Hepatol-ogy 2000;32: 1859. Scotland[a]	11/92-3/00	Assess changes in admission rate and patient demographics since September 1988	• Analyzed database of the Scottish Liver Transplant Unit for admissions with APAP poisoning	• 271 patients admitted between 11/92 and 8/98 for a mean of 3.9 admissions per month and 63 patients admitted between 9/98 and 3/00 for a mean of 3.5 admissions per month; no statistically significant difference was observed • The mean number of APAP tablets decreased from 69 to 58; no statistically significant difference was observed • The mean time to presentation significantly ($p<0.001$) decreased from 28 h to 13 h after the restrictions • There was a significant increase in patients with previous psychological illness (56% vs 40%, $p=0.02$) after the restrictions and previous overdose. • There was no significant difference in the % of patients who had died or had transplants after the restrictions	The change in packaging of APAP tablets in 1998 has not led to a significant decrease in the rate of admissions to the liver unit with APAP induced liver impairment

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Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Laing WJ, et al. J Toxicol Clin Toxicol 2001;39: 301. Scotland[a]	1996-2000	To ascertain whether recent UK legislation is impacting on calls to a poison center involving APAP	• Analyzed Scottish Poison Information Bureau telephone inquiry statistics for the 2 years before and after new legislation was introduced	• Number of APAP cases: 1996/1997-694, 1997/1998-620, 1998/1999-592, 1999/2000-546 • Number of total cases: 1996/1997-7175, 1997/1998-6781, 1998/1999-6704, 1999/2000-6121 • Number (%) of patients ingesting >8 g: 1996/1997-29 (44%), 1997/1998-67 (35%), 1998/1999-66 (33%), 1999/2000-49 (31%) • Number (%) of patients ingesting >16 g: 1996/1997-17 (26%), 1997/1998-25 (13%), 1998/1999-35 (17%), 1999/2000-25 (16%)	APAP inquiries, as a percentage of total inquiries, have fallen slightly. However, the proportion of calls regarding patients who have taken more than 16 g appears to have risen. Conversely, there has been little difference in the number of patients who have taken more than 8 g. These early data suggest that reduction in pack size has not had an impact on the scale of overdose commonly encountered, and has not deterred a small proportion of patients from consuming much higher doses of APAP

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Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Newsome PN, et al. Lancet 2001;358: 1612-13. Scotland[a]	1992-2001	To establish whether changes in the referral of patients with paracetamol-induced acute liver failure have occurred since the introduction of package restrictions	• Analyzed data from patients admitted to the Scottish Liver Transplantation Unit in 1992-1998 with those admitted in 1998-2001.	• Incidence of paracetamol-induced liver failure, severity of patient's illness, and outcome did not differ between the groups. • Patients with paracetamol-induced acute liver failure had higher Carstairs scores (ie, were more socially deprived) than patients with non-paracetamol-induced acute liver failure.	The introduction of package size restrictions did not affect the incidence of paracetamol-induced liver failure, severity of patient's illness, and outcome. An association between paracetamol-induced acute liver failure and social deprivation was shown.

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Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Sheen CL, et al. Pharmaco epi-demiology Drug Safety 2001;10:S 24 and Sheen C, et al. Gastroent-erology 2001;120 (suppl 1): A228 and Sheen CL, et al. Gut 2001;48 (Suppl 1):A105. Scotland[a]	9/95-9/00	Determine APAP overdose rates for patients presenting to Ninewells Hospital Dundee, using serum APAP levels as a robust marker of overdose and to assess whether the action of the MCA has had any measurable effect	• Examined biochemistry database of Ninewells Hospital, Dundee for all APAP assays	• A total of 6336 tests were performed of which 4454 were negative for APAP. • No significant difference was observed in the number of tests with APAP results >1.3 mmol/L: before September 1998- range was 23 to 27; after September 1998 - range was 27 to 28	Results do not suggest that the incidence of APAP overdose has been affected by the over-the-counter pack size reduction, at least in the Tayside region of Scotland

Summary of Published Clinical Studies of Acetaminophen Package Size Restrictions

Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Sheen CL et al, Br J Clin Pharmacol 2002;54: 430-2. Scotland[a]	1994-2000	Investigate the death rate due to APAP poisoning in Scotland and what effect the reduction in over-the-counter APAP pack sizes in 1998 had on the death rate	• Examined data from the General Register Office for Scotland to identify deaths related to APAP and deaths due to any poisonings	• Between 1994 and 2004 there were 3878 deaths due to poisoning in Scotland of which 644 (16.6%) involved APAP • Total number of deaths from all poisonings has increased (559 in 1994 and 574 in 2000) • There was no significant difference between 1996/1997 and 1999/2000 in the number of deaths to APAP alone (1994-38, 1995-27, 1996-27, 1997-31, 1998-20, 1999-20, 2000-31) or all APAP related deaths (1994-90, 1995-81, 1996-96, 1997-102, 1998-93, 1999-70, 2000-112) • The mean annual death rate from APAP alone from 1994 to 2000 was 5.4 per million • The mean annual death rate for all APAP-related deaths from 1994-2000 was 17.9 per million	There is no lasting effect of pack size changes on the number of deaths from APAP poisoning

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Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Bateman DN, et al. Q J Med 2003;96: 125-32. Scotland[a]	1990-1999	To examine trends in discharges for poisoning, in particular paracetamol, antidepressants, and opioids from 1990-1999	• Retrospective analysis • Analyzed data from the Scottish Morbidity Record for information on discharges and from the General Register Office for Scotland for mortality for all poisons, APAP, opioids, and antidepressants	• Over the 10-year period there were a total of 182,322 poisoning discharges recorded involving 119,044 patients • Between 1990 and 1997, annual discharge rates for total overdoses increased and after 1997 they fell • During the 10-year study period, there were 54,204 discharges in which APAP was ingested in 38,767 patients • Between 1990 and 1997, annual discharge rates for APAP overdoses increased and by 1999 they had fallen significantly • Overall mortality from overdoses decreased after 1993 • There was no significant trend in overall APAP overdose mortality • The discharge rate for antidepressant overdose increased two-fold over the study and did not decline after 1997 • The discharge rate for opioid overdose increased exponentially during the study	Reported that an increase in discharges secondary to self-poisoning with APAP has reversed following the change in over-the-counter pack size.

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Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Inglis JG. Scot Med J 2004;49: 142-3. Scotland[a]	1990-2002	Identify any effect on deaths and emergency admissions for poisoning resulting from restriction on APAP sales in 9/98	• Retrospective • Examined data on deaths from poisoning as reported in the General Registrar Scotland Office annual reports • Examined emergency admissions data from the Information and Statistics Division of NHS Scotland	• In early 1990s deaths from APAP poisonings were stable. After restrictions, deaths from APAP poisonings fell by 45% in 1998 but rose in each of the three years after to reach prerestriction levels. • Deaths from all poisonings remained stable throughout the study period. • Emergency admissions due to all poisonings rose in the early 1990s. Following restrictions, all admissions fell by 10% and APAP poisonings fell by 14% but both subsequently began to rise again.	Restricting APAP sales resulted in a significant health gain but benefits were short-lived

Summary of Published Clinical Studies of Acetaminophen Package Size Restrictions

Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Bateman DN et al J Toxicol: Clin Toxicol 2005;43(6):712. Scotland[a]	1995-2003	Not stated	• Examined hospital death and discharge data for all overdoses and those involving APAP • Examined death registration data for overdoses involving APAP	• The trend for rates of hospital poisoning death and discharges involving APAP was not significantly different during the study period (1995-30%, 1997-34%, 1999-30%, 2003-37%) • Number of deaths including APAP in the overdose cocktail was 83 in 1995, 110 in 1997, 79 in 1999, and 122 in 2000 • Number of in-hospital deaths showed no significant change over the time period	Restrictions on pack size of acetaminophen have not significantly reduced the proportion of overdose discharges involving acetaminophen or the mortality rates from this agent

Summary of Published Clinical Studies of Acetaminophen Package Size Restrictions

Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Laing WJ, et al. Clin Toxicol 2006;44 (5):648. Scotland[a]	2000-2005	Not stated	• Retrospective • Admission data in Scotland was analyzed and patients taking APAP preparations were identified	• From 2000-2005 there were 5500 APAP toxicology admissions • The percent of toxicology admissions due to APAP was 35.9% in 2000 and 40.6% in 2005 • Admissions involving a prescription only form of APAP with an opiate fell from 31.4% to 27.7% • Approximately two-thirds of cases involved APAP alone	Restriction of pack size has not reduced overdose behavior in Scotland

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Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Bateman DN, et al. Br J Clin Pharmacol 2006;62: 573-81. Scotland[a]	1995-2004	To describe how changes in legislation to restrict APAP sales have affected overdose discharges and death associated with the drug in Scotland	• Descriptive analysis • Analyzed number of deaths by poisoning due to APAP, based on death certificates provided by the General Register Office for Scotland from 1996-2003 • Examined number of hospital discharges where APAP overdose was recorded from 1995-2004 using the Scottish Morbidity Records scheme	• Most APAP-associated deaths occur outside of the hospital • The majority of APAP-associated deaths were due to co-proxamol • The proportion of in-hospital deaths attributed to APAP increased during the study • The overall number of cases discharged with poisoning decreased over time • The proportion of overdose cases involving APAP in any form increased significantly in all groups except for young men • Prescriptions for combination products that contain APAP remained stable or increased during this period	Legislation has not reduced mortality or proportional use of APAP in overdose, both of which appear to have increased in Scotland since pack-size restrictions.

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Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Bates CM, et al. Hepatol-ogy 2006;44(4 Suppl 1): 372A-373A. Scotland[a]	11/92-4/06	Examine the incidence of the outcome of fulminant hepatic failure due to APAP	• Observational study • Analyzed number of admissions with a severe liver injury based on data collected by the Scottish Liver Transplant Unit	• During the study period, 806 patients were admitted to the liver transplant unit • Of these, 579 (71.8%) had liver injury due to APAP and 302 (52.2%) developed fulminant hepatic failure • There were 278 admissions prior to restrictions (over 71 months) and 301 admissions subsequent to the restrictions (90 months to April 2006). • Overall mortality for all APAP overdoses was 24.1% prior to the restrictions and 31.2% after the restrictions.	There has been no significant reduction in the number of admissions or mortality from APAP poisoning following the changes in legislation. Staggered overdoses (intentional or therapeutic misadventure) are associated with poorer prognosis and have increased in number following packaging changes.

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Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Ott et al. J Int Med 1990;227: 423-8. Denmark[b]	1978-1987	Evaluate the effects of changes in APAP availability using data on salicylates (available OTC throughout study period), dextropropoxy-phene (available only by prescription), and other opioid drugs (available only by prescription) and total suicides for comparison	• Retrospective • Examined APAP, salicylate, dextropropoxyphene, and other opioid intoxications based on the National Board of Health Statistics (covers all hospital admissions and causes of death) • Examined Danish Drug Market Statistics on drug sales	• Availability of APAP over-the-counter led to doubling of sales • An increase in APAP sales [1 million defined daily doses (DDD) in 1978 to 47 million DDD in 1986]) was accompanied by a relative decrease in the number of hospital admissions (11.6 per million DDD sold in 1979 to 5.0 per million DDD sold in 1986) and deaths (0.45 per million DDD sold in 1979 to 0.07 per million DDD sold in 1986) from APAP overdose • Sales of salicylates had a minor decrease over the study period (113 to 94 million defined daily doses) but there was an increase in consumption-related hospitalizations and deaths due to salicylates • Sales of dextropropoxyphene were steady throughout study but consumption related morbidity and mortality increased • Sales of other opioids steadily increased during study. Number of admissions to hospital and mortality after overdose fluctuated during the study without relation to sales • The overall number of suicides and drug-related deaths was fairly stable throughout study	While sales of APAP increased after APAP was changed to over-the-counter, morbidity and mortality from APAP overdose was not significantly affected by changing the availability of APAP

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Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Donohoe E, et al. J Toxicol Clin Toxicol 2000;38: 251. Ireland[c]	1997-1998	Examine the impact of October 1997 restrictions on the number of tablets ingested in overdose	• Analyzed cases of acute APAP overdose in patients >10 years reported to the National Poison Information Center in Dublin in 1997 and 1998	• No significant difference in the total number of cases (1997-1044; 1998-976) • More than 50% of the cases involved 24 tablets or less • The number of cases involving more than 48 tablets fell slightly (127 vs 120) but was not statistically significant	Voluntary restrictions on the sale of APAP had no impact on the number of tablets being ingested in overdose

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Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Laffoy M, et al. Irish Med J 2001;94: 212-4. Ireland[c]	1993-1999	Determine whether hospital admissions due to APAP overdose dropped when the Irish Medical Board revised conditions for the supply and sale of APAP in 1997 and to determine compliance of non-pharmacy outlets with the conditions	• Data on hospital admissions were obtained from the Hospital Inpatient Enquiry System. • 100 non-pharmacy outlets in Dublin were surveyed to determine compliance with the Irish Medical Board's conditions	• APAP overdose was the main reason for hospital admission due to poisoning between 1993 and 1999 • APAP was responsible for one-quarter of all poisoning admissions • Hospital admissions due to APAP overdose increased by 29% between 1993 and 1999 • Hospital admissions due to APAP overdose dropped by 1.9% from 1997 to 1999 • All outlets visited allowed the purchase of 48 tablets of APAP • All tablets were sold in blister packs • APAP admission rate per 100,000 population was 31.1 in 1993, 32.4 in 1994, 36.2 in 1995, 35.6 in 1996, 39.9 in 1997, 39.7 in 1998 and 38.3 in 1999	Nonpharmacy outlets do not comply with the Irish Medical Board guidelines. APAP remains the most common form of overdose requiring hospital admissions in Ireland

Summary of Published Clinical Studies of Acetaminophen Package Size Restrictions

Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Prior MJ, et al. Am J Ther 2004;11: 443-452. Canada[d]	4/1995 – 3/2001	To explore the effect that lifting restrictions on APAP place of sale may have had on reported inpatient hospitalizations related to APAP overdose toxicity in Canada	• Retrospective • Examined effect of lifting restrictions on APAP sales (sales of >325 mg tablets and packages of >24 tablets of any strength to pharmacies only) • Examined hospital discharge abstract data from the Canadian Institute for Health Information related to APAP overdose for patients 12 years or older for the 1.5 year periods before and after September 15, 1999 • Examined APAP sales data from ACNielsen, a marketing research information company, for the period 1996-2001	• Total APAP sales remained stable throughout study • In areas where restrictions were lifted, no significant differences were observed in the incidence of inpatient hospitalization for APAP overdose (pre-restrictions-23.18 per 100,000; post-restrictions-22.33 per 100,000) or in the incidence of inpatient hospitalizations for APAP overdose and acute liver toxicity (pre-restrictions-0.49 per 100,000; post-restrictions-0.47 per 100,000) • In areas where there were no restrictions, no significant differences were observed in the incidence of inpatient hospitalization for APAP overdose (pre-restrictions-29.31 per 100,000; post-restrictions-30.55 per 100,000) or in the incidence of inpatient hospitalizations for APAP overdose and acute liver toxicity (pre-restrictions-0.70 per 100,000; post-restrictions-0.80 per 100,000) • In areas where restrictions were lifted, no significant differences were observed in the incidence of inpatient hospitalization for APAP overdose that included death (pre-restrictions-0.21 per 100,000; post-restrictions-0.19 per 100,000) or in the incidence of inpatient hospitalization for APAP overdose and acute liver toxicity that included death (pre-restrictions-0.13 per 100,000; post-restrictions-0.09 per 100,000)	Increasing APAP availability in six Canadian provinces and territories in September 1999 did not increase the incidence rate of reported cases of inpatient hospitalizations coded as acetaminophen overdose or with acute liver toxicity.

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Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Prior MJ, et al. Am J Ther 2004;11:443-452. (cont.) Canada[d]				• In areas where there were no restrictions, no significant differences were observed in the incidence of inpatient hospitalizations for APAP overdose that included death (pre-restrictions-0.36 per 100,000; post-restrictions-0.25 per 100,000) or in the incidence of inpatient hospitalizations for APAP overdose and acute liver toxicity that included death (pre-restrictions-0.22 per 100,000; post-restrictions-0.12 per 100,000)	

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Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Balit CR, et al. Med J Australia 2002;176: 162-6. Australia[e]	1997-2000	Determine whether the occurrence of APAP and non-APAP analgesic deliberate self-poisoning and accidental pediatric poisoning was affected by two periods of recall of APAP products	• Retrospective, observational • Examined data from a national poison information center [New South Wales (NSW) Poisons Information Center] and a regional toxicology service [Hunter Area Toxicology Service (HATS)] to determine the incidence of accidental and deliberate self-poisoning with APAP, ibuprofen, and aspirin over periods of different APAP availability	• The total number of calls to the NSW for deliberate self-poisoning was 14,775 from 1997-1999 and 4554 during the recall periods in 2000 • There was no significant change for APAP (1997-1999-8.6%; 2000-8.1%) or aspirin (1997-1999-1.1%; 2000-1.2%) deliberate self-poisonings calls to the NSW but there was a significant increase in calls about ibuprofen (1997-1999-0.9%; 2000-1.7%; p=0.001). • During the recall periods, there was a significant (p=0.001) increase in calls to the NSW for accidental pediatric poisonings with ibuprofen but no significant change in calls for APAP or aspirin • The total number of presentations to HATS for deliberate self-poisoning was 765 from 1997-1999 and 230 during the recall periods in 2000 • There was no significant change in the percentage of patients presenting to HATs for deliberate self-poisonings due to APAP (1997-1998-14.0%, 2000-15.7%) or ibuprofen (1997-1998-0.8%, 2000-0.9%) but there was a significant increase in presentations for aspirin (1997-1998-0.7%, 2000-2.2%; p=0.043)	Reduced APAP availability increased poisoning with alternative analgesics, but had little effect on the incidence of APAP poisoning. Restriction of APAP-containing products may inadvertently increase poisoning with potentially more toxic agents

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Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Kisely SR, et al. Med J Australia 2003;178: 72-74. Australia[e]	1996-2001	Assess the effect of two recalls of APAP products on rates of intentional and unintentional overdoses of APAP in all age groups, as well as any effect on poisoning by other agents	• Before and after • Analyzed data from the Western Australian Health Services Research Linked Database, which has records for all admissions to public and private hospitals throughout the state, to identify hospital admissions due to overdoses with APAP, ibuprofen, aspirin, and all other poisoning agents	• The rate of hospital admissions (per 100,000 person-years at risk) following overdose was 20.56 for APAP, 0.96 for aspirin, and 2.76 for ibuprofen when APAP was available in 1996-1999 and 2001 compared to 16.90 for APAP, 0.93 for aspirin, and 2.40 for ibuprofen when APAP availability was restricted in 2000; a significant (p=0.041) decrease in APAP admissions was observed when APAP sales were restricted with no increase in admissions for poisoning with other agents • Similar results were obtained when accidental poisonings and deliberate self-harm were considered separately.	Limiting access to APAP may reduce APAP poisonings without a coincident increase in the use of other agents

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Citation Country	Study Time Period	Study Objective	Study Design	Outcomes	Conclusion
Gunnell D, et al. J Epidemiol Commun-ity Health 1997;51: 175-9. France and UK[f]	1974-1994	To investigate whether trends in the availability of APAP affect the frequency of both non-fatal overdoses and suicides in which APAP is used, and to determine if differences in the availability of APAP in England and Wales and France affect morbidity and mortality from APAP overdose	• Retrospective • Examined annual APAP mortality statistics for England and Wales • Examined data from the Oxford monitoring system for attempted suicide with APAP • Examined data on sales of APAP in France and the UK from Intercontinental Medical Statistics • Data on mortality and morbidity of APAP poisoning in France was obtained from Poison centers	• Reported a correlation between APAP sales and trends in APAP non-fatal overdoses in Oxford (1976-1993, r=0.86; 95% CI 0.54, 0.96), and France (1974-1990, r=0.99; 95% CI 0.97, 1.00) • Reported a correlation between APAP sales and trends in APAP related suicides in England and Wales (1983-1991, r=0.72; 95% CI 0.11, 0.94), and France (1974-1990, r=0.79; 95% CI 0.50, 0.92) • Reported a gradual increase in APAP deaths and APAP overdoses over study period	Trends towards greater availability of APAP are paralleled by increases in its use for both non-fatal overdose and suicide.

a: In September 1998, APAP became available exclusively in blister pack form in the UK. Supermarket packs may contain a maximum of 16 APAP 500 mg tablets (8 g total) and pharmacy packs may contain a maximum of 32 APAP 500 mg tablets (16 g total). Up to 100 APAP tablets can be sold at the discretion of a pharmacist but a prescription is required for more than 100 tablets. Specific warnings on APAP are printed on packets and on leaflets supplied with packets.

b: In Denmark all drugs are sold only in pharmacies whether prescribed or over-the-counter. APAP changed from a prescription to an over-the-counter drug on January 1, 1984.

c: The October 1997 Irish Medicine Board guidelines for the sale and supply of APAP stated that non-pharmacy outlets should only sell emergency supplies of APAP in a maximum pack size of 12 tablets and just one pack should be sold on each occasion. These guidelines have no statutory basis. In October 2001 new regulations were to come into force that would give statutory effect to the early guidelines.

d: Six provinces and territories in Canada had restrictions on APAP sales (the sale of all APAP strengths >325 mg and packages with >24 tablets of any strength could only be sold in pharmacies) that were lifted in September 1999. Three provinces had no restrictions.

e: Products containing APAP were recalled on two occasions in 2000 following extortion threats to two pharmaceutical companies; Herron from March 16, 2000 until May 21, 2000 and Smith-KlineBeecham from June 6, 2000 until August 23, 2000.

f: At the time of this study, in the UK APAP was available in unlimited quantities from pharmacies and up to 12 g could be purchased in supermarkets; in France APAP could only be purchased in pharmacies and the contents of each pack of APAP was limited to 8 g.

Abbreviations: APAP = acetaminophen, CI = confidence interval; cont = continued, OTC = over-the-counter; UK = United Kingdom

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8 USE OF ACETAMINOPHEN IN POPULATION SUBGROUPS

In Section XIV, Part A of FDA's proposed rule [71 PR 77346], FDA has asked for additional comments and data on whether there are specific populations of people for whom the maximum daily dose for acetaminophen is not safe and effective and should be lowered. The safety of the maximum allowable daily dose of acetaminophen, 4 g/day in two populations, alcohol users and individuals with preexisting liver disease, is addressed previously in Item 1, Sections 6 and 7 of McNeil's response. In this section, McNeil provides comments and additional data on three other populations of people for whom the safety of the maximum daily dose for acetaminophen have supposed hypothetical risk: individuals with human immunosuppressive virus (HIV), individuals who are fasting or malnourished, and individuals with Gilbert's syndrome.

8.1 HIV-Positive Individuals

8.1.1 FDA Comments From the Proposed Rule

In the proposed rule, Section VII.B, FDA notes the receipt of a petition to consider the need for a warning about the increased risk of liver injury associated with the use of acetaminophen by HIV-positive individuals [1]. This petition alleges that glutathione deficiency may be associated with decreased survival in patients with HIV, and that use of acetaminophen may be more dangerous for HIV-infected individuals than previously thought. In the proposed rule, FDA writes "…there is no clinical evidence of toxicity or decrease survival that can be attributed to the recommended use of acetaminophen in HIV-infected individuals since GSH levels were never validated to predict survival" [71 FR 77338] and FDA "does not consider the current data a sufficient basis for a warning" [71 FR 77338].

8.1.2 McNeil's Position on HIV-Positive Individuals

Data do not support that individuals with HIV develop hepatotoxicity following ingestion of therapeutic doses of acetaminophen. A label warning for individuals with HIV who take acetaminophen at the maximum-labeled daily dose is not necessary. Any purported increased susceptibility to acetaminophen-induced hepatotoxicity in individuals with HIV, that may or may not affect acetaminophen metabolism, is purely hypothetical and unsubstantiated by data.

8.1.3 Key Points from Scientific and Clinical Data

- None of the subjects in the study by Herzenberg *et al* [2], which was the basis for a Citizen's Petition cited within FDA's proposed rule, were reported to be taking acetaminophen when plasma glutathione measurements were obtained. This study provides no data on the use of acetaminophen in individuals with HIV.
- Metabolism studies have not demonstrated that acetaminophen biotransformation in HIV positive individuals or AIDS patients is different from the general population.
- There are no data that the survival of HIV-infected individuals is negatively affected by the use of acetaminophen at the maximum allowable daily dose.
- The available data do not provide evidence of a drug interaction between zidovudine and acetaminophen.

8.1.4 The Hypothetical Risk of Glutathione Deficiency in Patients With HIV

In the Citizen Petition by Herzenberg and James, dated 2/14/97 [1], FDA was requested to consider the need for a warning for patients with HIV who use acetaminophen because of a hypothetical risk between pronounced glutathione deficiency and a decrease in survival. The petition was based on a study by Herzenberg *et al*. [2] that suggest glutathione concentrations are lower in subjects with CD4 T cell counts below 200/μL, and that glutathione deficiency in such subjects is associated with substantially decreased survival over a two-to-three year period. The petition states that based on observations where plasma glutathione deficiency is associated with a shorter survival time, some commonly available drugs, notably acetaminophen, that tend to decrease glutathione are potentially more toxic to glutathione-deficient individuals. Furthermore, the petition also states such drugs may be more dangerous for HIV-infected individuals than previously thought, and suggests the use of such drugs in the upper level of the safety range for uninfected individuals could be harmful to people with HIV infection, especially with AIDS.

McNeil disagrees with assertions in the Citizen Petition by Herzenberg and James, and has responded to the Docket on September 10, 1997 [3]. The scientific evidence does not support the claims that HIV infection is a risk factor for hepatotoxicity with therapeutic doses of acetaminophen or that survival in HIV infected patients is negatively affected by the use of acetaminophen at the current maximum allowable daily dose.

8.1.5 Glutathione Deficiency in Patients With HIV

The study by Herzenberg et al. [2] reports that low plasma glutathione concentrations predict poor survival in HIV-infected individuals. Specifically, the report shows that low levels of glutathione in HIV-infected individuals with CD4 T cell counts below 200/μL of blood were associated with decreased survival. The results also show that the probability of surviving two to three years increased dramatically in individuals with plasma glutathione concentrations in the normal range, implying that glutathione deficiency plays a pivotal role in determining disease progression in the final stages of HIV disease.

Because glutathione concentrations affect many immune functions, including the activation of lymphocytes, glutathione deficiency has been postulated to lead to the progression of immune dysfunction, which is the hallmark of AIDS [4]. Lower glutathione concentrations in plasma and in CD4-positive lymphocytes of patients with HIV and AIDS have been reported in previous studies [5,6,7,8,9,10]. There are conflicting reports on glutathione concentrations in erythrocytes and peripheral blood mononuclear cells of HIV patients [11,12,13,14]. Normal concentrations of glutathione have been measured in the alveolar fluid during the early phase of HIV [15], but concentrations have been shown to decreases over time [16].

The discrepancy between studies may be related to differential regulation of glutathione concentrations among different cell types [14]. Although it has been claimed that altered glutathione homeostasis is a result of decreased availability of the precursor amino acids for glutathione, such as glutamate, cysteine and glycine [17,18,19], these claims have not substantiated by other studies [8,14]. Notably, the instability of reduced glutathione and differences in assay techniques may explain some of the conflicting data noted between different reports [13,14]. The exact mechanism of glutathione deficiency in patients with HIV is yet to be fully understood.

8.1.6 Data Pertaining to Acetaminophen Metabolism

8.1.6.1 Role of Hepatic Glutathione

Alterations in glutathione concentrations or its activity have been hypothesized to place certain populations at risk of acetaminophen-induced hepatotoxicity at doses that do not cause hepatotoxicity in the general population. However, it is noteworthy that none of the HIV patients included in the study by Herzenberg *et al* [2], which was the basis of the petition, were reported to have taken acetaminophen when blood was sampled to estimate

plasma glutathione concentrations. Therefore, this study does not contain any data relevant to the assertions made in the petition concerning the effect of acetaminophen in patients with HIV.

Although a hypothetical risk has been expressed for HIV patients who take therapeutic doses of acetaminophen based on limited glutathione conjugation of activated acetaminophen, there is no evidence to support this concern. A critical review about the effect of analgesics on glutathione by Lauterburg indicated that the amount of toxic metabolite formed from a therapeutic dose of acetaminophen is too small to deplete glutathione and that true depletion of hepatic glutathione (< 10%) is seen only following excessive overdoses of acetaminophen [20]. In the same review, the author concludes that, "except for anecdotal reports, there is no convincing evidence that other populations in which low glutathione has been observed—such as patients with HIV infection or chronic hepatitis C, malnourished patients, and patients with cirrhosis—are at higher risk of experiencing adverse events from acetaminophen" [20].

In the 10 years since the petition was submitted to FDA, there have been few published reports of hepatotoxicity associated with acetaminophen in patients with HIV. Two case reports were identified; neither of which contains enough information to credibly implicate a true therapeutic dose of acetaminophen in the development of the hepatotoxicity [21, 22]. Limitations of cased reports and retrospectively acquired data have been discussed previously in Section 4 of Item 1 of this document.

A study in healthy volunteers (n=32), untreated symptom-free HIV-seropositive subjects (n=9), and subjects with AIDS (n=19), measured urinary acetaminophen and its glucuronide, sulfate, cysteine, and mercapturate conjugates after a single oral dose of 1.5 g acetaminophen [23]. Based on fractional excretion, there was a statistically significant decrease in the percent of glucuronide and a statistically significant increase in the percents of sulfate, cysteine and mercapturate conjugates, and unchanged acetaminophen in subjects with AIDS compared with healthy volunteers and symptom-free HIV positive subjects. There was no statistical difference between healthy volunteers and symptom-free HIV positive individuals or between AIDS patients receiving zidovudine compared with those not receiving zidovudine. The study is limited by the fact that the investigators did not control for variables that can affect certain metabolic pathways, such as smoking that can increase glucuronidation. Although the investigators refer to the relative changes in metabolism as abnormal for subjects with AIDS, the mean values reported for each of the metabolites fall within ranges reported for the general population [24].

In a larger more definitive study [25], the effect of disease state and disease progression on the glucuronidation and sulfation of acetaminophen was evaluated among HIV-positive patients (n=67) and patients with AIDS (n=41). A cohort of 36 healthy control subjects was included for comparison. The extent of conjugation was assessed using a spot urine sample collected four hours after the administration of 500 mg, assaying for acetaminophen and its glucuronide and sulfate metabolites, and constructing ratios of each metabolite to acetaminophen. There were no differences in the glucuronidation or sulfation in between healthy controls, HIV positive subjects, or subjects with AIDS. The subject population was studied over time, and disease progression did not significantly alter the calculated glucuronidation and sulfation indices. These findings have important implications when generating hypotheses with regard to acetaminophen safety based on metabolic theories. Such hypotheses should consider the amount of unchanged acetaminophen, and amounts of glucuronidation, sulfation, and oxidative-metabolites produced, not changes in one metabolic pathway.

8.1.7 Purported Interactions Between Acetaminophen and Zidovudine

Potential for drug-drug interactions are a concern among HIV positive patients. The possibility of a drug-drug interaction between acetaminophen and zidovudine (3′-azido-3′-deoxythymidine or AZT), the most widely used drug in patients with HIV has been raised. AZT is metabolized via hepatic glucuronidation,

Conflicting results with respect to an interaction between AZT and acetaminophen have been reported in animal studies [26, 27]. In an *in vitro* cell culture system, pre-exposure of freshly isolated rat hepatocytes to 50 μM acetaminophen for 30 minutes before treatment with zidovudine did not alter glucuronidation of zidovudine [26]. In contrast, enzyme kinetic studies to analyze the potential competition between acetaminophen and zidovudine as substrates for uridine diphosphoglucuronosyl transferase using rat liver microsome preparations demonstrated that acetaminophen glucuronidation was competitively inhibited by zidovudine, while zidovudine glucuronidation was only partially inhibited by acetaminophen when tested in a noncompetitive interaction [27].

A double-blind, placebo-controlled study in patients with AIDS or AIDS-related complex (N=282) reported that, of several concomitant medications that were given to AZT recipients (n=145), only acetaminophen-containing compounds (n=63) were associated with an increased frequency of bone marrow suppression. However, patients were not

randomized to acetaminophen-containing compounds and no data regarding acetaminophen use among placebo recipients were reported for comparison. Therefore, a causal relationship cannot be established [28]. The association of neutropenia in this study has been related to the competition for enzymes that metabolize zidovudine and acetaminophen, leading to increased plasma levels of non-metabolized zidovudine [28].

A pharmacokinetic analysis demonstrated that serum concentrations of AZT and its glucuronidated metabolite were similar with and without acetaminophen [29]. The investigators suggest that there was no significant metabolic interaction between acetaminophen and zidovudine and that the short-term use of moderate doses of acetaminophen (< 3.5 g/day) does not increase serum zidovudine concentrations [29]. In a drug-interaction study of patients receiving zidovudine, three different regimens of concomitant acetaminophen were evaluated: 325 mg acetaminophen and 200 mg zidovudine every four hours for 72 hours, 650 mg acetaminophen and 200 mg zidovudine every four hours for 72 hours, and 650 mg acetaminophen and 200 mg zidovudine every four hours for seven days. The clearance of zidovudine was increased, but the production of the glucuronide conjugate of zidovudine was not significantly affected. The study suggested that a pharmacokinetic interaction between zidovudine and acetaminophen was unlikely to increase the risk of toxicity associated with zidovudine due to the accelerated clearance [30].

Several other pharmacokinetic studies have suggested that there are no interactions between acetaminophen and zidovudine [31, 32, 33]. In an *in vitro* study in human liver microsomes, acetaminophen was non-inhibitory at concentrations up to 10 mM, which is four times the concentration of AZT that was used in the incubation reaction [31]. Two additional studies using human liver microsomes also demonstrated no effect of acetaminophen on zidovudine glucuronidation [32, 33]. In contrast, another study in HIV-positive patients and patients with AIDS, zidovudine increased concentrations of the nontoxic glucuronide metabolite of acetaminophen in a spot urine sample collected at four hours after the administration of 500 mg of acetaminophen [25].

In a patient with HIV infection, combined use of zidovudine 100 mg every six hours and acetaminophen 500 mg every four hours was safe and effective for at least eight months [34]. Moreover, zidovudine did not influence the pharmacokinetic profile of acetaminophen [34].

Overall, the absence of pharmacokinetic data supporting an interaction between zidovudine and acetaminophen indicates that such an interaction lacks biologic plausibility. The available data do not provide evidence of an interaction between zidovudine and acetaminophen.

8.2 Populations Who Are Malnourished or Fasted

8.2.1 FDA Comments from the Proposed Rule

FDA is seeking both comment and data on whether acetaminophen poses additional risk for certain population subgroups (eg, conditions in which glutathione is reduced) [71 FR 77346]. Malnutrition and fasting have been speculated to be risk factors for acetaminophen hepatotoxicity at therapeutic doses in some individuals.

8.2.2 McNeil's Position

Data do not support that individuals with malnutrition or fasting states develop hepatotoxicity following ingestion of therapeutic doses of acetaminophen. A label warning for individuals with malnutrition or fasting states who take acetaminophen at the maximum-labeled daily dose is not necessary. Any purported increased susceptibility to acetaminophen-induced hepatotoxicity in individuals with malnutrition or fasting states, that may or may not affect acetaminophen metabolism, is purely hypothetical and unsubstantiated by data.

8.2.3 Key Points of Scientific and Medical Data

- Any purported increase in susceptibility to acetaminophen-induced hepatotoxicity in the fasting or malnourished population due to glutathione depletion is purely hypothetical and unsubstantiated by data.
- Very few retrospective case reports and case series allege an association between acetaminophen-induced hepatotoxicity and fasting. The terms "malnutrition" and "fasting" are inconsistent across, and poorly defined within, these case reports. Fasting is a particularly elusive term, as people fast regularly overnight, for substantial portions of the day, and with common diseases, such as the flu. Medically prescribed fasting is not uncommon in hospitalized patients. With both the flu and medically prescribed fasting, use of acetaminophen is extremely common.

- It is inappropriate for the FDA to use historical methodologically flawed retrospective data from acetaminophen overdose cases to support proposed labeling recommendations that are designed to communicate information to consumers about the effects of taking therapeutic doses of acetaminophen (≤ 4 g/day).

- Most importantly, a prospective clinical study that evaluated the effect of fasting in humans on acetaminophen metabolism found no evidence for a shift from glucuronidation to oxidation of acetaminophen following calorie restriction.

8.2.4 Background

Malnutrition is defined as "faulty nutrition due to inadequate or unbalanced intake of nutrients or their impaired assimilation or utilization" [35]. Additionally, people are at risk for malnutrition if they meet one or more of the following criteria: unintentional loss of approximately 10% of usual body weight in the preceding three months, body mass index (BMI) less than 18.5 kg/m^2, and/or body weight less than 90% of ideal for height [36]. To fast is defined as "to abstain from food" or "to eat sparingly or abstain from some foods"[37].

Fasting and malnutrition have been purported to increase susceptibility of humans to acetaminophen hepatotoxicity via altered metabolism, extrapolated from experimental data in rodent studies. One supposition proposes that fasting depletes precursors for uridine diphosphoglucuronic acid (UDP-GA), a necessary co-factor for glucuronidation, and shifts metabolism of acetaminophen to the cytochrome P4502E1 (CYP2E1) pathway, increasing the production of the toxic intermediate, NAPQI. Another suggests that malnutrition or fasting may lead to low glutathione concentrations and induced CYP2E1 activity, which would also increase the production of NAPQI.

The ability to evaluate a reported association between fasting and malnutrition and acetaminophen-induced hepatotoxicity accurately depends on the quality of available data. Clinical evidence can be divided into two categories—analytical studies (eg, randomized controlled trials, cohort studies, case-control studies) and descriptive studies (eg, correlation studies, cross-sectional surveys, case series, and case reports) [38]. The highest levels of evidence-based clinical data, especially those from prospective human studies, are needed to establish causal associations. Data from descriptive studies cannot be used to establish causality and should be evaluated with caution [38,39]. To date, there

has only been one attempt to prospectively evaluate the possible role of food restriction on acetaminophen metabolism in humans [40].

8.2.5 UDP-GA or Precursor Depletion Hypothesis

Authors of published case series have suggested that hepatotoxicity following acetaminophen overdose is enhanced by fasting and alcohol use [41]. This retrospective review of patient discharge summaries identified 21 patients with varying degrees of hepatotoxicity following the use of acetaminophen at greater than the maximum daily dose for a therapeutic purpose (not intentional overdose). Ten cases had a history of chronic alcohol use and fasting, and 14 patients had been using greater than 4 g/d for three or more days. In this study, fasting was deemed by the investigators if there was "clear, documented evidence of fasting or inability to eat prior to acetaminophen ingestion". The investigators considered a person as fasted if he or she had a medical history of prolonged vomiting, dehydration, or an inability to eat for other reasons.

In this study [41], Whitcomb and colleagues hypothesize from animal data that fasting may enhance hepatotoxicity by shunting acetaminophen metabolism from glucuronidation to microsomal oxidation. They cite studies in rats given hepatotoxic doses of acetaminophen, in which fasting may have depleted precursors for UDP-GA and shifted metabolism of acetaminophen to the CYP2E1 pathway, increasing the production of NAPQI. The results of the retrospective case study do not provide any basis that individuals taking recommended doses of acetaminophen while fasting are at an increased risk for hepatotoxicity. Limitations to this study include possible inaccuracy of reported acetaminophen doses ingested, as the cases relied on patient recall and/or medical records. In addition, there was no consideration of confounding variables that could have contributed to hepatotoxicity. Also, acetaminophen levels were not available for all patients within 48 hours of ingestion.

Although complete caloric restriction for 24 hours can deplete UDP-GA precursors in laboratory animals, no clinical data indicate conclusively that this occurs in fasting or malnourished humans or that a decrease in glucuronidation would lead to an increase in the microsomal oxidation pathway of acetaminophen metabolism [42]. In a more recent study involving animals, the effect of coprophagy on the expression of hepatic CYP2E1 was assessed on starvation [43]. In this study, the effect of fecal matter (1.6 g/kg/day for three days) on CYP2E1 expression was assessed in fed or starving rats. The results of this study clearly demonstrate that starvation failed to affect hepatic expression of CYP2E1

while coprophagy (consumption of their own fecal matter) contributed to the induction of CYP2E1 in starved rats.

As stated earlier, to date, only one prospective clinical study, that evaluated the effect of calorie restriction on acetaminophen metabolism in humans. This study was conducted to test the precursor depletion theory [40]. Nine obese patients were given a two-gram dose of acetaminophen (twice the recommended single dose) before and immediately following food restriction. Food restriction was defined as either 500 calories/day for 5 days or 1000 calories/day for 13 days. The study found that there was no change in urinary metabolites of acetaminophen, and liver function tests were unaltered. The investigators conclude that there was no evidence for a shift from glucuronidation to oxidation of acetaminophen following calorie restriction. Glutathione levels were not measured in this study.

8.2.6 Glutathione Depletion Hypothesis

Limited human data are available regarding the effect of fasting and malnutrition on glutathione levels, and no studies have been conducted with acetaminophen in fasting or malnourished patients with documented glutathione depletion.

The assumption that malnutrition depletes glutathione stores and places an individual at elevated risk of acetaminophen toxicity ignores evidence that CYP2E1 levels are also decreased in malnutrition, and that CYP2E1 is inhibited by fatty acids mobilized by catabolism of fat, leading to a decreased capacity for synthesizing NAPQI. Cytochrome P450 levels are substantially reduced in malnourished monkeys [44]. Other human data from patients with disease states hypothesized to affect glutathione stores have also suggested that CYP2E1 levels are reduced as well [45, 46]. Therefore, any theoretical increased risk of acetaminophen-induced hepatotoxicity in the malnourished patient due to glutathione depletion is tempered by decreases in CYP2E1 metabolism. The clinical consequences of depleted glutathione in this population have not been determined.

Additionally, a study conducted in children with edematous protein-energy malnutrition (PEM) found that compared to controls, children with marasmus, severe marasmus, and kwashiorkor had a 15%, 40%, and 63% decrease, respectively, in erythrocyte glutathione concentrations [47]. In another study, eleven female patients with anorexia nervosa [mean BMI: 14.0 kg/m^2 (range: 16.3-11.6 kg/m^2)] were reported to have a 30% decrease in plasma glutathione concentrations, compared to healthy female controls [48]. In another recent study conducted in young healthy male volunteers, plasma and muscle glutathione

concentrations were unaffected by a three-day fast (noncaloric liquid intake) and two-day refeeding period [49]. In these studies, objective data pertaining to lower basal glutathione concentrations in subjects with decreased food intake are sparse and limited to severe malnutrition. More importantly, there are no data to substantiate that decreased glutathione results in clinical consequences.

In these studies, glutathione was measured in hepatocytes, erythrocytes and plasma. Plasma glutathione and hepatic glutathione concentrations have been correlated in rats [50] and humans [51,52], so plasma glutathione measurements are often obtained as an indirect and noninvasive approximation of hepatic glutathione concentrations. Erythrocyte glutathione concentrations do not correlate with hepatic glutathione concentrations. Importantly, the amount of toxic metabolite, NAPQI, formed from a therapeutic dose of acetaminophen is too small to deplete glutathione, as true depletion of hepatic glutathione (< 10%) is seen only following excessive overdoses of acetaminophen [20].

8.2.7 Prospective Study of CYP2E1 in Fasting Humans

Although some human studies show lower plasma glutathione concentrations with fasting and/or malnutrition, a metabolic study found that there was a decrease in CYP2E1 activity with fasting in humans [53]. In this study, chlorzoxazone was used as an *in vivo* probe to evaluate the effects of CYP2E1 in fasted subjects. The plasma concentration – time profiles were obtained for chlorzoxazone and its 6-hydroxy metabolite following oral administration of a 250-mg dose. The disposition profiles were obtained first after an overnight fast, and then after a 38 hour fast on a separate occasion. The oral clearance of chlorzoxazone was reduced ($p < 0.038$) by between 11% and 65% in six out of the seven subjects. This change was also associated with an increase ($p < 0.004$) in the elimination t½ of chlorzoxazone after fasting. The observed reduction in clearance and decrease in the elimination rate of chlorzoxazone was unexpected based on studies showing that fasting, in rats, results in enhanced CYP2E1 activity [54].

In another animal model (house musk shrew), fasting also reduced hepatic CYP2E1 levels [55], indicating species differences. An explanation may be based on recent findings that increased levels of CYP2E1 mediate the formation of reactive oxygen species [56,57,58]. These studies suggest that the depletion of tissue glutathione and cellular radical scavengers produced by fasting results in lipid peroxidation of the endoplasmic reticulum membrane and destruction of CYP enzymes, including CYP2E1 [59]. Based on these data, it may be possible that during a 24 to 30 hour fasting period, an induction in CYP2E1

activity was followed by a lipid-peroxidation induced reduction in the amount of the enzyme [53]. Therefore, in any condition, both glutathione levels and changes in CYP2E1 activity must be evaluated.

8.2.8 Case Reports in Calorie Restricted Individuals

Case studies have reported an association between fasting and/or malnutrition and acetaminophen-induced hepatotoxicity. FDA provided data from 307 AERS cases that were received by the agency from January 1998 through July 2001 that involved at least one APAP-containing product and resulted in hepatotoxicity without apparent suicide intent. A review of these cases identified 20 reports of hepatotoxicity in patients whose medical history alleged a period of fasting or malnutrition before acetaminophen ingestion. Three of these cases reported the use of therapeutic doses of acetaminophen ($\leq$ 4 g/day), and are reviewed in Table 4.3.4.1. Of the remaining 17 cases, the dose of acetaminophen was unknown in 13 cases and exceeded therapeutic recommendations in 4 cases (mean: 7 g/day; range: 5.1-10 g/day).

A search of the medical literature using the terms "(acetaminophen or paracetamol) and (diet restriction or nutritional disorder) and (fasting or malnutrition)", in OVID EMBASE (1988 to 2006 Week 17) plus MEDLINE (1966 to April 3 2006; de-duplicated) was conducted to identify case reports that alleged hepatotoxicity in fasting or malnourished individuals using acetaminophen. Sixty cases that met these criteria were identified. Five reported the use of therapeutic doses of acetaminophen ($\leq$4 g/day). Eleven reports could not classify a dosing regimen, and the remaining 44 cases reported use of acetaminophen above recommended doses (children < 12 years, n = 15, mean: 98.5 mg/kg/day, range: 2 to 200 mg/kg/day; adults $\geq$ 12 years, n = 29, mean: 10.7 g/day, range: 5 to 25 g/day).

Methodological weaknesses that are inherent to retrospective data collection include incomplete information, failure to rule out other potential causes and biases such as recall and referral. Most of the retrospective data rely on the assumption that a patient taking acetaminophen for a therapeutic purpose is following established dosing guidelines and using recommended doses, when in fact supratherapeutic doses may have been used. Additional limitations to these case reports include the absence of definitive criteria to what constitutes fasting or malnutrition, and no clear clinical evidence to objectively determine a patient's state of fasting or malnutrition. The retrospective case reports that appear in the literature cannot possibly be relied upon to conclude causality or even common association. They serve only to raise the question: "One condition has been observed in the presence of another, are they related?" They provide no information at all as to the answer.

Overall, the data summarized in Section 8.2 do not support that individuals with malnutrition or fasting states develop hepatotoxicity following ingestion of therapeutic doses of acetaminophen. Any purported increased susceptibility to acetaminophen-induced hepatotoxicity in individuals with malnutrition or fasting states, that may or may not affect acetaminophen metabolism, is simply hypothetical and utterly unsubstantiated by data. The only prospective clinical study that evaluated the precursor depletion theory in humans found no evidence for a shift from glucuronidation to oxidation of acetaminophen following calorie restriction.

8.3 Individuals With Gilbert's Syndrome

8.3.1 FDA Comments From the Proposed Rule

FDA has asked for additional comments and data on whether there are specific populations of people for whom the maximum daily dose for acetaminophen is not safe and effective and should be lowered (Section XIV, Part A of FDA's proposed rule [71 FR 77346]. A supposition exists in the published literature about a potential risk of acetaminophen hepatotoxicity in individuals with Gilbert's syndrome, because they generally have lower glucuronidation. Supposedly, diminished glucuronidation would lead to more acetaminophen oxidation by CYP2E1, resulting in more of the toxic intermediate, NAPQI, being produced and conjugated with glutathione.

8.3.2 McNeil's Position

The supposition regarding risk of acetaminophen hepatotoxicity at therapeutic doses in Gilbert's syndrome based on differences in glucuronidation is not scientifically valid, particularly in light of more sophisticated evidence of glucuronosyltransferase systems. Data do not support that individuals with Gilbert's syndrome develop hepatotoxicity following ingestion of the therapeutic doses of acetaminophen.

8.3.3 Key Points Supported by Scientific and Medical Data

- Individuals with Gilbert's syndrome have a defect in UDP-glucuronosyltransferase isozymes, UGT1A1.
- Glucuronidation of acetaminophen is mainly by UDP-glucuronosyltransferase isozymes UGT1A6 and UGT1A9, not UGT1A1, the affected isozymes in Gilbert syndrome.
- Acetaminophen metabolism studies in adults with Gilbert's syndrome show no reduction in glucuronidation capacity for acetaminophen metabolism.
    - The only study in patients with Gilbert's syndrome that has shown an increase in the proportion of glutathione-derived metabolites did not show the increase to be clinically meaningful.
    - No published data are available to suggest that plasma or hepatic glutathione is lower in patients with Gilbert's syndrome.

- In an analysis of 118 patients with liver failure due to an acute acetaminophen overdose (median dose of 28.5 g, range from 9 to 100 g), the UGT1A1 (TA 7/7) homozygosity associated with Gilbert's syndrome did not influence the severity or outcome of acute liver or multi-organ failure.

8.3.4 Background

Gilbert syndrome is a mild, asymptomatic, unconjugated hyperbilirubinemia in the absence of hemolysis or liver disease [60]. Commonly encountered in clinical practice, approximately 5% to 10% of the Caucasian population manifests serum bilirubin levels consistent with the syndrome, and no specific treatment is indicated [61].

The mechanism of Gilbert syndrome is a decreased activity of bilirubin UDP-glucuronosyltransferase (UDP-GT), an enzyme encoded by the somatic UGT1A1 gene [62]. While the genotype underlying Gilbert's may differ between populations, one variant present in 35 to 40% of Caucasians, UGT1A1*28, is a promoter region anomaly that reduces transcription of the otherwise intact gene to 20% of normal [61]. Although 16% of the Caucasian population are thought to be homozygous for the UGT1A1*28 variant, given that only 5 to 10% of the population actually manifest the syndrome, with a male-to-female ratio >1, factors other than genotype are likely involved [63].

Court and colleagues [64] confirmed the results of a previous study [65] indicating that UGT1A6 and UGT1A9 are the primary isoforms involved in the glucuronidation of acetaminophen. In addition, these investigators also found that UGT1A1 may have limited involvement in acetaminophen glucuronidation, but its activity varied considerably among human livers, enough to overshadow any changes that might be seen in Gilbert's syndrome.

A linkage between genetic polymorphisms of UGT1A1 and UGT1A6 has been demonstrated. The frequencies of UGT1A1*28 and UGT1A6*2 genotypes were determined in 245 healthy subjects from multiple ethnic/racial backgrounds, and the observed frequency of subjects homozygous for both variants were ten-fold more frequent than expected (7.8% observed versus 0.7% expected) [66]. However, at pH 7.2, cells expressing the UGT1A6*2 genotype have a capacity to conjugate acetaminophen at a rate more than three-fold that of cells expressing wild-type UGT1A6 [67], indicating a theoretical advantage in acetaminophen metabolism for a subset of patients with this genotype linkage.

8.3.5 Acetaminophen Metabolism Studies

Several studies in humans have examined the relationship between Gilbert syndrome and acetaminophen metabolism, with variable conclusions provided by the investigators. Two mechanisms are of interest: whether a difference in glucuronidation of acetaminophen is detected in groups of subjects with Gilbert syndrome versus controls, and whether such a difference is detected in the glutathione-derived metabolites of acetaminophen. The latter category reflects the detoxification pathway of the highly reactive, minor metabolite of acetaminophen, N-acetyl-p-benzoquinoneimine (NAPQI).

Acetaminophen metabolism was studied in six male subjects with "mild non-hemolytic hyperbilirubinemia" (1.5 to 3 mg/dL) and nine male controls, administered 30 mg/kg of acetaminophen as a single oral dose, or a 10 mg/kg as a single intravenous dose [60]. The intravenous experiment was repeated following 20 oral doses of acetaminophen 1.5 g, administered every six hours for five days. With a single oral dose, plasma acetaminophen glucuronide curves were similar between subjects and controls. In the intravenous experiments, no significant difference was observed in the urinary percentage recovery or glucuronide fraction between subjects and controls. The urine glucuronide fraction recovered was found to be lowest in two hyperbilirubinemic patients during the first intravenous dosing; following the five-day oral dosing period, repeat intravenous dosing demonstrated an increase in the glucuronide fraction recovered in urine from 22.8 and 26.7% to 41.9 and 43.4%, respectively. No significant changes in serum bilirubin were observed. Glutathione-derived metabolites formed from NAPQI were not assessed in this study.

In another study, 1 g of acetaminophen was administered orally to 11 subjects with Gilbert syndrome and 10 controls [68]. Following ingestion, an 8-hour urine sample was collected and analyzed for fractional excretion of acetaminophen and metabolites. No significant differences were detected between subjects with Gilbert syndrome and controls, with glucuronide conjugates at 37.5 ± 4.7% versus 32.4 ± 2.4%, respectively. Glutathione conjugates were also similar, with 5.2 ± 1.8% versus 4.6 ± 1.2% in subjects with Gilbert syndrome and controls, respectively.

Acetaminophen was given intravenously at 20 mg/kg to six subjects with Gilbert syndrome and six controls [69]. Acetaminophen and metabolites were assessed in two ways. Glucuronide metabolites were measured as the plasma area under the curve in the first two hours following administration (AUC0-2), as no differences in plasma glucuronide

metabolites were detected after two hours. Glutathione metabolites were measured over a 24-hour urine collection. The ratio of acetaminophen-glucuronide to acetaminophen concentration in plasma over the first two hours was 0.27 ± 0.05 in subjects with Gilbert syndrome versus 0.39 ± 0.03 in controls ($p<0.05$). The percentage of glutathione-derived metabolites recovered was 3.5 ± 0.4% in the Gilbert syndrome subjects versus 2.1 ± 0.3% in controls ($p <0.05$). Although the difference is statistically significant, it is a clinically irrelevant. These percentages of glutathione-derived metabolites in subjects with Gilbert syndrome and controls are within ranges previously reported in the general population.

A study of 1.5 g acetaminophen, comparing adults diagnosed with Gilbert syndrome and control subjects, quantified the elimination of acetaminophen and metabolites in urine [70]. When compared globally, there were no significant differences between subjects with Gilbert syndrome and controls in any of the study variables, including glucuronide and glutathione-derived metabolites. In a post-hoc analysis, subjects with Gilbert syndrome were then divided into two groups based on whether acetaminophen glucuronidation was greater or less than 50%. In the subset of subjects (n=7) with glucuronidation less than 50%, the average glutathione-derived metabolites were 14.01 ± 7.86% of total, versus 7.48 ± 1.64% in controls.

In this post-hoc analysis, a subset of subjects with glucuronidation less than 50% appear to have an increased fractional excretion of glutathione metabolites [70]; however, this cutoff value appears to be within one standard deviation of the mean value for 111 Caucasian volunteers (53.8 ± 6.2%) [71] and, therefore, the clinical significance is uncertain. Also, total recovery of acetaminophen and metabolites in urine was statistically significantly less than in the control group (82.56 ± 7.87% vs. 92.19 ± 7.94%, $p = 0.0193$). Other studies also help to place these data in perspective. For example, acetaminophen glucuronide excretion in subjects with the lowest fraction of glucuronide metabolites was found to substantially increase over five days of oral dosing, indicative of an adaptive response to continued therapeutic administration [60].

The metabolism of 1000 mg acetaminophen was determined in male volunteers, stratified by UGT1A1 genotype (six wild-type, nine homozygous for UGT1A1*28, and eight heterozygous) [72]. Urine was collected over eight hours following dosing. No statistically significant differences were detected in the metabolic ratio (of acetaminophen to glucuronide) between groups. While serum bilirubin correlated with subjects' UGT1A1 genotype, no correlation between the acetaminophen metabolic ratio and either the

UGT1A1 genotype or serum bilirubin was found. Glutathione-derived metabolites were not assessed in this study.

Taken as a whole, acetaminophen metabolism data demonstrate no significant differences between groups in acetaminophen glucuronidation [60,68,70,72], and no significant differences in glutathione metabolism [68].

8.3.6 Repeat Acetaminophen Dosing Increases Glucuronidation

Recently, acetaminophen was found to increase its own total clearance through enhanced glucuronidation when dosed repeatedly with 1000, 1500, and 2000 mg, totaling 4, 6, and 8 grams per day in healthy young adults [73,74]. Increases in total clearance from the first to final doses ranged from about 20% to 30% for all dose levels studied, and these changes were each statistically significant at $p < 0.0001$. In addition, plasma concentrations of the glucuronide metabolite were higher after repeat dosing than would predicted from single-dose pharmacokinetic data. Total acetaminophen clearance and glucuronidation were also increased with repeat dosing of 1000 mg in older healthy adults and in adults with moderate hepatic impairment (cirrhosis) [75].

A comprehensive review of the historic literature revealed supportive evidence for increased acetaminophen glucuronidation with repeat dosing [76,77], although it was not recognized at the time or its potential implications in the safety and tolerability of multiple days of continuous acetaminophen use. The amount of glucuronide metabolite excreted in urine by nine healthy subjects increased from $47.7 \pm 9.3\%$ after a single 650-mg dose to $55.6 \pm 6.8\%$ ($p < 0.05$) after a regimen of 650 mg acetaminophen every six hours [76]. A similar increase in urinary glucuronide metabolite was reported in another group of healthy subjects dosed with 650 mg acetaminophen every six hours [77]. Overall, increasing glucuronidation with repeat dosing has important implications in the tolerability of therapeutic and supratherapeutic doses of acetaminophen.

Although not studied prospectively, there is evidence that acetaminophen glucuronidation may also increase with repeat dosing in individuals with Gilbert's syndrome [60]. In an early study, metabolites were measured in two subjects after an intravenous 10-mg/kg dose of acetaminophen was administered before and again after 20 oral doses of 1.5 g acetaminophen. The amount of glucuronide metabolite excreted increased from 37% to 59% and 45% to 62% of the acetaminophen dose in each subject, respectively.

8.3.7 Acetaminophen Overdose Outcomes Study

The relationship between UGT1A1 promoter variants and subsequent acute liver failure secondary to acetaminophen overdose was assessed in 118 patients admitted to a liver intensive care unit with acetaminophen overdose [78]. The median dose ingested was 28.5 g, ranging from 9 to 100 g. Coded DNA samples from these patients were analyzed along with 128 control samples. Homozygotes of the TA7 variant of UGT1A1 (TA 7/7) is associated with Gilbert's syndrome, and occurred at a frequency of 6.8% in the acetaminophen overdose patients and in 8.6% of controls ($p > 0.05$). The results show that the allele frequencies did not differ significantly between survivors or those who died or were transplanted. There were no statistical differences between median INR or Apache score in any of the cohorts. The investigators conclude that the UGT1A1 promoter variants did not influence the outcome and the severity of liver or multiorgan failure following acute acetaminophen overdose.

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9 LABELING AND HEALTHCARE PROVIDER PRACTICES IN PATIENTS WITH UNDERLYING LIVER DISEASE

In Section XIV. Request for Comments of FDA's proposed rule [71 FR 77346], FDA requests comments "on the proposal to include a warning on acetaminophen products for patients with liver disease to ask their doctor for advice. Also, request information and data on the current dosing practices of health providers who treat patients with underlying liver disease."

9.1 Request for Comment on Proposal "to Include a Warning on Acetaminophen Products for Patients With Liver Disease to Ask Their Doctor for Advice"

In the proposed rule, FDA notes that, "NDAC briefly discussed this issue (ie, preexisting liver disease as a potential risk for acetaminophen toxicity) in 2002, but concluded that there were not sufficient data to make specific recommendations. After the 2002 NDAC meeting, FDA conducted a literature review (1966 to January 2003) and determined that the certain factors may place patients with preexisting liver disease at greater risk for acetaminophen toxicity. FDA has reconsidered its previous position on this issue and now believes that the current evidence now supports a warning. FDA proposes the following warnings:

- Ask a doctor before use if you have liver disease. (products labeled for adults only)
- Ask a doctor before use if the child has liver disease. (products labeled for children < 12 years of age only)
- Ask a doctor before use if the user has liver disease. (products labeled for adults and children < 12 years of age)

9.2 McNeil's Position

McNeil disagrees with FDA's tentative conclusion that preexisting liver disease is a risk factor for developing hepatotoxicity with therapeutic doses of acetaminophen. The experimental and clinical data that FDA reviewed and summarized in the proposed rule are incomplete and do not support the supposition that individuals with liver disease develop hepatotoxicity with the maximum-labeled daily dose of acetaminophen. Based on the most currently available science (Item 1, Sections 4-6), stable chronic liver disease, in the presence or absence of alcohol, does not result in hepatotoxicity with maximum-labeled daily doses of acetaminophen.

9.3 McNeil's Comments on the Proposed Labeling and Data Supporting the Position

McNeil provides specific comments to this request from FDA in Item 1, Section 2 of this submission. Scientific and clinical data supporting the position are provided in Item 1, Sections 5 and 6. In Item 1, Section 5, McNeil has analyzed the published literature up to April of 2007 and conclude the suppositions regarding risks in liver disease are theoretical and not supported by the available data. Specifically, the experimental evidence does not support the hypothesis that individuals with liver disease develop hepatotoxicity with therapeutic doses of acetaminophen. McNeil's position is also supported by prospective scientific and clinical evidence from several acetaminophen metabolism studies in adults and children with liver disease of varying severity and etiology, including a recently completed study in hepatic-impaired adults sponsored by McNeil. These acetaminophen clinical data are reviewed in Item 1, Section 6.

Based on the most currently available science, the addition of FDA's proposed labeling text: "Ask a doctor before use if you have liver disease" is not warranted. However, should FDA continue to believe that individuals diagnosed with liver disease, including those with chronic stable liver disease, should talk to their doctor before using acetaminophen, this warning should be appropriately considered for OTC NSAID products, as discussed in Item 3 of this response, because acetaminophen is the recommended analgesic of choice in individuals with liver disease and the use of OTC NSAIDs should be used with caution in this subset population. Also, in the proposed rule, FDA cites evidence that individuals with liver dysfunction and ascites are at risk for a variety of adverse renal effects from OTC NSAIDs, but fails to apply a preexisting liver disease warning on OTC NSAID products. If the OTC NSAID standard was used, it would preclude such a warning on OTC acetaminophen products as well.

9.4 Request for Information and Data on Healthcare Professional Practices

9.4.1 New McNeil Healthcare Professional Market Survey

A market-research firm, TNS™, conducted a survey on behalf of McNeil Consumer Heathcare [1]. The objective was to determine which OTC pain reliever (acetaminophen, ibuprofen, aspirin, or naproxen) gastroenterologists recommend and recommend most often to their patients with liver disease. Using a validated US-based physician panel, 450 physicians were sent email invitations with a unique link inviting them to participate in a brief (5 to 10 min) internet-based survey in April 2007. Physicians accessing the link were first taken through a series of three to four screening questions, determining their qualifications to participate in the survey. In order to qualify, physicians needed to:

- specialize in gastroenterology, or if a primary care physician, have a subspecialty in gastroenterology,
- treat patients with liver disease,
- recommend OTC pain relievers to their patients with liver disease.

The survey was completed by 151 office-based gastroenterologists (150 gastro-enterologists and one primary care physician with a subspecialty in gastroenterology), and their responses are included in the results.

In this survey of 151 office-based gastroenterologists, acetaminophen was typically recommended as an OTC pain reliever to liver disease patients by more gastroenterologists (86%) than each of the other OTC pain relievers (ibuprofen, aspirin, naproxen), which belong to the NSAID class. When asked which OTC pain reliever they recommend <u>most often</u> to this population, the majority of gastroenterologists again chose acetaminophen (55%).

Of the 83/151 gastroenterologists who recommended acetaminophen <u>most often</u> to patients with liver disease, their reasons are primarily based on the safety of acetaminophen, although 25% of them recommended acetaminophen to avoid using an NSAID. Another third recommended acetaminophen most often because they say it is safe at lower doses. About half (41/83) of these gastroenterologists also commented on the potential adverse effects of NSAIDs in liver disease patients, namely, GI bleeding, GI effects, renal effects, hepatotoxicity, and hematological effects.

9.5 Reference List

1. Recommendations Given to Liver Disease Patients by Gastroenterologists, 2007. Data on file at McNeil Consumer Healthcare.