

**SAFETY ASSESSMENT SUPPORTING CAFFEINE 130MG WHEN COMBINED
WITH ACETAMINOPHEN OR ASPIRIN/ACETAMINOPHEN**

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Abbreviations Used in This Document

AAN	Analgesic-Associated Nephropathy
AE	Adverse Event
APAP	Acetaminophen
ASA	Aspirin
BMS	Bristol-Myers Squibb
CAF	Caffeine
CDH	Chronic Daily Headache
CNS	Central Nervous System
DAWN	Drug Abuse Warning Network
ED	Emergency Department
ESRD	End-Stage Renal Disease
FDA	Food and Drug Administration
GI	Gastrointestinal
ISS	Integrated Summary of Safety
NAPQI	N-acetyl-p-benzoquinoneimine
NDA	New Drug Application
NEC	Not Elsewhere Classified
NOS	Not Otherwise Specified
NSAID	Nonsteroidal Anti-Inflammatory Drug
OTC	Over-the-Counter
SAMHSA	Substance Abuse and Mental Health Services Administration
TESS	Toxic Exposure Surveillance System
WHO	World Health Organization

EXECUTIVE SUMMARY

1.0 SUMMARY

In a 1995 FDA Feedback Letter to Industry, the Agency stated its view that "it is prudent to limit the amount of caffeine contained in OTC analgesic products to 65mg (per dose) until such time as more definitive data on caffeine's potential to foster misuse are available." To address this issue, Bristol-Myers Squibb (BMS) has conducted a comprehensive analysis of the worldwide safety literature, adverse event databases, expert reports and consumer use data including both single and multiple dose use, and new information that has become available since 1995. To further address questions from the Agency's April 13, 2001 letter, the assessment includes a review of the worldwide literature related to animal and human studies investigating potential acetaminophen/caffeine interactions.

This document examines the safety profile of caffeinated (65mg or 130mg) analgesics containing aspirin (ASA)/acetaminophen (APAP), APAP alone and ASA alone. Early sections review the safety profile of caffeine alone and the important toxicities seen with ASA and APAP alone, and then compare them to the combination analgesics to assess how caffeinated analgesics are used and whether any new or enhanced toxicities have been found. Later sections review key safety issues related to analgesic misuse and discuss their clinical relevance.

This document establishes that:

- The addition of caffeine to oral analgesic products does not negatively impact the safety profile of individual or combination analgesics, such that unique or enhanced toxicities are produced.
- There is no evidence that there is a difference in the safety profile between analgesics co-formulated with caffeine 130mg versus 65mg.
- In consumer use surveys, the usage pattern of caffeinated analgesic products is no different from that of non-caffeinated analgesics.
- Caffeine does not foster analgesic misuse.

2.0 BACKGROUND

BMS markets the Excedrin[®] line of over-the-counter (OTC) internal analgesic drug products, including Excedrin[®] Extra Strength (ASA 500mg/APAP 500mg/caffeine 130mg per dose) and Aspirin Free Excedrin[®] (APAP 1000mg/caffeine 130mg per dose), which are regulated under the Proposed Rule for Internal Analgesic, Antipyretic and Antirheumatic Drug Products for OTC Human Use. The current labeled indications for these products are "for the temporary relief of minor aches and pains associated with headache, sinusitis, a

cold, muscular aches, premenstrual and menstrual cramps, toothache, and for the minor pain from arthritis." The current formulation of Excedrin[®] Extra Strength has been marketed in the US since 1978, and Aspirin Free Excedrin[®] has been marketed in the US since 1990. BMS also markets Excedrin[®] Migraine (ASA 500mg/APAP 500mg/caffeine 130mg per dose), which is regulated under NDA 20-802. The current indication is for the OTC treatment of migraine. This product was first approved in 1998. Since 1978, over 47 billion tablets of Excedrin[®] Extra Strength, Aspirin Free Excedrin[®] and Excedrin[®] Migraine have been distributed.

Caffeine is regularly consumed by more than 80% of the US population with daily consumption of 170-300mg (2.4-4.0 mg/kg) per adult, mostly as coffee and caffeinated soft drinks. Medicinal sources of caffeine account for less than 5% of caffeine use and consist primarily of single ingredient caffeine and caffeine co-formulated with other therapeutically active ingredients. The caffeine content ranges from 100-200mg per dose in CNS stimulant products and from 32-130mg per dose in caffeinated analgesic products. For perspective, 100mg caffeine is roughly equivalent to the amount contained in a cup of coffee.

Caffeine is a well-documented analgesic adjuvant. The results of numerous trials indicate that approximately 40% more analgesic base would be required to provide pain relief equivalent to that of the caffeinated analgesic. Therefore, the addition of caffeine to analgesics allows consumers to receive greater pain relief than could be expected with the analgesic base alone. In addition, given the known safety concerns associated with excessive analgesic use, the "analgesic sparing" effect of caffeine may actually offer significant therapeutic benefit. Furthermore, APAP 500mg/ASA 500mg/CAF 130mg has been demonstrated to be more efficacious than APAP 1000mg in multiple analgesic models and has also been shown to be more efficacious than ibuprofen 400mg in the treatment of acute migraine headache.

3.0 METHODS

The Degge Group, Ltd. conducted the data assessment. Sources of data, which were reviewed for this assessment, include:

- Published literature including clinical trials, individual case reports, epidemiological studies
- Bristol-Myers Squibb-sponsored clinical trials data on Excedrin[®] Extra Strength, Excedrin[®] Migraine, and Aspirin Free Excedrin[®]
- BMS data from the Excedrin[®] Migraine NDA and sNDA
- FDA documents relating to OTC Monographs on Internal Analgesic Products and Stimulant Products
- Worldwide spontaneous adverse event data (internal BMS; World Health Organization; FDA Spontaneous Adverse Event Databases)
- Data obtained through the American Association of Poison Control Centers, Toxic Exposure Surveillance System (TESS),

- Data from the Drug Abuse Warning Network (DAWN)
- Drug distribution data (BMS data on file)
- Consumer usage data (The Gallup Organization)

4.0 HUMAN EXPOSURE DATA FOR EXCEDRIN® PRODUCTS

Excedrin® products are sold worldwide with the majority of sales in the US. Excedrin® Extra Strength has been marketed in the US in its current formulation since 1978 and Aspirin Free Excedrin® since 1990. Excedrin® Migraine, which is the identical formulation to Excedrin® Extra Strength, was approved under NDA 20-802 and launched in 1998. US Sales estimates for each product are as follows:

	Excedrin® Extra Strength 1978-Apr 2001	Excedrin® Migraine 1998-April 2001	Aspirin Free Excedrin® 1990-Apr 2001	Total
Total Tablets Sold (billions)	41.2	2.9	2.9	47

Since OTC products such as Excedrin® are often used by more than one family member, it is difficult to estimate consumer exposure from sales data. However, considering the extensive exposure based on sales combined with consumer use patterns, it is reasonable to estimate that hundreds of millions of consumers worldwide have been exposed to Excedrin® since market introduction.

5.0 SAFETY ASSESSMENT OF CAFFEINE AS A SINGLE INGREDIENT

The most notable effects of caffeine are its behavioral effects, which are exhibited with considerable inter-subject variability. At low to moderate doses, these effects are often perceived as positive (e.g. increased mental alertness, increased energy, increased ability to concentrate). As the dose of caffeine increases above 200mg, caffeine can induce undesirable effects (e.g. headache, anxiety, nervousness, irritability, GI disturbances). This pattern of effects, described as an "inverted-U-shape," leads most consumers to adjust their intake of caffeine in order to minimize the undesirable effects.

The long-term health consequences of caffeine have been extensively debated. Most of the epidemiologic research on these issues has found a weak to no association with caffeine, especially in amounts of less than 5 cups of coffee per day. Furthermore, some recent data suggests that caffeine may even exert some positive health effects, such as prevention of colorectal cancer and Parkinson's Disease.

An examination of the spontaneous AEs from the BMS, FDA, and WHO AE databases for single ingredient caffeine revealed that the reported AEs were generally consistent with the pharmacologic properties of caffeine and the safety profile described in the literature.

Based on data from the BMS, FDA, WHO, and TESS databases, the majority of caffeine single ingredient overdoses resulted in mild to non-existent clinical events and full recovery, although rare deaths were reported. In the FDA database, which contained 2 reports of fatal overdose with single ingredient caffeine, the consumers had ingested other drugs concurrently with caffeine which were also considered suspect by the reporter.

These data do not signal any new or unexpected safety concerns with caffeine single ingredient products.

6.0 SAFETY ASSESSMENT OF OTC CAFFEINATED ANALGESIC PRODUCTS

The focus of this section is a brief review of the established overall safety profile of acetaminophen, aspirin and caffeinated analgesic products, followed by a discussion of available information on specific safety issues that have been identified by various authors, researchers, and health authorities to be of potential concern. These include the following:

- Analgesic nephropathy
- Aspirin GI bleeding
- Acetaminophen hepatotoxicity
- Overdose of caffeinated analgesics
- Rebound headache
- Caffeine dependence

For each topic, relevant information from the published literature, BMS-conducted clinical trials, spontaneous AE reports, TESS, and DAWN were reviewed.

6.1 Overall Safety Profile of Single Ingredient OTC Analgesics

Acetaminophen and aspirin are two of the most frequently used medications worldwide for relief of pain and reduction of fever. Both have a long history of safe and effective OTC use.

APAP, in situations of overdose or significantly impaired hepatic function, is associated with the development of dose-dependent hepatotoxicity. Risk factors for the development of hepatotoxicity include chronic or binge alcohol use, fasting, and concomitant use of drugs that enhance cytochrome P-450 activity. The mean single threshold dose associated with development of hepatotoxicity is approximately 15g or thirty 500mg tablets in a 60kg individual.

Gastrointestinal symptoms are among the most common adverse events associated with ASA. While most GI symptoms are mild and self-limiting, more serious events also occur. GI complications secondary to NSAIDs, including ASA, account for an estimated 16,500 deaths each year among arthritis patients. Among the various NSAIDs, ASA ranks among those with the lowest relative risk of producing GI complications. Risk factors for the development of GI complications include advanced age, history of ulcer disease, concomitant use of corticosteroids, higher doses and use of multiple NSAIDs, duration of therapy <3months, concomitant use of anticoagulants, and other serious coexisting illnesses. The risk of GI complications exists at all dose levels, though it appears to increase with increasing doses.

6.2 Overall Safety Profile of OTC Caffeinated Analgesic Products

OTC caffeinated analgesic products have been used widely for over 40 years. The current formulations of Excedrin® Extra Strength/Excedrin® Migraine, and Aspirin Free Excedrin® have been marketed since 1978 and 1990, respectively, and have been used safely and effectively by more than 200 million consumers in the US alone. BMS clinical trial data in 17,000 subjects and 27 studies across various pain models demonstrate their safety and tolerability in short term studies.

In the postmarketing setting, a comparison of the spontaneous AEs in the BMS, FDA, and WHO databases for these products confirms that their safety profiles are generally consistent in nature and severity with the known pharmacologic profiles of the individual ingredients. Despite the frequent lack of medical confirmation and detailed medical information, these data do not signal any new or unexpected safety issues with these products.

Human Pharmacokinetic studies and postmarketing AE data do not appear to signal a clinically significant interaction between caffeine and APAP when administered concurrently in doses typically used in caffeinated analgesics.

When examined specifically for AEs of special interest with caffeinated analgesics, *i.e.*, analgesic nephropathy, hepatotoxicity, GI bleeding, overdose, rebound headache, and caffeinated analgesic dependence, the spontaneous AEs across the various databases appear to be consistent with the published literature.

Phenacetin appears to be the only clear risk factor for the development of analgesic nephropathy. Based on spontaneous AE data, analgesic nephropathy does not appear to be a clinically significant issue with caffeinated analgesics. Hepatotoxicity with caffeinated analgesics (due to the APAP component) appears to occur rarely, and based on spontaneous AE data, is not always the sole inciting drug. GI bleeding (associated with the ASA component), while relatively uncommon, is often associated with the presence of additional risk

factors for GI bleeding, e.g. history of ulcer disease, concomitant medications also associated with GI bleeding. In overdose settings, severe toxicity will most likely be associated with the analgesic component rather than the caffeine component due to the relative toxicities of each. Most cases of overdose are associated with minimal to no symptoms and result in complete recovery. Rare occurrences of significant toxicity are frequently associated with the ingestion of multiple drugs. Epidemiologic and consumer usage data demonstrate that rebound headache is less common than previously believed and associated with the use of all analgesic products, not specifically caffeinated analgesics. And finally, while caffeine appears to possess some of the attributes of drugs of dependence (*i.e.*, psychoactive effects, drug reinforcing effects, tolerance, physical dependence), these effects are weak, often inconsistently demonstrated in humans, and do not resemble the effects produced by typical drugs of abuse such as d-amphetamine and cocaine. Caffeine and caffeinated analgesics are used safely by the vast majority of users. Rare instances of drug seeking behavior associated with caffeine are usually associated with underlying psychological illness and are frequently associated with abuse of multiple drugs, not just caffeine or caffeinated analgesics.

It is often difficult to assess the postmarketing AE reports due to the paucity of detailed medical information and presence of multiple concomitant medications and illnesses; however, when examined in the context of the extensive use of caffeinated analgesics for over 40 years, these events appear to occur infrequently, are often associated with additional risk factors, and only rarely are they associated with severe morbidity and mortality.

7.0 CONSUMER USAGE PATTERNS OF CAFFEINATED ANALGESIC PRODUCTS

Data obtained from various sources do not show a difference between the consumer usage of caffeinated and non-caffeinated analgesic products. According to data collected by The Gallup Organization on OTC analgesics, there was no meaningful difference between consumption of caffeinated analgesics versus non-caffeinated analgesics regardless of the consumption level or amount of caffeine in the product. Furthermore, in a study of analgesic use among migraine headache patients in the UK, there was no meaningful difference in usage between caffeinated and non-caffeinated analgesics.

8.0 DISCUSSION

This section discusses the key issues and provides the basis for the conclusion that caffeine 130mg is safe and well tolerated as an OTC analgesic adjuvant.

The addition of caffeine to oral analgesic products does not negatively impact the safety profile of individual or combination analgesics, such that unique or enhanced toxicities are produced.

The market experience and research over the past 40 years confirm that caffeinated analgesic products are generally well tolerated and used safely by the vast majority of consumers. However, there are several safety issues that are of potential concern with these products, due to either the individual components or the combination of ingredients. These are discussed below.

Analgesic Nephropathy

The only clear risk factor for analgesic nephropathy identified and agreed upon by experts is previous use of phenacetin-containing analgesics. A recent panel of experts convened by the regulatory authorities of Germany, Austria, and Switzerland concluded that there is insufficient evidence to conclude that analgesics, in the absence of phenacetin, are causally associated with nephropathy. Similarly, there is no evidence that the addition of caffeine to analgesics is associated with nephropathy.

The data on renal events from the BMS, FDA, and WHO revealed no spontaneous reports suggestive of analgesic nephropathy with caffeinated analgesic products.

Hepatotoxicity

Hepatotoxicity is a well-recognized complication of APAP overdose and is not usually associated with the use of ASA or caffeine. In examining the spontaneous reports for Excedrin,[®] non-BMS caffeinated analgesics, and the WHO data for caffeinated analgesics, there were only 3 reports of severe hepatic injury. Alcohol was a known concurrent drug in 2 of these cases. While the scant information available for these reports limits their meaningful assessment, given the extensive population exposure of caffeinated analgesics consumed during this time period, severe hepatotoxicity appears to be a rare occurrence with caffeinated analgesics containing APAP.

GI Bleeding

GI Bleeding is a recognized complication of ASA use and is not typically associated with the use of APAP or caffeine. Over the period reviewed, BMS, FDA, and WHO received 12, 20, and 46 reports, respectively, of GI bleeding events. It is not possible to determine if some of the WHO reports are duplicates of the BMS reports. Detailed information on dose, duration, concomitant drugs and prior history of ulcer disease is not available for many of these reports; however, in the BMS data, 9 consumers reported long term use of Excedrin[®] and in 4 of these consumers, a history of ulcer disease was noted. In the FDA data, 10/20 cases reported additional suspect drugs which are known to also be associated with GI bleeding. Despite the limited information available for these

reports, cases across the databases appear to be similar in nature and severity. Furthermore, the occurrence of GI bleeding appears to be relatively uncommon with caffeinated analgesics when considering the widespread use of these products.

Overdose

In combination analgesic products, severe toxicity will most likely be associated with the analgesic component rather than the caffeine component, due to the relative toxicities of the individual ingredients. Therefore, the dose of caffeine, 130mg, in co-formulated analgesic products, is unlikely to be a contributing factor to serious toxicity from these products.

Based on data from the BMS, FDA, WHO, and TESS databases, the majority of caffeine single ingredient and caffeinated analgesic product overdoses were associated with mild to non-existent clinical events and resulted in full recovery, although rare deaths were reported. In the FDA database which contained 2 reports of fatal overdoses with caffeine single ingredient and 3 reports of fatal overdoses with APAP/CAF, all 5 consumers had ingested additional drugs concurrently with the caffeine containing product, which were also considered suspect drugs by the reporter. The TESS data, in which co-ingestions of additional drugs were excluded from our analysis, showed a generally similar profile across all products.

Rebound Headache

Rebound headache is a recognized potential consequence of frequent analgesic use. Based on epidemiologic data, it is believed to be uncommon (<2% in a study of 1,883 subjects with chronic daily headache), and caffeine-containing analgesics are no more likely to be associated with rebound headache than any other type of analgesic medication. When caffeine-containing analgesics are involved, the consumption level of caffeine associated with rebound headache is greater than 15g per month. The etiology of rebound headache remains unclear, however addictive behavior does not appear to be a factor for the vast majority of analgesic users. Based on this evidence, there is no reason to believe that caffeine doses of 130mg in caffeinated analgesics would result in a greater incidence of rebound headache than caffeine doses of 65mg.

Dependence

Habitual use of caffeine has been well demonstrated among the millions of daily consumers of coffee, however, true compulsive drug seeking behavior appears to be exceedingly rare and limited to a very small subset of individuals.

The psychoactive effects of caffeine show considerable inter-individual variation, but for most individuals, positive effects are seen at low to intermediate doses, with undesirable effects becoming more prominent as doses exceed 200mg. Doses greater than 500mg are usually associated with caffeine intoxication.

Moreover, caffeine's effect on the dopaminergic system has been shown to be different from that of drugs of abuse such as d-amphetamine and cocaine.

Caffeine has also been shown to exhibit weak drug reinforcing effects. The reinforcing effects of caffeine have been described as an inverted U-shape. Lower doses (up to 50mg) are reinforcing for a small proportion of subjects and increase in frequency as the dose rises. A plateau is reached between 50-150mg and then the reinforcing effects decrease with higher doses of caffeine, due to its aversive effects.

Tolerance has been demonstrated in animals. The data are less conclusive in humans and may reflect differences in inter-individual metabolism of caffeine.

Physical dependence, characterized by sudden caffeine withdrawal, has been observed with caffeine; however, it may not be as common as previously believed and symptoms rarely interfere with daily activities. It does not appear to be a dose related phenomenon and occurs inconsistently even within individuals. The majority of data on caffeine withdrawal refers to caffeinated beverages, so it is unclear if this phenomenon would also occur with caffeinated analgesic products. However, given the time lag of 12 to 24 hours until the occurrence of symptoms following complete deprivation and the ubiquitous nature and easy availability of caffeine in beverages, a withdrawal syndrome resulting solely from discontinuation of caffeine-containing analgesics is unlikely to develop under daily conditions.

In the spontaneous AE databases for caffeinated analgesic products, there were 49 reports of Drug Dependence and 2 reports of Drug Abuse, the majority originating from the BMS AE database. Most of these reports were not medically confirmed and typically describe a scenario of long term Excedrin[®] use and the inability to discontinue use. Many of the consumers were receiving other medications and had a history of psychiatric conditions. In the absence of detailed medical data regarding dose, duration of use, concurrent medications and illnesses, meaningful assessment of these reports is difficult.

Summary

In summary, while there are reported occurrences of important safety issues with caffeinated analgesic products, these appear to be relatively rare given the long and widespread usage of these products, and are generally associated with other risk factors. No unique toxicities or signals for enhanced toxicities were observed with caffeinated analgesics compared to the individual components.

There is no difference in the safety profile between analgesics co-formulated with caffeine 130mg versus 65mg.

Based on the available evidence, it is not possible to differentiate the effects of 130mg versus 65mg of caffeine. Published studies demonstrate that there is

considerable inter-individual variability in response, which may in part be due to differences in metabolism of caffeine. Caffeine withdrawal syndrome, less common than previously believed, does not demonstrate a dose response relationship; therefore, the specific amount of caffeine in an analgesic product is unlikely to be a factor.

A comparison of the safety profiles of 65mg and 130mg of caffeine in the BMS Aspirin Free Excedrin[®] trials does not show any meaningful differences in the nature, severity, or frequency of AEs between the products, although head-to-head clinical trials of 65mg versus 130mg have not been conducted.

In the spontaneous AE databases, the majority of non-BMS reports are for Anacin[®], a combination analgesic containing ASA 800mg and caffeine 64mg per dose. Given the limited information available for the FDA and WHO data and the fact that Excedrin[®] also contains APAP, it is difficult to do more than a gross comparison of AEs reported with analgesics containing caffeine 130mg versus 65mg across databases. However, the AEs reported for both Excedrin[®] and Anacin[®], including those reported in overdose situations, appear to be generally similar in nature and severity and do not indicate any particular trends or patterns with one product versus the other.

The usage of caffeinated analgesic products is no different than that of non-caffeinated analgesics.

In the US, The Gallup Organization has been measuring oral analgesic consumption since 1984. According to the Gallup tracking study of several caffeinated and non-caffeinated OTC analgesics, the mean number of OTC analgesic tablets consumed per average 4-week period per consumer over the past 10 years (1990-2000) ranged from 17.8 – 21.9 (N=50,751). The mean tablet consumption during this period was no different for caffeinated analgesic products than for non-caffeinated analgesic products. Furthermore, there was no apparent difference in consumption between caffeinated analgesics containing 130mg caffeine (Excedrin[®]) and those containing 64mg caffeine (Anacin[®]) (see table below).

**Gallup Tracking Data on Oral Analgesic Mean Tablet Consumption
per Average 4-Week Period
1990-2000**

	Excedrin[®] ES (130mg caffeine per dose)	Anacin^{®*} (64mg caffeine per dose)	Aspirin (w/o caffeine)**	Advil[®] (ibuprofen)	Tylenol[®] Extra Strength (excl. PM) (acetaminophen)
No. consumers	3,433	1,492	14,227	10,838	20,761
Mean no. of tablets per average 4-week period	17.8	20.3	21.9	17.9	17.8

* Anacin data was available only for 1990-1997 due to low sales volume post 1997.

**Aspirin data post 1997 does not specifically exclude caffeine.

A similar usage profile was also observed for "heavy users" (>30 or >180 pills per average 4-week period) of analgesics.

In a study of analgesic usage among migraine patients in the UK, there was also no difference in usage between caffeinated and non-caffeinated analgesics.

Caffeine does not foster analgesic misuse.

Despite extensive caffeine research over many decades, the weight of the evidence does not support the concern that the addition of caffeine to analgesic products will foster misuse. Further, there are no published experimental studies that clearly implicate caffeine in misuse, nor does consumer use experience demonstrate a misuse problem.

Given the widespread and inexpensive availability of caffeine-containing beverages, it is unlikely that analgesic combinations would be purchased for their caffeine content by those who might be attracted to caffeine's stimulant effect. Indeed, caffeine stimulant tablets (No Doz,[®] Vivarin,[®] etc.) are readily available over-the-counter, and cases of abuse are rare. This conclusion is also supported by caffeine's physiologic profile, which is quite different from drugs of abuse, such as d-amphetamine and cocaine.

Studies in normal subjects show that reinforcement follows an inverted U-shaped function, with reinforcement rising with increased doses until it reaches a plateau between 50-150mg. With higher doses, caffeine's aversive effects discourage misuse. This opinion was corroborated by the FDA Medical Reviewer during the review of the Excedrin[®] Migraine NDA.

The theoretical concern that rebound or withdrawal headache may occur with cessation of caffeinated analgesic use, encouraging additional dosing, is not supported by the evidence. We now know that caffeine has low potential for

drug dependence and that dependence is less common than previously thought. We also now understand that rebound headache occurs with all analgesics.

Recognizing the breadth of new data that has emerged in recent years addressing caffeine safety, other drug regulatory bodies have sought to resolve the question of potential misuse of caffeinated analgesics. In January 2000, the drug regulatory authorities of Germany, Switzerland, and Austria convened a committee of international experts to review all the relevant published literature on caffeine and caffeinated analgesics relative to misuse potential. The committee concluded that caffeine's dependence potential is low, and it appears unlikely that withdrawal could play a causative role in stimulating or sustaining analgesic intake. In addition, it concluded that, in the absence of phenacetin, there is insufficient evidence to claim that analgesics co-formulated with caffeine stimulate or sustain overuse or lead to dependence behavior.

9.0 CONCLUSIONS

Based on this review of the worldwide safety literature, adverse event databases, expert reports and consumer use data that includes both single and multiple dose use, it can be concluded that:

- The safety profiles of analgesics containing 130mg caffeine per dose (ASA 500mg/APAP 500mg/caffeine 130mg; APAP 1000mg/caffeine 130mg) are well characterized and consistent with those of the individual components.
 - No new or enhanced toxicities have been found compared to the individual components.
 - Most adverse events are of a mild and self-limiting nature.
- The potential for caffeinated analgesics to foster analgesic misuse is low.
 - Caffeine has a low potential for drug dependence.
 - Caffeine's U-shaped reinforcement pattern discourages use of high doses due to aversive effects.
 - There are no published experimental studies that clearly implicate caffeine in analgesic misuse.
 - Consumer usage patterns for caffeinated analgesics are similar to those for non-caffeinated analgesics.
- The safety profile of analgesics co-formulated with caffeine at 130mg and 65mg appear to be similar, based on evaluation of the worldwide safety data and consumer usage patterns.
- Caffeine at a 130mg dose is a proven analgesic adjuvant, providing statistical and clinical efficacy improvements to that of the analgesic base alone.
- The Excedrin[®] formulations containing caffeine 130mg have a long history of safe and effective use, and should be included in the Final Monograph.
 - Since 1978, more than 47 billion Excedrin[®] tablets have been used by more than 200 million US consumers.

SAFETY ASSESSMENT SUPPORTING CAFFEINE 130MG WHEN COMBINED WITH ACETAMINOPHEN OR ASPIRIN/ACETAMINOPHEN

1.0 PURPOSE

In a 1995 FDA Feedback Letter to Industry, the Agency stated its view that "it is prudent to limit the amount of caffeine contained in OTC analgesic products to 65mg (per dose) until such time as more definitive data on caffeine's potential to foster misuse are available." To address this issue, BMS has conducted a comprehensive analysis of the worldwide safety literature, adverse event databases, expert reports and consumer use data including both single and multiple dose use, and new information that has become available since 1995. To further address questions from the Agency's April 13, 2001 letter, the assessment includes a review of the worldwide literature related to animal and human studies investigating potential acetaminophen/caffeine interactions.

This document examines the safety profile of caffeinated (65mg or 130mg) analgesics containing aspirin (ASA)/acetaminophen (APAP), APAP alone and ASA alone. Early sections review the safety profile of caffeine alone and the important toxicities seen with ASA and APAP alone, and then compare them to the combination analgesics to assess how caffeinated analgesics are used and whether any new or enhanced toxicities have been found. Later sections review key safety issues related to analgesic misuse and discuss their clinical relevance.

This document addresses the following issues:

- Does the addition of caffeine to oral analgesic products negatively impact the safety profile of individual or combination analgesics, such that unique or enhanced toxicities are produced?
- Is there a difference in the safety profile between analgesics co-formulated with caffeine 130mg versus 65mg?
- Is the use of caffeinated analgesic products different than that of non-caffeinated analgesics?
- Does caffeine foster analgesic misuse?

2.0 BACKGROUND

BMS markets the Excedrin[®] line of over-the-counter (OTC) internal analgesic drug products including Excedrin[®] Extra Strength (ASA 500mg/APAP 500mg/caffeine 130mg per dose) and Aspirin Free Excedrin[®] (APAP 1000mg/caffeine 130mg per dose), which are regulated under the Proposed Rule for Internal Analgesic, Antipyretic and Antirheumatic Drug Products for OTC Human Use. The current labeled indications for these products are "for the temporary relief of minor aches and pains associated with headache, sinusitis, a cold, muscular aches, premenstrual and menstrual cramps, toothache, and for the minor pain from arthritis." The current formulation of Excedrin[®] Extra

Strength has been marketed in the US since 1978, and Aspirin Free Excedrin[®] has been marketed in the US since 1990. BMS also markets Excedrin[®] Migraine (ASA 500mg/APAP 500mg/caffeine 130mg per dose), which is regulated under NDA 20-802. The current indication is for the OTC treatment of migraine. This product was first approved in 1998. Since 1978, over 47 billion tablets of Excedrin[®] Extra Strength, Aspirin Free Excedrin[®] and Excedrin[®] Migraine have been distributed.

The safety and efficacy of caffeine as an analgesic adjuvant was initially reviewed by FDA's Advisory Review Panel for OTC Internal Analgesic, Antipyretic and Antirheumatic Drug Products (Panel) during the period 1972 through 1977. Although the Panel stated that the inclusion of caffeine theoretically "could be a factor in analgesic abuse," it concluded that (a) there was "insufficient evidence" to justify a warning regarding caffeine, and (b) the "potential benefits outweigh this risk" (42 FR 35484-85). The Panel thus placed caffeine in Category I for safety. With respect to effectiveness, the Panel found there was evidence to suggest that caffeine-containing analgesics were more effective than non-caffeinated analgesics alone (42 FR 35483). Because the data available at that time were considered limited, however, the Panel concluded that additional clinical studies needed to be performed in order to conclusively determine that caffeine was an effective analgesic adjuvant when used in combination with ASA and APAP, or APAP alone (42 FR 35482). Accordingly, the Panel placed caffeine in Category III for effectiveness with the expectation that it could attain Category I status if one or more adequate and well-controlled studies were performed demonstrating that caffeine provides a statistically significant contribution to the overall effectiveness of the analgesic product (42 FR 35483, 35489)].

Subsequently, BMS engaged in a continuing dialogue with the Agency in an effort to address the Panel's and FDA's concerns regarding the efficacy of caffeine as an analgesic adjuvant. As part of that dialogue, BMS conducted new trials and submitted significant new data and information in filings dating from 1973 through 1988. The submissions included adequate and well-controlled studies involving different designs (bioassay, parallel head-to-head, crossover head-to-head), different pain models (tension headache, dental, postpartum), and different analgesic bases (ASA/APAP combinations and APAP alone). These filings included a 1982 Citizen Petition to reopen the administrative record to include new clinical studies designed to address the Agency's concerns. While the Petition was denied in 1983, the Agency requested and received further detail on several of the studies submitted in the Citizen Petition. The following year, Laska et al. provided a meta-analysis of the results of studies conducted by BMS in over 10,000 subjects, comparing the potency of various analgesic bases combined with caffeine, relative to an analgesic alone. A series of meetings, discussions and submissions followed over the next few years.

In November 1988, FDA published the Proposed Rule for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for OTC Human Use (53 FR 46204) and concluded that additional data were needed to classify caffeine as Category I as an analgesic adjuvant. Based upon comments related to the caffeine dose, FDA agreed to change "the Panel's recommended single dose of 65mg caffeine to 75mg caffeine as an analgesic adjuvant, not to exceed a single adult dose of 150mg or a maximum daily dose of 600mg" (53 FR 46251). In making this change, the Agency noted that a 150mg single adult dose was well within the 100-200mg dose range for caffeine recommended by the Sleep-Aid Panel for stimulant drug products (53 FR 46244).

In response to the 1988 Proposed Rule, BMS submitted data from six additional clinical trials which demonstrated that the combination of ASA 500mg/APAP 500mg/caffeine 130mg provided superior efficacy to APAP 1000mg alone, and that this difference was statistically and clinically significant. The following year, BMS submitted the results from three new clinical trials (two crossover headache studies and one dental pain study) comparing the efficacy of the combination of APAP 1000mg/caffeine 130mg with APAP 1000mg alone. The headache studies demonstrated that the combination of APAP 1000mg/caffeine 130mg provided superior efficacy to APAP 1000mg alone. Although the results of the parallel design dental study did not achieve statistical significance, the differences between APAP 1000mg/caffeine 130mg and APAP 1000mg alone were supportive of caffeine adjuvancy.

The Office of OTC Drug Evaluation (Office) concluded, in an April 1995 Feedback Letter to Industry, that while caffeine was an effective analgesic adjuvant when combined with ASA or the ASA/APAP combination, the evidence was insufficient to conclude the analgesic adjuvancy of caffeine when combined with APAP alone. The Office based the decision relative to APAP/caffeine on the conclusion that the statistically significant differences between the caffeinated and non-caffeinated analgesics observed in the crossover design headache clinical trials could be due to a potential carryover effect. Moreover, the Office, in its April 1995 Feedback Letter, advised BMS that it would recommend to the Commissioner that the single dose of caffeine for use as an analgesic adjuvant be limited to 64/65mg. This recommendation was based upon the Office's conclusion that "it is prudent to limit the amount of caffeine contained in OTC analgesic drug products until such time as more definitive data on caffeine's potential to foster analgesic misuse are available." In order to reduce this potential risk, the Office concluded, "the final monograph will limit the maximum amount of caffeine permitted in analgesic combinations to the minimum effective caffeine dose demonstrated by the data." In August 1995, BMS submitted a response to the Office's Feedback Letter setting forth the scientific basis in support of the Category I status of caffeine 130mg as an analgesic adjuvant in combination with APAP alone, as well as information confirming the safety of the 130mg formulation.

In 1997, FDA again reviewed caffeine 130mg safety as part of its review of NDA 20-802 for Excedrin[®] Migraine. In July 1997, a joint meeting of the FDA Advisory Committees reviewed the safety and efficacy of Excedrin[®] for the treatment of migraine headache pain and recommended approval of the NDA. The Agency approved the NDA in January 1998 with a dosing regimen of 2 tablets (ASA 500mg, APAP 500mg, caffeine 130mg) every 6 hours, not to exceed 8 tablets in 24 hours. On October 7, 1999, following another FDA review, Supplement No. 002 to NDA 20-802 was approved to expand the indication to treat the entire migraine complex, with a dosing regimen in line with prescription migraine treatments, *i.e.*, 2 tablets in a 24-hour period.

Since that time, BMS has conducted three new parallel design clinical trials designed to conclusively establish caffeine adjuvancy with APAP. One study was conducted in a tension headache model and two in a dental model. The new tension headache trial was conducted as a parallel group study designed to confirm the results of the earlier crossover studies, thereby addressing the Agency's concern about potential carryover effect. The two new parallel group dental studies were conducted to supplement the earlier dental study.

The individual study reports for these trials are included in Appendices A, B and C of this Citizen Petition. Presented in this document is a comprehensive safety assessment of caffeine 130mg in combination with ASA/APAP or APAP alone. This assessment includes a review of worldwide literature, adverse event databases, and expert reports. To further address questions from the Agency's April 13, 2001 letter, the assessment includes a review of consumer use data that includes both single and multiple dose use, as well as a summary of the worldwide literature related to animal and human studies investigating potential acetaminophen/caffeine interactions.

2.1 Sources of Caffeine

Caffeine is the most widely used psychoactive substance in the world. It is a ubiquitous natural substance found in coffee beans, tea leaves, kola nuts, and cocoa seeds. The main dietary sources of caffeine consumed worldwide include coffee, tea, caffeinated soft drinks, and cocoa beverages. The caffeine content of these food items ranges from 71-220mg/5oz for coffee, 32-42mg/5oz for tea, 32-70mg/11oz for soft drinks and 4mg/5oz for cocoa beverages (Nehlig 1999).

Daily consumption of caffeine varies by geographic region and culture. In the United States, more than 80% of the adult population regularly consumes caffeine at an estimated daily consumption rate of 170-300mg (2.4-4.0 mg/kg) per adult, mostly as coffee and caffeinated soft drinks (Barone 1996).

Medicinal sources of caffeine account for less than 5% of caffeine use and consist primarily of single ingredient caffeine and caffeine co-formulated with other therapeutically active ingredients (Fredholm 1999). Both OTC and

prescription combination analgesic products may contain caffeine in combination with other ingredients including acetaminophen (APAP), aspirin (ASA), codeine, propoxyphene, butalbital, orphenadrine, and/or ergotamine. In non-analgesic oral OTC products, caffeine is available as a tablet for use as a mild CNS stimulant to help restore mental alertness or wakefulness in fatigued or drowsy consumers. The caffeine content ranges from 100-200mg per dose in CNS stimulant products and from 32-130mg per dose in caffeinated analgesic products (Facts and Comparisons 2001). For perspective, 100 mg caffeine is roughly equivalent to the amount contained in a cup of coffee.

2.2 Pharmacology of Caffeine

Caffeine is a methylxanthine chemically related to theophylline. Due to its hydrophobic properties, it easily crosses the blood brain barrier and all biological membranes.

Caffeine exerts its primary mechanism of action by blockade of adenosine receptors, which are widely distributed throughout all physiological systems in the human body (Fredholm 1999). Concentrations of caffeine achieved after the ingestion of 1-3 cups of coffee are sufficient to block adenosine receptors A₁ and A_{2A}, 2 of the 4 major human adenosine receptor subtypes. Adenosine receptors A_{2B} and A₃ are also blocked by caffeine, but at much higher levels than would be achieved by ingestion of usual amounts of coffee or caffeine-containing medicines. This blockage of tonically activated adenosine receptors accounts for most of caffeine's biological effects, including its effects on central nervous stimulation. Caffeine also inhibits phosphodiesterase, mobilizes calcium from intracellular storage sites in skeletal and cardiac muscle and neural tissue, and at higher than usual doses, can potentially alter nucleotide metabolism and inhibit benzodiazepine receptor binding (Sawynok 1995). Pharmacodynamic effects include decreasing gastric pH, constriction of intracranial and extracranial cerebral blood vessels, and decreasing the duration of theta (slow-wave) activity on electroencephalogram (National Headache Foundation 2000).

Caffeine is primarily metabolized in the liver via demethylation to dimethylxanthines and monomethylxanthines. Under chronic dosing conditions, caffeine metabolism has been shown to be dose-dependent, resulting in nonlinear accumulation of methylxanthines in the body (Denaro 1990).

2.3 Rationale for Caffeine in Caffeinated Analgesic Products

Caffeine has been a constituent of OTC and prescription analgesic products since the early 1900s. The medical literature provides strong evidence that caffeine enhances the analgesic effects of ASA, APAP, and ASA/APAP combinations in a variety of pain models (Beaver 1966, Beaver 1981, American Medical Association 1983, Aaron 1966, Herxhaimer 1980). The effect of caffeine as an analgesic adjuvant has been studied in numerous trials. In 1984,

Laska et al published a meta-analysis of the results of 30 clinical bioassay studies in more than 10,000 subjects which demonstrated that caffeine enhances the pain relieving potency of caffeinated analgesic formulations (Laska 1984) containing APAP and ASA. The authors analyzed the relative potency of caffeinated and non-caffeinated analgesics in studies conducted from 1975-1981 utilizing various pain models. They concluded that the addition of caffeine to APAP, ASA, and the combination of APAP and ASA, resulted in a 41% increase in analgesic activity [Relative potency 1.4 (95% confidence interval 1.23 – 1.63)]. The significance of these findings is that it would require approximately 40% more analgesic base (e.g. 1400mg of APAP alone) to provide pain relief equivalent to that provided by the caffeinated analgesic (EG. APAP 1000mg/CAF 130mg; ASA 500mg/APAP 500mg/CAF 130mg).

APAP/ASA/CAF 130 has also been shown to be more efficacious than ibuprofen. In a multi-centered, double-blind study by Goldstein et al, the combination of APAP 500mg/ASA 500mg/CAF 130mg demonstrated superior overall analgesic efficacy and faster onset of meaningful pain relief than ibuprofen 400mg in the treatment of acute migraine attacks (Goldstein 2001).

The mechanism of caffeine's analgesic adjuvant effect is not completely understood but it is thought that caffeine's inhibitory effect on adenosine receptors may play a significant role (Sawynok 1995, Bach 1998). Given the known safety concerns associated with excessive analgesic use, such as hepatotoxicity with APAP and gastrointestinal (GI) bleeding with ASA, the "analgesic sparing" effect of caffeine may actually offer a significant therapeutic benefit.

3.0 METHODS

The Degge Group, Ltd. conducted the data assessment. Sources of data reviewed for this assessment include:

- Published literature, including clinical trials, individual case reports, epidemiological studies
- Bristol-Myers Squibb-sponsored clinical trials data on Excedrin[®] Extra Strength, Excedrin[®] Migraine, and Aspirin Free Excedrin[®]
- BMS data from the Excedrin[®] Migraine NDA and sNDA
- FDA documents relating to OTC Monographs on Internal Analgesic Products and Stimulant Products
- Worldwide spontaneous adverse event data (internal BMS; World Health Organization; FDA Spontaneous Adverse Event Databases)
- Data obtained through the American Association of Poison Control Centers, Toxic Exposure Surveillance System (TESS)
- Data from the Drug Abuse Warning Network (DAWN)
- Drug distribution data (BMS data on file)
- Consumer usage data (The Gallup Organization)

3.1 Published Literature

The published literature relevant to caffeine was searched for the period 1996 to present for human data on: adverse reactions; safety; drug interactions; toxicity; and poisoning. The databases search included Medline, Embase, Derwent, and International Pharmaceutical Abstracts.

3.2 Bristol-Myers Squibb-Sponsored Clinical Trials on Excedrin[®] Extra Strength, Excedrin[®] Migraine and Aspirin Free Excedrin[®]

Safety data were reviewed from BMS clinical trials of Excedrin[®] Extra Strength, Excedrin[®] Migraine, and Aspirin Free Excedrin[®].

3.3 BMS Excedrin[®] Migraine NDA and sNDA (20-802)

The Integrated Summary of Safety (ISS) was reviewed from the original NDA, which summarized all domestic and foreign safety data for the treatment of migraine headache as of August 31, 1996 (cut-off date). This included data from 3 clinical efficacy studies, 1 bioequivalence study, and previous human postmarketing experience. The sNDA safety summary covered the time period January 1998 – September 1998 and included a Safety Update of the spontaneous adverse event data collected for both Excedrin[®] Extra Strength and Excedrin[®] Migraine, since they are identical formulations.

3.4 Worldwide Spontaneous Adverse Event Data

Marketed product spontaneous adverse event (AE) reports for caffeine single ingredient and caffeinated analgesic products received by BMS, FDA, and the World Health Organization (WHO) were evaluated for the entire period for which this data was available. Spontaneous AE reports from these sources were reviewed to identify frequently reported AEs, serious¹ outcomes, medical confirmation, and AEs of medical significance, including drug withdrawal, drug dependence, drug abuse, tolerance, drug withdrawal syndrome, rebound headache, overdose, renal effects, hepatotoxicity, GI bleeding, and death. There is no regulatory requirement for manufacturers to report AE information to the FDA on OTC products regulated under the monograph process, so the majority of the data consists of that collected by BMS through its internal data collection process.

While spontaneous AE reports are useful, they are limited to providing descriptive information on suspected cases. It should be emphasized that

¹ The current FDA definition of "serious" is an AE which is fatal, life-threatening, results in or prolongs inpatient hospitalization, or is a congenital anomaly, or considered medically important. This definition has been modified since first issued in 1985. Reports designated as "serious" were classified as such by the report originator and are based on the definition of "serious" at the time of the report.

spontaneous report data only serve as a signal of the presence of likely cases. Due to the lack of information on exposure and incomplete ascertainment of confounders and other explanatory factors on most cases, any qualitative judgment about safety and actual estimates of the rate of occurrence of these events in the population (i.e. incidence) must come from structured studies such as clinical trials and epidemiological studies.

3.4.1 BMS Adverse Event Data

The vast majority of BMS postmarketing AE data originates from the United States and covers the time periods listed in the table below. This data includes BMS-manufactured caffeine-containing products, both single ingredient and caffeinated analgesics. Excedrin[®] Migraine is the only product of this group approved under an NDA (20-802).

BMS Drug Product	Dates Available
Excedrin [®] Extra Strength (APAP 500mg, ASA 500mg, CAF 130mg per dose)	January 1984 – February 2001
Excedrin [®] Migraine (APAP 500mg, ASA 500mg, CAF 130mg per dose)	January 1998 – February 2001
Aspirin Free Excedrin [®] (APAP 1000mg, CAF 130mg per dose)	October 1995 – February 2001
No Doz [®] (200mg CAF per dose)	October 1995 – February 2001

3.4.2 FDA Adverse Event Data

The data obtained from FDA covers the time period January 1991-December 2000 and contains AE reports submitted by manufacturers of caffeine single ingredient and caffeinated analgesic products, or directly reported to FDA by consumers or health professionals. BMS reports were not included in this dataset since they are discussed separately as part of the BMS AE data. The FDA data includes AE reports contained in the Spontaneous Reporting System (SRS) and Adverse Event Reporting System (AERS) databases.² A list of caffeine single ingredient products and caffeinated analgesics contained in these AE databases is included in Appendix 1.

3.4.3 World Health Organization (WHO) Data

WHO data is collected from participating worldwide National Health Authorities, including FDA, and is comprised of spontaneous AE reports from manufacturers, health professionals, and consumers. The data provided are for the period 1995 to March 27, 2001 and included two data sets. The first data set is a tabulation by country of all AEs (terms only) received by WHO. The second data set is a line listing of reports that contained a WHO-designated Critical Term. The total

² The Degge Group, Ltd. maintains a current copy of FDA's Adverse Event Database in-house which has been customized for retrieval of the data in various formats. This is updated and quality controlled on a regular basis.

number of reports received by WHO cannot be determined from this data since the line listing report is a subset of the total reports. Based on the AE tabulations by country, for the caffeine single ingredient and caffeinated analgesic products, the majority of AEs originated from the United States. A list of caffeine single ingredient products and caffeinated analgesics contained in the WHO AE database is included in Appendix 2.

3.5 Toxic Exposure Surveillance System (TESS) Data

The TESS database is a comprehensive poisoning surveillance database containing more than 18 million poison exposures in the US since 1983 which is compiled from 67 US poison centers. TESS data was reviewed from 1995 to 2000 for reports with the following products of toxic exposures, in the absence of concurrent ingestions:

- caffeine single ingredient
- acetaminophen/caffeine (APAP/CAF)
- aspirin/caffeine (ASA/CAF)
- acetaminophen/aspirin/caffeine (APAP/ASA/CAF)

3.6 Drug Abuse Warning Network (DAWN) Data

DAWN data from 1995 to 1999 was reviewed for reports of drug abuse with caffeine and caffeinated analgesic products. DAWN is an ongoing drug abuse data collection system sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA) that includes estimates of drug abuse-related Emergency Department (ED) visits. These estimates are based on data submitted by a representative sample of 477 non-Federal, short-stay, general medical and surgical hospitals with 24-hour ED facilities.

Not all OTC drugs are reportable to DAWN. DAWN cases do not include accidental ingestions or inhalation of substances with no intent of abuse, or adverse reactions to OTC medications taken as prescribed. Accidental overdoses of OTC drugs taken as directed are reportable only when used in combination with an illicit drug.

“ED drug abuse episode” or “ED” episode refers to any ED admission that was induced by or related to drug abuse. “ED drug mention” or “ED mention” refers to a substance that was mentioned in a drug abuse episode. Up to 4 substances can be reported for each ED episode.

3.7 Drug Distribution Data

Distribution data (expressed as “Tablets Sold”) for BMS Excedrin[®] products sold in the US (Excedrin[®] Extra Strength, Excedrin[®] Migraine, Aspirin Free Excedrin[®]), were obtained from BMS internal data on file for 1978 to April 2001.

3.8 Consumer Usage Data

Consumer usage data on OTC analgesics was obtained from The Gallup Organization. Beginning in June 1984 and continuing to the present time, Gallup has been conducting a tracking study of 650 interviews per month of a nationally representative group of adults over age 18. Interview questions focus on OTC analgesic use over the previous 4 weeks. The time period used for this safety assessment was 1990-2000.

4.0 HUMAN EXPOSURE DATA FOR EXCEDRIN® PRODUCTS

Excedrin® products are sold worldwide with the majority of sales in the US. Excedrin® Extra Strength has been marketed in the US in its current formulation since 1978 and Aspirin Free Excedrin® since 1990. Excedrin® Migraine, which is the identical formulation to Excedrin® Extra Strength, was approved under NDA 20-802 and launched in 1998. Sales estimates were obtained for the time period 1978-April 2001 for Excedrin® Extra Strength, 1998-April 2001 for Excedrin® Migraine, and 1990-April 2001 for Aspirin Free Excedrin®.

US sales estimates for the above time periods for the Excedrin® products, expressed in "Tablets Sold" are as follows:

US Sales Estimates for Excedrin® Extra Strength

YEAR	NUMBER OF TABLETS SOLD* (billions)
1978-1997	36.1
1998	1.4
1999	1.9
2000	1.4
Jan. - Apr. 2001	0.4
Total	41.2

Source: BMS internal data on file

*Tablets, caplets, geltabs

US Sales Estimates for Excedrin® Migraine

YEAR	NUMBER OF TABLETS SOLD* (billions)
1998	0.7
1999	0.9
2000	1.0
Jan. - Apr. 2001	0.3
Total	2.9

Source: BMS internal data on file

*Tablets, caplets, geltabs

US Sales Estimates for Aspirin Free Excedrin®

YEAR	NUMBER OF TABLETS SOLD* (billions)
1990 - Sept. 1999	2.5
Oct. 1999 - Dec. 1999	0.1
2000	0.2
Jan. - Apr. 2001	0.1
Total	2.9

Source: BMS internal data on file

*Tablets, caplets, geltabs

Since OTC products such as Excedrin[®] are often used by more than one family member, it is difficult to estimate consumer exposure from sales data. However, based on data from 1978 – April 2001, approximately 47 billion tablets of Excedrin[®] products, or 23.5 billion doses (2 tablets per dose) have been consumed. If one assumes that an average consumer who took an Excedrin[®] product in any given year consumed a mean of 100 doses, based on the Gallup data (1990-2000) estimate of a mean average 4-week consumption of 17.8 tablets (8.9 doses), it is estimated that, since 1978, more than 200 million consumers have taken an Excedrin[®] product in the United States alone. Therefore, since market introduction, it is reasonable to estimate that hundreds of millions of consumer worldwide have been exposed to Excedrin.[®]

5.0 SAFETY ASSESSMENT OF CAFFEINE AS A SINGLE INGREDIENT

This section provides a brief review of the safety profile of caffeine as a single ingredient. Since the majority of the published literature is on caffeine as an ingredient in food products, this assessment focuses on the data on caffeine in both food and drug products. For each topic, relevant information from the published literature, BMS-conducted clinical trials, spontaneous AE reports, TESS, and DAWN are discussed.

5.1 Overall Safety Profile of Caffeine

5.1.1 Published Literature

The most notable effects of caffeine are its behavioral effects, which are exhibited with considerable inter-subject variability. At low to moderate doses (50-300mg), caffeine produces increased mental alertness, increased energy and increased ability to concentrate. Other stimulant effects include decreasing psychomotor reaction time and increasing sleep latency and waking time. Caffeine may even enhance performance on specific tests, though to a modest extent (O'Brien 1996). As doses increase above 200mg, caffeine can induce negative effects such as headache, anxiety, nervousness, irritability, restlessness, insomnia, palpitations, tachycardia, and gastrointestinal disturbances (Nehlig 1999, Sawynok 1995). This pattern of effects is described as biphasic or "inverted U-shaped" (Griffiths 1995). Most individuals adjust their intake of caffeine in order to minimize the undesirable effects.

The long-term effects of caffeine, mostly in the form of coffee, have been suggested to have various adverse effects on human health. Numerous studies conducted to examine the effects of caffeine are confounded by the presence of smoking and alcohol consumption, both of which limit the ability to attribute effects specifically to caffeine. The consensus of studies examining caffeine's relationship to myocardial infarction is that consumption of less than 5 cups per day of coffee has no negative consequences. While early research suggested

that coffee consumption could increase lipid levels, it is now understood that this was associated with the old coffee brewing process and was not associated with caffeine itself.

With respect to other adverse health associations, there has been no demonstrated relationship between caffeine/coffee intake and low birthweight, prematurity, delayed conception and infertility or congenital malformations. In the late 1970s, caffeine was implicated in elevating the risk of fibrocystic breast disease; however, subsequent epidemiologic evaluations found weak evidence of an association (Minton 1979, Lubin 1985, Levinson 1986). There is also no meaningful association between caffeine intake and the most common cancers including pancreatic, bladder and colorectal cancers. In fact, some data have even suggested that caffeine may have a protective effect in colorectal cancer (Sawynok 1995). More recently, epidemiologic and neurobiologic studies have suggested that caffeine may reduce the risk of development of Parkinson's Disease by attenuating loss of striatal dopamine and dopamine transporter binding sites by adenosine receptor (A_{2A}) blockade (Ross 2000, Chen 2001).

5.1.2 Spontaneous Adverse Event Reports for Caffeine Single Ingredient Products

The following section is a review of the spontaneous AE reports for single ingredient caffeine from the BMS, FDA, and WHO AE databases.

5.1.2.1 BMS AE Database for No Doz[®]

Historical postmarketing AE data on No Doz[®] (caffeine 200mg) for the time period October 1995 – April 1997 was assessed by BMS in preparation for the July 15, 1997 Excedrin[®] Migraine Advisory Committee meeting. During this time period BMS received 601 AE reports. The most frequently reported AEs (>5%) occurred in the Body as a Whole, Nervous System, Cardiovascular, and Digestive body system organ classes and included the following AEs: Maladministration Adult (N=102, 17%), Overdose (N=64, 10.6%), No Drug Effect (N=39, 6.5%), Nervousness (N=49, 8.2%), Nausea (N=47, 7.8%), Vomiting (N=35, 5.8%), and Tachycardia (N=27, 4.5%).

The BMS AE database was reviewed for the period January 1999 to February 2001. During this time period, BMS received a total of 233 reports which described 488 individual adverse events (A case report may describe more than one AE). The vast majority of reports originated from consumers and were not medically confirmed by a health professional. The AE profile of these reports is generally consistent in nature and severity with the known pharmacologic effects of caffeine.

The most frequently reported AEs (>5%) are presented in the table below:

**BMS AE Database Reports (N=233) of the Most
Frequently Reported AEs with No Doz[®]
1999 – February 2001**

AE PREFERRED TERM (MEDDRA)	AE TERM COUNT
Nausea	48 (20.6%)
Vomiting NOS	42 (18%)
Drug ineffective	39 (16.7%)
Dizziness (exc vertigo)	36 (15.5%)
Drug maladministration (package directions not followed)	36 (15.5%)
Nervousness	20 (8.6%)
Feeling jittery	18 (7.7%)
Tachycardia NOS	18 (7.7%)
Tremor NEC	15 (6.4%)
Abdominal pain upper	12 (5.2%)
Headache NOS	12 (5.2%)
Insomnia NEC	12 (5.2%)

There were 15 reports meeting the FDA criteria for "serious" which include 6 reports of Overdose, 4 reports of Drug Dependence, 2 reports of Convulsions, 2 reports of Hallucinations, and 1 report of Induced Abortion. None of these reports were confirmed by a health professional and detailed information regarding dose, duration, past medical history, and outcome is not available, thereby limiting meaningful interpretation of these reports. Overdose is further discussed in Section 5.1.3.1.

Of the nonserious AEs of special interest with No Doz,[®] there was 1 report of Drug Withdrawal Headache which was not medically confirmed by a health professional. Due to the lack of relevant details such as a confirmatory diagnosis, other concomitant drugs, medical history, other caffeine consumption, and outcome, meaningful assessment of this report is difficult. There were no reports of Tolerance or Drug Abuse. Details of the reports of Drug Dependence and Drug Withdrawal Headache are summarized below:

**BMS AE Database Reports of Drug Dependence with No Doz[®]
January 1999 - February 2001**

CASE NUMBER	AGE	SEX	DOSE	ADDITIONAL AE TERMS	OUTCOME
10008415	54	F	100-200 mg qd x 18 months	Edema lower limb Asthenia	Unknown
10060168	Unk	M	600 mg qd x unknown	None	No data
10060218	22	F	200 mg qd x 24 days	None	No data
10064533	16	F	1600 mg biw x 4 months	None	No data

Note: no concomitant medications reported; no reports medically confirmed.

**BMS AE Database Reports of Drug Withdrawal Headache with No Doz®
January 1999 - February 2001**

CASE NUMBER	AGE	SEX	DOSE	ADDITIONAL AE TERMS	OUTCOME
10606531	Unk	Unk	Unknown	None	No Data

Note: no concomitant medications reported; no reports medically confirmed.

5.1.2.2 FDA AE Database for Non-BMS Caffeine Single Ingredient Products

The FDA AE database was searched from 1990-2000 for reports of AEs with single ingredient caffeine products, excluding BMS No Doz.® The suspect drug most frequently mentioned was Vivarin.® There were 140 reports containing 483 AEs during this time period (a report can describe multiple AEs). The most frequently reported AEs (>5%) were generally consistent with the known pharmacologic profile of caffeine and included 21 reports of Drug Interaction. An examination of the 21 reports of Drug Interaction revealed no specific pattern of interacting suspect drugs or adverse events. Co-suspect drugs included primarily cardiovascular and psychiatric agents, with isolated reports of antidiabetic agents and anticonvulsants. In 5 of these reports, there were more than 2 suspect drugs identified.

The majority of AEs were reported directly by a consumer and were not medically confirmed. As with the BMS spontaneous reports, the lack of relevant medical details limits assessment of these reports. In general, the FDA AE Database profile for single ingredient caffeine is consistent with the pharmacologic properties of caffeine.

The most frequently reported AEs with non-BMS caffeinated analgesics are summarized below:

**FDA AE Database Reports (N=140) of the Most Frequently Reported AEs
with Non-BMS Caffeine Single Ingredient Products
1991 - 2000**

AE PREFERRED TERM	AE TERM COUNT
Drug Interaction	21 (15%)
Dizziness	19 (13.6%)
Insomnia	10 (7.1%)
Headache	9 (6.4%)
Agitation	9 (6.4%)
Hypotension NOS	9 (6.4%)
Palpitations	8 (5.7%)
Vomiting	8 (5.7%)
Nervousness	8 (5.7%)
Thinking Abnormal NEC	8 (5.7%)

Fifty-four (54) of the reports were classified as "serious." There were no events associated with serious reports which occurred at a frequency of greater than 5% of events. Serious events occurring at a frequency greater than 2% included Atrial Fibrillation (N=7), Dermatitis NOS (N=5), and Hypotension NOS (N=5) and were usually reported in conjunction with multiple suspect drugs and multiple adverse events. Twelve (12) cases reported a fatal outcome. Two (2) of these describe overdoses, which are discussed in the section on Overdose with Single Ingredient Caffeine Products (Section 5.1.3.1). Two (2) reports describe severe sensitivity reactions, one with caffeine alone, and the other in conjunction with use of Arthrotec[®] 50, APAP, Belladonna Extract, and opium. Two (2) reports describe suicide attempts with multiple drugs including caffeine, midazolam, fentanyl, and metoclopramide in one case and caffeine, Halcion,[®] ASA/dihydrocodone, and APAP/dihydrocodone in another case. Both suicide attempts resulted in a fatal outcome.

Also included in the FDA AE database for non-BMS caffeine single ingredient products were 4 reports of Drug Withdrawal Syndrome, 1 report of Drug Abuse, and 1 report of Drug Dependence. Of the Drug Withdrawal Syndrome reports, 2 resulted in hospitalization and 1 resulted in death. In all of these reports, the patients were also taking other suspect medications which are known to be associated with withdrawal phenomena. With the exception of the one report describing headache, the events described are more likely associated with the other suspect medications than caffeine, based on their known pharmacologic profiles. In the absence of more detailed information on these reports, it is difficult to assess the causal relationship between caffeine and the reported events.

In the one report of Drug Dependence with caffeine single ingredient, the patient was also receiving multiple psychiatric medications and ingesting alcohol, thereby raising the question of whether this patient had an underlying problem with drug-seeking behavior.

There were no reports of Tolerance in the FDA AE database for non-BMS single ingredient products.

A summary of the individual reports of Drug Withdrawal Syndrome and Drug Dependence with non-BMS caffeine single ingredient products is presented below:

**FDA AE Database Reports of Drug Withdrawal Syndrome with Non-BMS
Caffeine Single Ingredient Products
1991 - 2000**

IMAGE ID	AGE	SEX	CAFFEINE DOSE	CONCOMITANT MEDICATIONS	TERMS	OUTCOME
M01779522	43	F	Unk	Suspect: • Effexor • Benadryl • Trazodone • Xanax	Bundle branch block NOS Drug withdrawal syndrome Emotional disturbance NOS Hypertension NOS	Death
M02036475	49	M	Unk	Suspect: • Vasotec • Ephedrine HCl	Drug withdrawal syndrome Syncope Renal impairment NOS	Hospitalized
3103605-3	41	M	Unk	Suspect: • Propofol Concomitant: • Terazosin	Photophobia Drug withdrawal syndrome Headache NOS	Hospitalized
3145205-5	Unk	F	Unk	Suspect: • Effexor	Drug withdrawal syndrome	Other

**FDA AE Database Reports of Drug Dependence with Non-BMS Caffeine
Single Ingredient Products
1991 - 2000**

IMAGE ID	AGE	SEX	CAFFEINE DOSE	CONCOMITANT MEDICATIONS	TERMS	OUTCOME
M01495014	22	F	Unk	Suspect: Xanax Alcohol Tylenol PM	Tremor NEC Hostility Drug dependence Major depressive disorder NOS	Hospitalized

5.1.2.3 WHO AE Database for Caffeine Single Ingredient Products

From 1995 until March 27, 2001, WHO received an unknown number of reports describing 267 AEs with caffeine single ingredient products. Individual case information is only provided for those cases which contain a Critical Term, therefore it is not possible to determine a total number of reports received during this time period. The most frequently reported events are summarized below:

**WHO Database Reports of Most Frequently Reported AEs
with Caffeine Single Ingredient
1995 - March 27, 2001**

AE Term	Count	Percent (N=267)
Insomnia	13	4.9
Dizziness	10	3.7
Palpitation	9	3.4
Drug Abuse	9	3.4
Nervousness	8	3.0
Headache	7	2.6

There were 41 reports designated by WHO as containing a Critical Term; 37 originated from the US and the remaining 4 reports were submitted by Australia, Canada, Netherlands, and Great Britain. Twenty-six (26) reports were submitted by manufacturers and 14 were unclassified spontaneous reports. All BMS reports which were submitted to the FDA during this time period should also be listed in the WHO data, however, it was not possible to match the individual reports between these databases, since the WHO data does not provide the BMS manufacturer control number. Details regarding dose, duration of therapy, age, sex, time to event onset, other suspect or concomitant medications, and past medical history are frequently absent from the WHO case information, limiting meaningful assessment of these cases.

There were 5 reports of Death received during this time period and were all from the US. These reports included 3 females ages 43, 39, and 47. The other 2 patients were males with no ages provided. Known information is summarized below:

**WHO Database Reports of Deaths with Caffeine Single Ingredient Products
1995 – March 27, 2001**

RECNO	AGE	AGEUNIT	SEX	ONSET	CRITICAL TERM	FREQ
000401434	UNK	UNK	M	19-Apr-00	Death Enterocolitis	UNK
001102345	UNK	UNK	M	12-Sep-00	Death Pulmonary Hemorrhage Respiratory Insufficiency	UNK
960648245	43	Y	F		Death Hypertension	Daily
981966218	39	Y	F	02-Feb-98	Death Suicide Attempt	UNK
991256181	47	Y	F	26-Jul-99	Death	UNK

There were 18 events which may be related to caffeine dependence: 6 reports of Tolerance (Therapeutic Response Decrease), 3 reports of Withdrawal Syndrome, and 9 reports of Drug Abuse. The majority of these reports were non-manufacturer reports originating from the US. There is no other information available for these reports.

5.1.3 Overdose with Caffeine Single Ingredient Products

There is no persuasive evidence that moderate amounts of caffeine are harmful to the average healthy adult (Institute of Food Technologists 1988). Untoward effects usually occur at doses >1g, which corresponds to plasma concentrations of >30ug/ml (150 umol/L). However, signs of intoxication have been observed at

doses greater than 250mg, particularly in those sensitive to caffeine. In some caffeine-sensitive patients, even modest amounts of caffeine can provoke symptoms, as this population appears to have an enhanced response to caffeine. Symptoms of caffeine intoxication include:

- Restlessness
- Nervousness
- Excitement
- Insomnia
- Rambling flow of thought and speech
- Periods of inexhaustibility and psychomotor agitation
- Facial flushing
- Diuresis
- Gastrointestinal disturbances
- Muscle twitching
- Tachycardia
- Cardiac arrhythmias

High dose caffeine consumption (>600mg/day, equivalent to about 5-6 5oz cups of strong coffee) may produce "caffeinism", a syndrome characterized by anxiety, restlessness and sleep disorders, similar to anxiety states (Sawynok 1995). The short term lethal dose for caffeine is estimated at 8-10g (80-100 cups of coffee or 200 cans of cola consumed within 30 minutes), but fatal poisoning by caffeine is rare (Institute of Food Technologists 1988).

5.1.3.1 Spontaneous Reports of Overdose with Caffeine Single Ingredient Products

5.1.3.1.1 BMS AE Database Reports of Overdose with No Doz[®]

A review of spontaneous AE reports in the BMS data with No Doz[®] for the period January 1999 to February 2001 revealed 10 cases of overdose (intentional, accidental, or unspecified). All reports originated from consumers except one report, which originated from a pharmacist. Where the information was available, the age range was 13-21 years (6 cases) and gender breakdown was 3 females and 6 males. In the 8 reports where the amount ingested was available, caffeine amounts ranged from 1 gram to 8 grams. In 8 cases, there were no additional drugs ingested. Ethanol was concurrently ingested in 1 report and Prozac[®] was also ingested with caffeine in another report. Outcome was unknown or the event was still ongoing at the time of the report (not recovered) in 8 of 10 cases; in 2 cases the patient recovered. A summary of the individual reports is presented below:

BMS AE Database Reports of Overdose with No Doz[®]
January 1999 - February 2001

CASE NUMBER	AGE	SEX	DOSE	CONCOMITANT MEDICATIONS	ADDITIONAL AE TERMS	OUTCOME
10679132	16	F	8000 mg x 1 dose	None	Vomiting NOS	No data
10717460	15	M	2400 mg x 1 dose	None	None	No data
10540391	UNK	UNK	2000 mg x 1 dose	None	Fatigue Palpitations	Not recovered
M081303	UNK	F	1200 mg	None	Vomiting NOS	Unknown
10254852	18	M	200 mg x 11 doses over 7.5 hours	None	Paresthesia NEC Headache NOS Nervousness Nausea	Not recovered
10608529	21	M	200 mg x 11 doses over one evening	None	Nervousness Hematemesis Taste disturbance Insomnia NEC Headache NOS Feeling jittery	Not recovered
M077301*	13	F	Unknown – 19 tabs within 30 min	Prozac	Vomiting NOS	Recovered
10064632	16	M	Unknown	None	Vomiting NOS Tremor NEC	Recovered
10150225	UNK	M	Unknown	Ethanol	Twitching	Unknown
10493559	UNK	M	200mg every 15 min (10 total tablets)	None	Hypoesthesia	Not recovered

* Report source is health professional (pharmacist). All other reports not medically confirmed.

5.1.3.1.2 FDA AE Database Reports of Overdose with Non-BMS Single Ingredient Caffeine Products

The FDA AE database was searched from 1991-2000 for reports of overdose with single ingredient caffeine products, excluding BMS No Doz.[®] There were 11 reports of overdose during this time period. In 5 cases, the patient required hospitalization and in 2 cases, the outcome was death. In one report of death, the patient was also receiving several psychiatric drugs (Effexor,[®] Clozapine), an antiseizure medication (carbamazepine) and methadone. The amount of caffeine ingested is unknown. In the second report of death, the patient ingested 75gm of caffeine and was also receiving the anti-anxiety medication Xanax.[®] Of the remaining 9 cases, the caffeine dose was reported as 200 (unit known) in 2 cases and unknown for 6 cases.

The profile of these reports is similar to that of BMS No Doz[®] and does not signal any new safety concerns. Details of the cases are presented below:

**FDA AE Database Reports of Overdose with Non-BMS
Single Ingredient Caffeine Products
1991 - 2000**

IMAGE ID	AGE	SEX	CAFFEINE DOSE	CONCOMITANT MEDICATIONS	AE TERMS	OUTCOME
3425995-4	47	F	Unk	Suspect: • Effexor • Carbamazepine • Clozapine • Methadone HCl	Drug interaction NOS Drug effect increased Overdose NOS Weight decreased Drug level NOS above therapeutic	Death
3001867-4	27	M	75 gm	Suspect: • Xanax	Mucous membrane disorder NOS Medication error Accidental overdose Collapse	Death
3007299-7	Unk	Unk	200 (unit unk)	None	Tachycardia NOS Nausea Accidental overdose Dizziness	Hospitalized Life-threatening
M01779461	28	M	Unk	Suspect: • Lodine • Nicotine • Pseudoephedrine	Overdose NOS Agitation Dyspnea NOS	Hospitalized Life-threatening
M01408382	Unk	M	200 (unit unk)	None	Overdose NOS Hyperkinetic syndrome	Hospitalized
M01923342	28	F	Unk	Suspect: • Oruvail • Ascorbic acid • Paracetamol • Chlorpheniramine	Asthenia Jaundice NOS Overdose NOS Liver function tests NOS abnormal	Hospitalized
M01601304	14	F	4800	None	Vomiting NOS Nonaccidental overdose Tremor NEC	Hospitalized
M00749790	Unk	Unk	Unk	Suspect: • Prozac • Triazolam	Extrasystoles NOS Supraventricular arrhythmia NOS Nonaccidental overdose	Unk
M01553192	34	M	Unk	Suspect: • Acetaminophen • Codeine • Doxylamine	Pain NOS Hepatocellular damage Nonaccidental overdose Sweating increased	Other
M01867223	43	M	Unk	Suspect: • Zyrtec	Accidental overdose Somnolence Paresthesia NEC Dizziness	Other
M00818404	40	M	Unk	Suspect: • Soma • Fioricet • Xanax • Tylenol	Nonaccidental overdose	Other

5.1.3.1.3 WHO AE Database Reports of Overdose with Single Ingredient Caffeine Products

In the WHO spontaneous AE database, for the period 1995 to March 27, 2001 there were 3 reports of suicide attempt (no cases with the AE code of "overdose" were identified) with caffeine single ingredient products. In one manufacturer report describing a 39-year old female who died, there was no additional

information available with regard to amount ingested, concomitant drugs, or other relevant medical history, therefore a meaningful assessment of this case cannot be performed. There was no additional information provided for the remaining 2 reports.

5.1.3.2 Toxic Exposure Surveillance System (TESS) Database of Single Ingredient Caffeine Exposures

TESS data was examined from 1995-2000 for poison center exposures with single ingredient caffeine in the absence of other concurrent drugs. During this period there were 28,962 exposures which reported 42,804 clinical effects (an exposure can present with multiple clinical effects). Approximately one-third (33%) of exposures had no reported clinical effects. Over 96% of these exposures were categorized as "acute," defined as a single, repeated or continuous exposure occurring over a period of 8 hours or less. Approximately 55% of exposures were classified as "intentional" and the majority (74%) occurred in children <20 years old. Amount ingested was not presented in the data provided. The majority of reported clinical effects were consistent with the expected safety profile of caffeine and included vomiting, nausea, agitation/irritability, tachycardia and tremor. Almost half (45%) of exposures were treated in a health care facility with the majority of these (over 64%) treated/examined and released; only 14% resulted in hospital admission. Over 70% of exposures resulted in minor or no clinical effects and approximately 90% of all exposures resolved within 24 hours. There were 3 deaths reported over this 5-year period. The most frequently reported clinical effects, medical outcomes, and details of the deaths are presented below:

TESS Database Reports of Most Frequently Reported Clinical Effects with Caffeine Single Ingredient Exposure 1995 - 2000

CLINICAL EFFECT	COUNT	PERCENT OF REPORTS (N=28962)	PERCENT OF EVENTS (N=42804)
Vomiting	8218	28.4	19.2
Nausea	7332	25.3	17.1
Agitated/irritable	5468	18.9	12.8
Tachycardia	4678	16.2	10.9
Other	3585	12.4	8.4
Tremor	3070	10.6	7.2
Dizziness/vertigo	2028	7.0	4.7

**TESS Database Reports of Caffeine
Single Ingredient Exposures by Medical Outcome
1995 - 2000**

OUTCOME	NUMBER OF EXPOSURES
Minor Effect	9361
No Follow-Up/Minimal Toxicity	7122
No Follow-Up/Potentially Toxic	3808
Moderate Effect	3727
No Effect	3711
No Follow-Up/Non-Toxic	634
Unrelated Effect	531
Major Effect	65
Death	3
Death Indirect Report	0
TOTAL	28962

**TESS Database Reports of Caffeine Single Ingredient
Exposures Resulting in Death
1995 - 2000**

YEAR	AGE	REASON	SEX	CLINICAL EFFECTS	THERAPIES
1996	32	Intentional suspected suicide	F	Cardiac arrest Acidosis Diaphoresis Seizures (multi/discrete) Respiratory arrest	Charcoal, single dose Lavage Alkalinization Atropine Calcium CPR IV fluids Intubation Oxygen
1996	39	Intentional suspected suicide	F	Cardiac arrest Dysrhythmia Hypertension Hypotension Tachycardia Acidosis Fever/hyperthermia Rhabdomyolysis Agitated/irritable Muscle rigidity Oliguria/anuria Urinary retention Hyperventilation/tachypnea Respiratory arrest	Lavage Alkalinization Antiarrhythmic Anticonvulsants Intubation Vasopressors Ventilator
1998	20	Intentional abuse	M	Cardiac arrest Dysrhythmia Hypotension Tachycardia Pallor Vomiting Other coagulopathy PT prolonged Acidosis Electrolyte abnormality Seizures (multi/discrete) Mydriasis Respiratory arrest	Charcoal, single dose Antiarrhythmic Anticonvulsant Cardioversion CPR Intubation Oxygen Vasopressors Ventilator

5.1.4 Conclusion - Overall Safety Profile of Caffeine

The most notable effects of caffeine are its behavioral effects, which are exhibited with considerable inter-individual variability. At low to moderate doses, these effects are often perceived as positive and include increased mental alertness, increased energy, and increased ability to concentrate. As the dose of caffeine increases to >200mg, caffeine can induce aversive effects such as headache, anxiety, nervousness, irritability, and GI disturbances. This pattern of effects, described as an "inverted-U-shape," leads most consumers to adjust their intake of caffeine in order to minimize the undesirable effects (Griffiths 1995).

While long term use of caffeine has been implicated in the development of several adverse health consequences, including cardiovascular effects, various cancers, effects on fertility and the fetus, and fibrocystic breast disease, most of the epidemiologic research on these issues has found a weak to no association with caffeine, especially in amounts of <5 cups coffee per day. Furthermore, some recent data on caffeine suggests that caffeine may even exert some positive health effects, such as prevention of colorectal cancer and Parkinson's Disease (Giovannucci 1998, Chen, 2001).

Based on data from the BMS, FDA, WHO, and TESS databases, the majority of caffeine single ingredient overdoses resulted in mild to non-existent clinical events and full recovery, although rare deaths were reported. In the FDA database which contained 2 reports of fatal overdose with single ingredient caffeine, the consumers had ingested other drugs concurrently with caffeine which were also considered suspect by the reporter.

The spontaneous AEs from the BMS, FDA, and WHO AE databases for single ingredient caffeine revealed that the reported AEs were generally consistent with the pharmacologic properties of caffeine and the safety profile described in the literature. These data do not signal any new or unexpected safety concerns with caffeine single ingredient products.

6.0 SAFETY ASSESSMENT OF OTC CAFFEINATED ANALGESIC PRODUCTS

The focus of this section is a brief review of the established overall safety profile of acetaminophen, aspirin and caffeinated analgesic products, followed by a discussion of available information on specific safety issues that have been identified by various authors, researchers, and health authorities to be of potential concern. These include the following:

- Analgesic nephropathy
- Aspirin GI bleeding
- Acetaminophen hepatotoxicity

- Overdose of caffeinated analgesics
- Rebound headache
- Caffeine dependence

For each topic, relevant information from the published literature, BMS-conducted clinical trials, spontaneous AE reports, TESS, and DAWN will be discussed.

6.1 Overall Safety Profile of Single Ingredient OTC Analgesics

6.1.1 Acetaminophen

Acetaminophen, also known as paracetamol, is a synthetic non-opiate derivative of p-aminophenol (N-acetyl-p-aminophenol) and an active metabolite of phenacetin. It was first introduced as a therapy in 1893, but was not widely used until the 1950s in either the US or UK. Since then its use has gained widespread popularity and today it is one of the most frequently used medicines for pain and fever. APAP is available as a single ingredient in analgesic/antipyretic products in both oral and rectal products, as well as in combination products co-formulated with non-narcotic and narcotic analgesics, muscle relaxants, antihistamines, decongestants, sleep aids, and diuretics.

In OTC products, the recommended adult dose for analgesic and antipyretic use is 650-1000mg every 4-6 hours as necessary, or 1300mg tid, not to exceed 4g daily. Lower doses are recommended for children depending on body weight. Tablets/caplets are available in strengths of 325mg, 500mg, and 650mg in both immediate-release and extended-release dosage forms. Chewable tablets, sprinkles, suspensions, and solutions are also available. Similar dosage strengths of APAP are contained in combination products.

APAP is rapidly and almost completely absorbed from the GI tract. Following oral administration of immediate-release or extended-release preparations, peak plasma concentrations are attained within 10-60 or 60-120 minutes, respectively. It is rapidly and uniformly distributed into most body tissues, with around 25% being bound to plasma proteins. Plasma half-life is 1.25-3 hours. In therapeutic doses, APAP is metabolized predominantly in the liver where over 90% of the dose undergoes glucuronidation or sulfation, producing nontoxic metabolites that are excreted in the urine. Approximately 5% is excreted unchanged in the urine and the remainder is metabolized by the hepatic mixed function oxidase system, primarily cytochrome P-450 2E1 (AHFS Drug Information 2000, Makin 1997).

APAP is relatively nontoxic in therapeutic doses. The most commonly reported AEs are dermatologic rashes and other sensitivity reactions including laryngeal edema, angioedema and anaphylactoid reactions, which have been reported rarely. Neutropenia and thrombocytopenic purpura have also been reported with APAP use (AHFS Drug Information 2000). The most significant toxicity with

APAP is hepatotoxicity, which can result from an overdose situation or in cases of severely impaired hepatic function. APAP hepatotoxicity is discussed in greater detail below in Section 6.1.3.1.

6.1.2 Aspirin

Aspirin, also known as acetylsalicylic acid, is the salicylate ester of acetic acid. It is the prototype of the salicylates and the first nonsteroidal anti-inflammatory drug (NSAID). As with APAP, ASA has been extensively used for over a century, primarily as an OTC analgesic. NSAIDs constitute one of the most widely used classes of drugs with more than 70 million prescriptions and more than 30 billion OTC tablets sold annually in the US (Wolfe 1999).

ASA exhibits analgesic, anti-inflammatory, and antipyretic properties. In addition, it is unique among the salicylates in its ability to acetylate proteins (e.g. platelet proteins, hormones, DNA, hemoglobin) which results in effects not observed with other salicylates (such as inhibition of platelet aggregation). The primary mechanism of ASA's analgesic, anti-inflammatory, and platelet effects is inhibition of prostaglandin synthesis. ASA irreversibly acetylates and inactivates cyclooxygenase in circulating platelets, an effect which has led to extensive investigation of ASA as an antithrombotic agent.

As a single agent, the oral analgesic and antipyretic dose for adults and children >12 is 325-650mg every 4 hours as necessary, or 500-1000mg every 4-6 hours, not to exceed 4g daily. For self-medication, use is not recommended for greater than 10 days for pain and no more than 3 days for fever. Higher doses are used for inflammatory diseases and rheumatic fever. Lower doses are used for prophylactic treatment of recurrent stroke or transient ischemic attacks (50-325mg) and unstable angina/recurrent myocardial infarction (75-325mg daily). ASA is also frequently co-formulated with other agents such as narcotic and non-narcotic analgesics, caffeine, muscle relaxants, antihistamines, decongestants, antitussives, and sleep aids.

In therapeutic doses, ASA is generally well tolerated. Among the most common side effects are symptomatic GI disturbances such as dyspepsia, heartburn, epigastric distress and nausea. Sensitivity reactions, such as rashes and bronchospasm, occur rarely. Prolonged ingestion of high doses of salicylates can result in "salicylism," which is characterized by tinnitus, hearing loss, dimness of vision, headache, dizziness, mental confusion, lassitude, drowsiness, sweating, thirst, hyperventilation, tachycardia, nausea and vomiting (AHFS Drug Information 2000). One of the most significant AEs associated with ASA is GI bleeding, which is discussed in greater detail below in Section 6.1.3.2.

6.1.3 Safety Issues of Special Interest with Individual Analgesic Ingredients

6.1.3.1 Acetaminophen Hepatotoxicity

While APAP is generally considered to be a safe analgesic and antipyretic agent when used in therapeutic doses, in overdose situations it is associated with the development of dose-dependent hepatotoxicity. According to data collected by the Toxic Exposure Surveillance System (TESS) in 1999 from 64 poison control centers, analgesics accounted for the greatest percentage of all poison exposures in adults (N=74,602, 1.3%) and the third highest percentage (N=87,471, 7.6%) in children. In addition, analgesics led the categories with the largest numbers of deaths (N=340, 0.159%). The majority of analgesic fatalities (71%) were associated with APAP, ASA, and other salicylates (Litovitz 2000).

APAP hepatotoxicity usually presents as one of two distinct patterns. The first is an overdose situation in which a consumer attempts suicide and depending on the dose ingested, can develop acute liver failure which may be associated with renal failure and multiorgan failure. The second pattern of hepatotoxicity occurs secondary to accidental overdose or "therapeutic misadventure." These patients usually take APAP for pain and are often alcohol users or are fasting and typically present to the hospital with severe liver failure 3-4 days after ingesting APAP (McClain 1999).

The liver injury is characterized by centrilobular necrosis. The mechanism of liver injury in APAP overdose involves the saturation of the glucuronidation and sulfation metabolic pathways and excess formation of the toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI) through the alternate cytochrome P-450 pathway. As overproduction of NAPQI uses up the available glutathione stores that normally bind to the metabolite and prevent liver injury, excess NAPQI binds to liver cell proteins and causes hepatic necrosis. In addition, recent studies have shown that activated Kupffer cells and their secreted toxic agents, such as cytokines, may also play a role (McClain 1999). Risk factors for the development of hepatotoxicity include chronic or binge alcohol use, fasting, and concomitant use of drugs which enhance cytochrome P-450 activity.

The minimum amount of APAP thought to be capable of producing hepatotoxicity is 125mg/kg. In adults the mean single threshold dose that has been absorbed for hepatotoxicity to develop is approximately 250mg/kg (equivalent to 15g or thirty 500mg tablets in a 60kg individual). Severe hepatic damage is defined as an aspartate aminotransferase (AST) level of more than 1000 IU/L, which usually occurs when more than 350mg/kg of APAP has been absorbed (Makin 1997).

Treatment is aimed at decreasing the absorption of APAP using activated charcoal, replacing hepatic glutathione using acetylcysteine, and supportive care

in the event of hepatic failure. The prognosis depends on the amount ingested and the time of presentation after ingestion. Fatal hepatic failure occurs in 1-2% of untreated patients who have an APAP level in the toxic range. In patients with APAP concentrations of more than 300mg/L 4 hours after ingestion and more than 50mg/L 15 hours after ingestion, the probability of resultant severe or fatal liver damage is 90% (Salgia 1999).

6.1.3.2 Aspirin Gastrointestinal Bleeding

GI symptoms are among the most common adverse events associated with NSAID therapy. Conservative estimates are that approximately 107,000 patients are hospitalized annually for NSAID-related GI complications and at least 16,500 NSAID-related deaths occur each year among arthritis patients alone (Singh 1998). In an evaluation of studies comparing the risk of GI complications between ASA and non-aspirin NSAIDs, the risk was found to be similar for both groups, 3.1% (95% CI 2.0-4.8) vs. 3.5% (95% CI 2.4-5.3) (Smalley 1996). When the relative GI toxicity of NSAIDs was compared in rheumatoid arthritis patients in the ARAMIS database, ASA was ranked the third lowest risk of 12 NSAIDs identified, with a GI toxicity index of 1.18 (range was from 0.81 for salsalate to 3.91 for meclofenamate) (Singh 1998). In another study comparing the variability of risk of GI complications among various NSAIDs, ASA ranked 5th lowest risk out of 12 in relative risk, behind ibuprofen, diclofenac, diflunisal, and fenoprofen (Garcia Rodriguez 1998).

NSAID-induced GI injury is believed to be the result of a dual insult to the GI mucosa (Lichtenstein 1995). The initial injury is due to direct damage by the NSAID followed by a systemic effect in which prostaglandin synthesis is inhibited. In the majority of patients, NSAID-induced GI mucosal injury is superficial and self-limiting (Wolfe 1999). The spectrum of GI injury includes punctate subepithelial hemorrhages, erosions, and ulcerations. In a small number of patients the development of peptic ulcers leads to GI hemorrhage, perforation and death. Only a small minority of patients who experience serious GI complications report any antecedent dyspepsia. Furthermore, dyspeptic symptoms are poorly correlated with the endoscopic appearance and severity of the mucosal injury. Up to 40% of persons with endoscopic evidence of erosive gastritis are asymptomatic and conversely, as many as 50% of patients with dyspepsia have normal-appearing mucosa (Wolfe 1999, Singh 1999).

Risk factors for the development of GI complications include advanced age (with the risk increasing linearly with age), history of ulcer disease, concomitant use of corticosteroids, higher doses of NSAIDs (including the use of more than one NSAID), duration of therapy <3 months, concomitant use of anticoagulants, and the presence of other serious coexisting conditions. Other possible risk factors are *H. Pylori* infection, cigarette smoking, and alcohol consumption (Wolfe 1999). The type, dose, and duration of NSAID therapy appear to independently determine the risk for development of gastroduodenal ulcers and their

complications. The ulcer risk is present throughout the duration of therapy, but is believed to be greatest within the first month (Lichtenstein 1995).

The risk of GI complications exists at all dose levels, although it appears to increase with increasing aspirin doses. In the 1988 UK TIA trial, varying doses of aspirin were compared for the development of GI bleeding, upper GI symptoms, and withdrawal due to side effects. The odds ratio for GI bleeding was 2.8 (1.3-5.7) for the 1200mg daily dose and 1.6 (0.7-4.0) for 300mg. The smaller dose was also associated with a lower risk for all upper GI symptoms and for hospital admissions due to a GI bleed (Roderick 1993). In a study by Cryer and Feldman which investigated doses of 10mg, 81mg, and 325mg daily for 3 months, all 3 doses produced gastric injury, however only 325mg produced duodenal injury and prostaglandin inhibition all the way into the rectal mucosa (Cryer 1999).

The recommended treatment of GI injury is discontinuation of the NSAID and substitution of therapy with APAP or a nonacetylated salicylate. However, if discontinuation is not possible, treatment with an H₂ antagonist or proton pump inhibitor has also been shown to be effective.

6.1.4 Conclusion – Overall Safety Profile of Single Ingredient OTC Analgesics

APAP and ASA are two of the most frequently used medications worldwide for pain and fever. Both have a long history of safe and effective use by the majority of users.

APAP is associated with the development of dose-dependent hepatotoxicity in situations of overdose or significantly impaired hepatic function. The liver injury is characterized by centrilobular necrosis and is caused by saturation of the glucuronidation and sulfation metabolic pathways and excess formation of a toxic metabolite (NAPQI) through the alternate cytochrome P-450 pathway. NAPQI uses up the glutathione stores in an overdose setting and subsequently binds to liver cell proteins leading to hepatic necrosis. Risk factors for the development of hepatotoxicity include chronic or binge alcohol use, fasting, and concomitant use of drugs which enhance cytochrome P-450 activity. The mean single threshold dose associated with development of hepatotoxicity is approximately 15g or thirty 500mg tablets in a 60kg individual.

Gastrointestinal symptoms are among the most common adverse events associated with NSAID therapy, including ASA, and GI complications account for an estimated 16,500 deaths each year among arthritis patients. Among the various NSAIDs, ASA ranks in the top half of NSAIDs with the lowest relative risk of producing GI complications. NSAID-induced GI injury is believed to be due to a dual insult to the GI mucosa. The initial injury is the result of direct damage to the mucosal wall followed by a systemic effect due to inhibition of prostaglandin

synthesis. The spectrum of injury ranges from punctate subepithelial hemorrhages all the way to GI hemorrhage, perforation, and death. Risk factors for the development of GI complications include advanced age, history of ulcer disease, concomitant use of corticosteroids, higher doses and use of multiple NSAIDs, duration of therapy <3 months, concomitant use of anticoagulants, and other serious coexisting illnesses. The risk of GI complications exists at all dose levels, though it appears to increase with increasing doses.

6.2 Overall Safety Profile of OTC Caffeinated Analgesic Products

Caffeine has been a constituent of OTC and prescription analgesic drug products since the early 1900s. Caffeinated analgesics containing various combinations of APAP, ASA, and caffeine are among the most widely used OTC analgesic products.

Considerable clinical experience has been gained with these products in clinical trials using various pain models and through postmarketing experience. Given the widespread use of OTC caffeinated analgesics for over 40 years, these products have been shown to be generally well tolerated when used as directed. However, specific safety issues have been identified with the individual active ingredients APAP and ASA as discussed previously, as well as with caffeinated analgesic products.

This section reviews the following safety data for caffeinated analgesic products:

- BMS clinical trial data with the three currently available caffeinated Excedrin[®] products: Excedrin[®] Migraine, Excedrin[®] ES, and Aspirin Free Excedrin[®]. Since Excedrin[®] Migraine and Excedrin[®] ES are identical formulations, although they are approved for different indications, they will be discussed together.
- Spontaneous AE reports for caffeinated analgesic products
- Safety issues of special interest with caffeinated analgesic products
 - Analgesic nephropathy
 - Hepatotoxicity
 - GI Bleeding
 - Overdose
 - Rebound headache
 - Caffeine dependence

6.2.1 BMS Controlled Clinical Studies

In the summaries below, incidence rates of AEs are summarized for clinical trials using APAP 1000mg/caffeine 130mg, APAP 1000mg/caffeine 65mg, and ASA 500mg/APAP 500/caffeine 130 mg per dose. Where possible, AE rates are grouped by pain model (tension headache, dental pain, migraine). All adverse events in these summaries were "treatment emergent" (defined as any new or worsening illness, sign or symptom complained of by the subject or noted by the

investigator during the course of treatment, regardless of the investigator's assessment of the relationship between the event and study drug). A serious adverse event (SAE) is defined as an AE that meets at least one of the following criteria: fatal, life threatening, permanently disabling, resulting in hospitalization, leading to prolonged hospitalization, congenital anomaly, cancer, or overdose.

Three tension headache studies (HPD-H203, 170-01-88, 170-02-88), which compared APAP 1000mg/caffeine 130mg to APAP 1000mg and placebo were conducted in a total of 2,828 subjects. In HPD-H203, a single headache was treated in a parallel design study, while 4 headaches were treated in studies 170-01-88 & 170-02-88 in a 2-period crossover design. Four studies (131-01-86, 131-02-86, 131-03-86, 131-04-86), compared ASA 500mg/APAP 500mg/caffeine 130mg to APAP 1000mg and placebo, in a total of 3,503 subjects. Four headaches were treated in these 2-period crossover design studies. Adverse event rates are summarized for the single treated headache parallel group study and the 4 treated headaches crossover studies separately. For both the parallel-groups and crossover studies, the proportion of subjects reporting any adverse event was significantly ($p < 0.05$) greater for the combination product than for APAP 1000mg alone or placebo. The proportion of subjects reporting digestive system/gastrointestinal events and nervous system/nervousness/dizziness events were also significantly ($p < 0.05$) greater for the combination than for APAP 1000mg alone.

No SAEs were reported in these studies. There were two discontinuations prompted by AEs (one subject in study 170-01-88 discontinued because of stomach pain and dry mouth after treating 1 headache with APAP 1000mg, and one subject in study 170-02-88 discontinued because of nervousness after treating 2 headaches with APAP 1000mg/caffeine 130mg).

Table 6.2.1
Incidence (%) of AEs in Tension Headache Studies for Aspirin Free Excedrin®

Parallel-Groups Study HPD-H203			
Event	Aspirin Free Excedrin® APAP 1000mg/ CAF 130mg (N = 438)	Extra Strength Tylenol® APAP 1000mg (N = 441)	Placebo (N = 225)
Adverse Events	52 (12%)	27 (6%)	12 (5%)
Digestive System	22 (5%)	6 (1%)	5 (2%)
Nervous System	28 (6%)	15 (3%)	6 (3%)
Nervousness	7 (2%)	1 (<1%)	2 (1%)
Dizziness	15 (3%)	6 (1%)	4 (2%)
Nervousness and dizziness are included here as specific preferred COSTART terms, part of the Nervous System.			
Crossover Studies 170-01-88, 170-02-88			
Event	Aspirin Free Excedrin® APAP 1000mg/ CAF 130mg (N = 692)	Extra Strength Tylenol® APAP 1000mg (N = 691)	Placebo (N = 341)
Adverse Events	144 (21%)	90 (13%)	41 (12%)
Gastrointestinal ^A	59 (9%)	45 (7%)	19 (6%)
Nervousness	50 (7%)	10 (1%)	2 (1%)
Dizziness	34 (5%)	11 (2%)	4 (1%)
Gastrointestinal includes:	stomach burning, stomach cramp, heartburn, dyspepsia, nausea, stomach pain, stomach ache, stomach upset, vomiting, bloated, stomach unsettled, stomach irritation		
Nervousness includes:	hyperactive, insomnia, jittery, nervousness, shaky, tense, agitated, sleeplessness, tremors, anxiety		
Dizziness includes:	dizziness, lightheaded, euphoria, weakness		

^A In this table, adverse events from studies 170-01-88 and 170-02-88 categorized here as gastrointestinal events were categorized as stomach discomfort in the original study reports.

Table 6.2.2
Incidence (%) of AEs in Tension Headache Studies for Excedrin® Extra Strength
Crossover Studies 131-01-86, 131-02-86, 131-03-86, 131-04-86

Event	Excedrin® Extra Strength ASA 500mg/APAP 500mg/ CAF 130mg (N = 1400)	Extra Strength Tylenol® APAP 1000mg (N = 1401)	Placebo (N = 702)
Adverse Events	241 (17%)	136 (10%)	61 (9%)
Gastrointestinal ^A	130 (9%)	67 (5%)	28 (4%)
Nervousness	61 (4%)	13 (1%)	4 (0.6%)
Dizziness	58 (4%)	22 (2%)	7 (1%)
Gastrointestinal includes:	burning stomach, burning GI, indigestion, gastrointestinal irritation, belching, heartburn, nausea, pain stomach, stomach ache, stomach upset, vomit, stomach unsettled, irritated stomach, upset gastrointestinal		
Nervousness includes:	hyperactive, jittery, nervousness, shaky, restless, anxiety		
Dizziness:	dizzy, lightheaded, weakness includes		

^A In this table, adverse events from studies 131-01-86, 131-02-86, 131-03-86, and 131-04-86 categorized here as gastrointestinal events were categorized as stomach discomfort in the original study reports.

Two dental pain studies (HPD-D104, 171-01-88) which compared APAP 1000mg/caffeine 130mg to APAP 1000mg and placebo were conducted in a total of 1,543 subjects. A third dental pain study (HPD-D105) compared APAP 1000mg/caffeine 65mg to APAP 1000mg and placebo in 1,015 subjects. Two additional dental pain studies (132-01-86, 132-02-86) compared ASA 500mg/APAP 500mg/caffeine 130mg to APAP 1000mg and placebo in a total of 1,125 subjects. No statistically significant differences in incidence of adverse events were detected between any of the treatment groups (Table 3). The incidences and patterns for AEs in the APAP1000/CAF130 APAP1000/CAF65 groups were similar.

No SAEs were reported in these studies and no discontinuations were prompted by AEs.

Table 6.2.3
Incidence (%) of AEs in Dental Pain Studies for Aspirin Free Excedrin®

Studies HPD-D104, HPD-D105				
Event	Aspirin Free Excedrin® APAP 1000mg/ CAF 130mg (N = 403)	Aspirin Free Excedrin® APAP 1000mg/ CAF 65mg (N = 407)	Extra Strength Tylenol® APAP 1000mg (N = 807)	Placebo (N = 407)
Adverse Events	120 (30%)	101 (25%)	218 (27%)	115 (28%)
Digestive System	98 (24%)	67 (16%)	159 (20%)	91 (22%)
Nervous System	18 (4%)	20 (5%)	30 (4%)	11 (3%)
Nervousness	3 (1%)	0 (0%)	0 (0%)	0 (0%)
Dizziness	6 (1%)	5 (1%)	3 (<1%)	3 (<1%)
Somnolence	0 (0%)	3 (1%)	4 (<1%)	0 (0%)
Nervousness, dizziness, and somnolence are included here as specific preferred COSTART terms, part of the Nervous System.				
Study 171-01-88				
Event	Aspirin Free Excedrin® APAP 1000mg/ CAF 130mg (N = 212)	Extra Strength Tylenol® APAP 1000mg (N = 214)	Placebo (N = 108)	
Adverse Events	40 (19%)	44 (21%)	22 (20%)	
Gastrointestinal problems	10 (5%)	19 (9%)	10 (9%)	
Jitteriness	4 (2%)	1 (<1%)	1 (<1%)	
Dizziness/lightheadedness	5 (2%)	5 (2%)	1 (<1%)	
Sleepiness	7 (3%)	12 (6%)	2 (2%)	
Gastrointestinal problems include:	heartburn, nausea, vomiting, stomach upset, diarrhea			
Dizziness/lightheadedness includes:	dizziness, lightheaded			
Sleepiness includes:	sleepy, drowsy			
Jitteriness includes:	jittery, agitated, shaky			

Table 6.2.4
Incidence (%) of AEs in Dental Studies for Excedrin® Extra Strength
Studies 132-01-86, 132-02-86

Event	Excedrin® Extra Strength ASA 500 mg/APAP 500mg/CAF 130mg (N = 446)	Extra Strength Tylenol® APAP 1000mg (N = 451)	Placebo (N = 228)
Adverse Events	35 (8%)	22 (5%)	18 (8%)
Gastrointestinal problems	15 (3%)	8 (2%)	10 (4%)
Dizziness/lightheaded	9 (2%)	2 (<1%)	1 (<1%)
Sleepiness	4 (1%)	3 (<1%)	2 (<1%)
Gastrointestinal problems include:	heartburn, nausea, vomiting, stomach unsettled, stomach upset, abdominal cramps, difficulty swallowing, stomach ache, stomach pain		
Dizziness/lightheadedness includes:	dizziness, lightheaded		
Sleepiness includes:	sleepy, drowsy		

Three migraine studies (GHBA-840, GHBA 841, GHBA 842) which compared ASA 500mg/APAP 500mg/caffeine 130mg to placebo were conducted in a total of 1,250 subjects. An additional study (134-01-99), compared ASA 500mg/APAP 500mg/caffeine 130mg to Ibuprofen 400mg and placebo in 1,250 subjects. The proportion of subjects reporting any adverse event was significantly ($p < 0.05$) greater for the combination product than for placebo. The proportion of subjects reporting nervous system/nervousness events was also significantly ($p < 0.05$) greater for the combination than for placebo.

No SAEs were reported in these studies and no discontinuations were prompted by AEs.

Table 6.2.5
Incidence (%) of AEs in Migraine
Studies 134-01-99 and GHBA-840, 841, 842

Event	ASA 500 mg/APAP 500mg/ CAF 130mg (N = 1287)	Placebo (N = 853)
Adverse Events	176 (14%)	80 (9%)
Digestive System	69 (5%)	32 (4%)
Nervous System	93 (7%)	29 (3%)
Nervousness	40 (3%)	6 (<1%)
Dizziness	28 (2%)	11 (1%)
Nervousness and dizziness are included here as specific preferred COSTART terms, part of the Nervous System.		

6.2.1.1 Conclusions – BMS Controlled Clinical Trials

The nature of the adverse events reported in the clinical trials is consistent with those associated with the individual active ingredients. The data demonstrates the formulations have excellent safety profiles and were well tolerated.

6.2.2 Spontaneous AE Reports for Caffeinated Analgesic Products

6.2.2.1 BMS AE Database for Excedrin® Products

Excedrin® Migraine and Excedrin® Extra Strength (APAP 500mg/ASA 500mg/CAF 130mg per dose)

Historical postmarketing AE data on Excedrin® Extra Strength for the time period 1984 – April 1997 was assessed by BMS in preparation for the July 15, 1997 Excedrin® Migraine Advisory Committee meeting. During this time period BMS received a total of 2,427 AE reports. The majority of AEs occurred in the Digestive, Nervous System, and Body as a Whole body system organ classes. The most frequently reported AEs (>5%) were Dyspepsia (N=293, 12.1%), Nausea (N=234, 9.6%), Dizziness (N=228, 9.4%), Nervousness (N=168, 6.9%), No Drug Effect (N=164, 6.7%), and Pain Abdomen (N=150, 6.2%). Included in these 2,427 reports were 12 reports classified as “serious,” all of which were reported by a consumer and are not medically confirmed. Notable AEs in these serious AE reports were 2 reports of GI bleeding events which are discussed in greater detail in Section 6.3.3.1.1.

From January 1998 – February 2001, BMS received a total of 3,739 adverse event reports which described 5,719 individual events (a report can describe multiple clinical events). The vast majority of these reports were classified as nonserious (N=3,619) and were not medically confirmed. The most frequently reported AEs (>5% of reports) were generally consistent with the known safety profiles of APAP, ASA, and caffeine.

BMS AE Database Reports (N=3739) of Excedrin® Migraine and Excedrin® Extra Strength Most Frequently Reported AEs 1/1/98 to 2/28/01

AE TERM	FREQUENCY
Drug ineffective	1486 (39.7%)
Nausea	628 (16.8%)
Dizziness (exc vertigo)	238 (6.4%)
Insomnia NEC	192 (5.1%)

Included in these 3,739 reports were 120 reports classified as serious of which 2 resulted in death. One report of death described a 7 year-old female who “died because the aspirin thinned her blood.” This report originated from the child’s mother who reported that she was instructed by a physician to give her daughter 1 tablet Excedrin® Extra Strength for headache. She gave her daughter Excedrin® Extra Strength for approximately 1 year (frequency not specified), when her daughter experienced a more severe headache and was taken to the ER where she was diagnosed with a large brain aneurysm by a neurosurgeon.

The child died during surgery. According to the mother, the surgeon told her that her daughter had been misdiagnosed and should have undergone testing when her headaches persisted. This report was not medically confirmed.

The second report of death is a literature report originating from a consumer who reported that a female friend died after using Excedrin[®] for pain and Vioxx[®] for arthritis. She reported that the combination "destroyed her stomach." No additional information was provided in the literature report.

The most frequently reported (>5%) serious AE reports describe Drug Dependence, Deafness, Overdose, Gastric Ulcer Hemorrhage, and Headache. The reports of Drug Dependence, Gastric Ulcer Hemorrhage, and Overdose are described in more detail in their respective sections of this report.

**BMS AE Database Reports (N=120) of Excedrin[®] Migraine
and Excedrin[®] Extra Strength Most Frequently Reported
Serious Events
1/1/98 to 2/28/01**

AE TERM	FREQUENCY
Drug dependence	38 (31.7%)
Deafness NOS	15 (12.5%)
Overdose NOS	13 (10.8%)
Gastric ulcer hemorrhage	11 (9.2%)
Headache NOS	6 (5.0%)

There were 15 reports coded as "Deafness" and categorized as serious. Hearing loss is a recognized complication of excessive ASA use. Eleven of these reports originated directly from consumers and only 4 were medically confirmed by a health professional. Twelve reports described tinnitus as a concurrent AE, which is also a known side effect of excessive ASA use. In one medically confirmed report, the patient had a prior medical history of deafness and multiple sclerosis. In 10 of 15 reports where information on duration of use was available, the duration of use ranged from 1 dose to 30 years. Seven of the 10 reports described use of Excedrin[®] for greater than 14 days. No information on duration was available for 5 reports. One patient was reported to recover. Information on outcome is unknown for 14 of 15 cases. In the absence of information on hearing testing and past medical history on hearing function, it is difficult to conduct a meaningful assessment of the causal relationship between the events reported and the use of Excedrin[®]. Details of individual reports are presented below:

**BMS AE Database Reports of Deafness
January 1998 - February 2001**

CASE NO.	AGE	SEX	DOSE	CONCOMITANT MEDICATIONS	ADDITIONAL HISTORY	ADDITIONAL AE TERMS	OUTCOME
10107241	46	F	2 Tabs X Unk Duration	Unk	Unk	Tinnitus	Not recovered
10287597	50	M	1 Tab PRN X Unk Duration	Flonase	Sinusitis Rhinitis	Tinnitus	Not Recovered
10310019	Unk	F	Unk	Unk	Unk	Tinnitus	Unk
M078675	57	F	2 tabs once	Unk	Unk	Tinnitus	Unk
M079882*	66	M	6 tabs qd x 10 yrs	Xanax Surmontil	Multiple sclerosis Depression Deafness	Tinnitus	Not recovered
M082898	36	F	2 tabs prn x 25 yrs	Thyroid medication	TMJ Thyroid condition Allergies Gastric acidity Stress Headache Sinusitis	Laryngitis NOS Dyspepsia	Unk
M083532	43	F	1-3 tabs qd prn x 3 months	None	Drug allergies	Tinnitus	Unk
M088663*	40	F	2 tabs x 1 dose	Prempro Toprol	Mitral valve prolapse Back disorder NOS	Tinnitus Dizziness Drug ineffective Vision blurred Paresthesia NEC Asthenia Vomiting NOS	Not recovered
M089066	62	F	8 tabs qd x 35 yrs	Claritin	Migraines	None	Unk
M089074*	56	M	2-4 tabs qd x 10 yrs	Multivitamin Vitamins C, E Celebrex Zyban	Headache	Tinnitus	Not recovered
M090477*	59	M	9-18 tabs qd x 30 yrs	Buspar Phenergan Remeron Amerge Migranal Prilosec Zolofl Librium Sudafed	Migraines Rebound headaches Depression Anxiety Peptic ulcer disease Tobacco use	Tinnitus Condition aggravated Drug dependence Blindness transient Gastric ulcer hemorrhage Headache NOS Depression NEC	Unk

CASE NO.	AGE	SEX	DOSE	CONCOMITANT MEDICATIONS	ADDITIONAL HISTORY	ADDITIONAL AE TERMS	OUTCOME
						Anxiety NEC Photophobia	
M092227	Unk	F	2 tabs q 6 hrs x 14 days	Biaxin Theraflu Tylenol Cold Robitussin Pediacare	Ear infection	Tinnitus Earache Ear disorder NOS	Recovered
M092781	51	F	2 tabs prn x "yrs"	None	Migraines	Tinnitus	Unk
M093238	28	F	2 tabs x 1 dose	None	Migraines	Tinnitus	Unk
M096312	44	F	Unk x 5- 6 doses	Amoxicillin Premarin Provera Synthroid	Allergies Sinusitis Hypothyroidism	None	Unk

*Medically confirmed

The AE reports are generally consistent in nature and severity with those seen with the individual components. They do not signal any new or unexpected safety concerns with Excedrin® Extra Strength.

Aspirin Free Excedrin® (APAP 1000mg/CAF 130mg per dose)

Historical postmarketing AE data for the time period October 1995 – April 1997 was assessed by BMS in preparation for the July 15, 1997 Excedrin® Migraine Advisory Committee meeting. During this time period BMS received 544 AE reports for Aspirin Free Excedrin®. The most frequently reported AEs (>5%) were in the Body as a Whole, Nervous System and Digestive body system organ classes and included No Drug Effect (N=114, 21%), Insomnia (N=59, 10.9%), Nervousness (N=40, 7.4%), and Nausea (N=36, 6.6%).

From January 1999 – February 2001, BMS received a total of 262 AE reports which described 396 individual events (a report can describe multiple clinical events). The vast majority of these were classified as nonserious (N=259) and were not medically confirmed. There were 3 reports classified as serious. One report (M095121) describes impaired hearing, tinnitus, dizziness, and taste disturbance in a 54 year-old female. Another report (10242261) describes aggravation of nausea in a 33 year-old female. The third report (10062867) describes drug dependence in a female of unknown age, which will be described in greater detail in Section 6.3.6.1.1. These reports do not signal any new or unexpected safety concerns with Aspirin Free Excedrin®.

The most frequently reported AEs (>5%) were consistent with the known safety profile of APAP and caffeine and are presented below:

**BMS AE Database (N=262) of Aspirin Free Excedrin®
Most Frequently Reported AEs
1/1/99 - 2/28/01**

AE TERM	FREQUENCY
Drug Ineffective	103 (39%)
Nausea	30 (11.4%)
Insomnia NEC	21 (8%)
Abdominal Pain NOS	15 (5.7%)
Dizziness (exc vertigo)	13 (5.0%)

6.2.2.2 FDA AE Database for Non-BMS Caffeinated Analgesic Products

Between 1991-2000, the FDA received a total of 44 reports describing 132 adverse events for all non-BMS caffeinated analgesic products (ASA/CAF, APAP/CAF, APAP/ASA/CAF). Included in these reports were 6 reports of Overdose and 13 reports of GI hemorrhage, which are addressed in more detail in the sections on Overdose (Section 6.3.4.1.2) and GI Bleeding (Section 6.3.3.1.2) with caffeinated analgesic products. The most frequently reported events were Gastrointestinal Hemorrhage NOS (N=13), Hematemesis (N=9), Anemia NOS (N=6), Overdose (N=6), Hypochromic anemia (N=4), Melena (N=4), Nausea (N=4), and Vomiting NOS (N=4). When examined by specific product, these AEs were reported only for the ASA-containing products, which is consistent with the known pharmacologic profile of ASA.

Reports classified as "serious" include 25 (90 events) with ASA/CAF, 7 with APAP/CAF (16 events), and 5 reports with ASA/APAP/CAF (13 events). The most frequently reported serious AEs in these reports were Gastrointestinal Hemorrhage (N=13), Hematemesis (N=8), and Anemia NOS (N=6). Also of note was 1 report of Drug Abuse with APAP/CAF that is discussed in more detail in Section 6.3.6.1.2.

The AE reports received by the FDA for non-BMS caffeinated analgesic products are generally consistent in nature and severity with those received by BMS for Excedrin® and do not signal any new or unexpected safety concerns.

6.2.2.3 WHO Adverse Event Database for Caffeinated Analgesic Products

Between 1995 and March 27, 2001, WHO received an unknown number of reports describing 343 AEs with caffeinated analgesic products (APAP/ASA/CAF – 253, ASA/CAF – 79, APAP/CAF – 11). The most frequently reported events are summarized below:

**WHO Database Reports of Most Frequently Reported AEs
with Caffeinated Analgesic Products
1995 – March 27, 2001**

AE Term	Count	Percent (N=363)
GI Hemorrhage	19	5.5
Melena	15	4.4
Nausea	15	4.4
Abdominal Pain	12	3.5
Therapeutic Response Decreased	12	3.5
Dyspnea	9	2.6
Face Edema	8	2.3
Hematemesis	8	2.3
Stevens Johnson Syndrome	8	2.3
Vomiting	8	2.3
Dizziness	7	2.0
Tremor	7	2.0

During this time period WHO received 71 reports designated as containing a Critical Term (APAP/ASA/CAF – 44, ASA/CAF – 25, APAP/CAF – 2). Twenty-four (24) reports were submitted by manufacturers and 47 were unclassified spontaneous reports. The majority of the reports originate from the US, however, it was not possible to distinguish how many of these reports were from BMS.

The most commonly reported Critical Terms were related to GI bleeding events which are discussed in greater detail in Section 6.3.3.1.3. All reports describing a GI bleeding event were associated with ASA-containing products. Details regarding dose, duration of therapy, age, sex, time to event onset, other suspect or concomitant medications, and past medical history are frequently absent from the WHO case information, limiting meaningful assessment of these cases.

There were 2 reports with the outcome of Death, both reported with APAP/ASA/CAF. In one report, the patient experienced Stevens Johnson Syndrome and cardiac arrest. In the second report, the patient experienced multiorgan failure. Unfortunately, there is no additional information on concomitant drugs, past medical history, dose, or duration of therapy, thereby limiting assessment of these cases. Details of the reports are presented below:

**WHO AE Database Caffeinated Analgesic Reports with Fatal Outcome
1995 - March 27, 2001**

YEAR	RECNO	AGE	SEX	ONSET	CRITICAL TERMS	REPORT TYPE	SOURCE	OUTCOME
1998	981562653	45Y	F	17-Mar-98	Death Cardiac Arrest Stevens Johnson Syndrome	NC:spont	Not spec.	Died
1999	992330768	30Y	F	01-Jan-99	Death Hypertension Encephalopathy GI Hemorrhage Hepatic Failure Acidosis	Mf:Spont	G.P.	Died

*All reports including death as an outcome were received from the United States. Amounts/units were omitted because none were reported.

6.2.2.4 Conclusions from Spontaneous AE Reports

The reported AEs in the WHO database are generally consistent in nature and severity with the known pharmacologic profiles of ASA and APAP, as well as the AEs reported to both BMS and the FDA, and do not signal any new safety concerns.

6.3 Safety Issues of Special Interest with Caffeinated Analgesic Products

6.3.1 Analgesic Nephropathy

One of the most significant toxicities associated with analgesic products is analgesic nephropathy. End-stage renal disease (ESRD) is estimated to occur at a rate of 0.02% annually in the US. The etiology is varied, however, analgesic-associated nephropathy (AAN) only accounts for approximately 0.8% of cases (United States Renal Data System 1996). A Group Health Cooperative study confirmed the rare occurrence of AAN in a study conducted in 378,769 OTC analgesic users from 1984-1989. Among this group, only 17 cases of newly diagnosed, unexplained renal disease were identified. Only 2 of these cases were suspected to have a possible association with OTC analgesic, however, other causes were also considered as equally likely (Derby 1991).

Phenacetin-containing analgesics have been shown to be the most important risk factor for the development of AAN (Delzell 1998, Bach 1998). However, the association between nonphenacetin-containing combination analgesics, the development of ESRD and AAN disease, and their possible association with past use of phenacetin, is still the subject of considerable debate.

In an effort to address this issue, the regulatory agencies of Germany, Austria, and Switzerland convened a group of experts in 1999 to review the worldwide literature on analgesic nephropathy and answer the primary question of whether the literature contained sufficient evidence to conclude that combined nonphenacetin-containing analgesics cause nephropathy. Another question was whether scientific evidence exists to show that the combination of analgesic drugs with caffeine increases nephrotoxicity (Ad Hoc Committee of the International Study Group on Analgesics and Nephropathy 2000). The committee examined the following data:

Epidemiologic studies

The committee identified 4 analytic and 2 ecologic studies that investigated the association between nephropathy and the use of various analgesics in combination, 1 cohort study and 3 case-control studies (Elseviers 1995, Pommer 1989, Morlans 1990, Murray 1983, Elseviers 1994, Michielsen 1998).

The committee, as well as several other authors who separately reviewed these data, found methodological weaknesses with all of these studies and were therefore unable to concur with the authors' earlier conclusions. Examples of some of these methodological limitations are inclusion of subjects with pre-existing renal abnormalities, poor or no exposure measurement, inadequate consideration of predisposing factors to renal disease or heavy analgesic use, possible selection biases, failure to distinguish between prior drug use relative to renal disease onset, inappropriate control selection, and confounding by phenacetin. In addition, studies that directly compared combination analgesics without phenacetin to single ingredient analgesics did not take into account the significantly different doses of analgesic taken by each group (Bach 1998, Shapiro 1998).

With respect to appropriate diagnosis of AAN, the committee felt that identification criteria for AAN should be reappraised with scientific methods that validate the diagnostic tests, independent of exposure information. This conclusion was based on the fact that papillary calcification is not specific for AAN and in clinical practice a specific diagnosis of AAN is almost never accompanied by histologic evidence, but is usually based on information about exposure before or during the early stages of the disease.

Experimental Pharmacologic Evidence

After reviewing the studies exploring the mechanism of AAN in animals, in vitro systems, and humans, the committee concluded that the limited amount of experimental pharmacologic data in humans and animals offered no convincing evidence that non-phenacetin combined analgesics are either as safe as or more nephrotoxic than single formulations. Furthermore, the currently available evidence did not associate a specific harmful effect with caffeinated analgesics versus non-caffeinated formulations.

The committee's conclusions were based on the following data:

- The hypotheses for the medullary toxicity of APAP and its increased toxicity in the presence of salicylate are largely unverified extrapolations to humans from artificial in vitro systems.
- The essential cofactor of a suggested synergistic toxicity of APAP plus salicylates is the depletion by salicylate of glutathione in the renal medulla, but this effect is not well documented in animals.
- Humans given APAP for 2 consecutive days showed no indication of a potentiating effect on the inhibition of prostaglandin synthesis by ASA.
- Long-term toxicological studies, carcinogenicity studies, and animal experiments trying to induce analgesic nephropathy did not show an additional nephrotoxic effect when caffeine was added to combined analgesics.

From the available epidemiologic evidence, the committee decided that the existing data were inconclusive regarding the relationship between non-phenacetin combination analgesics and the occurrence of nephropathy. Furthermore, no data was found to support or refute the hypothesis that co-formulation with caffeine elevated the risk of nephropathy.

This opinion is supported by other authors, who have concluded that the most significant risk factor for the development of AAN appears to be phenacetin. While there are rare reports of AAN in patients who received only acetaminophen, due to limited information on concomitant or prior use of other analgesics, it is difficult to assess the causal relationship to APAP alone (Bach 1998). With regard to ASA/APAP mixtures, there is no evidence to support the proposition that they are associated with a higher degree of risk of AAN than either substance alone (Delzell 1996).

Furthermore, there is no evidence that the addition of caffeine to analgesic products increases the risk of AAN compared to non-caffeinated analgesics. Rather, the analgesic adjuvancy property of caffeine which enables smaller doses of analgesics to be used in caffeinated analgesics may be advantageous in helping decrease the risk of analgesic overuse.

6.3.1.1 Spontaneous AE Reports of Renal Events with Caffeinated Analgesics

6.3.1.1.1 BMS AE Database Reports of Renal Events with Excedrin® Products

BMS spontaneous AE reports were examined for reports of renal events possibly associated with AAN for Excedrin® Migraine, Excedrin® Extra Strength, and Aspirin Free Excedrin.® From January 1998 - February 2001, there were 13 reports for Excedrin® Migraine and Excedrin® Extra Strength that contained a renal event. From January 1999 - February 2001, there were 3 reports of renal

events with Aspirin Free Excedrin[®]. For all 3 products, the reported events were generally nonspecific events such as urinary frequency, urogenital disorder NOS, micturition difficulty and renal impairment NOS, which could be associated with a variety of clinical conditions. None of the reported events were classified as "serious" and all were reported by consumers and not medically confirmed. These reports lack sufficient details on medical history, therapy duration, and concomitant medications, thereby limiting interpretation of the data. There were no events suggestive of end-stage renal failure.

6.3.1.1.2 FDA AE Database Reports of Renal Events with Non-BMS Caffeinated Analgesic Products

From 1991-2000, the FDA received 2 reports of renal events. One report was a Urinary Tract Infection in association with a suicide attempt with Anacin[®] and Aleve[®]. The second report was coded as "BUN Increased" and "ALT Increased" and describes a 39 year-old male who was hospitalized after ingesting Anacin[®], Excedrin[®], Tylenol[®] with Codeine, Excedrin PM[®], and phenobarbital. Neither of these reports contained events suggestive of analgesic nephropathy, although without more detailed information regarding the cause and course of hospitalization for the report of BUN and ALT elevations, evaluation of this case is limited.

6.3.1.1.3 WHO AE Database Reports of Renal Events with Caffeinated Analgesic Products

The WHO database from 1995 to March 27, 2001 revealed one report of renal function abnormality and hypercalcemia with APAP/ASA/CAF in a 74 year-old female and one report of interstitial nephritis with ASA/CAF. There was no additional information available for either of these cases.

6.3.1.1.4 Summary – Analgesic Nephropathy

The relationship between analgesics and the development of analgesic nephropathy is still the subject of debate, however, the only clear risk factor identified and agreed upon by experts is previous use of phenacetin-containing analgesics. Many experts in this area, including a recent panel of experts convened by the regulatory authorities of Germany, Austria, and Switzerland, have concluded that there is insufficient evidence to claim that analgesics, in the absence of phenacetin, are causally associated with nephropathy. Similarly, there is no evidence that the addition of caffeine to analgesics is associated with nephropathy.

The data on renal events from the BMS, FDA, and WHO revealed no spontaneous reports suggestive of analgesic nephropathy with caffeinated analgesic products.

6.3.2 Effect of Caffeine on the Biotransformation of Acetaminophen

The effect of caffeine on the biotransformation of APAP has been studied in various animal species and in humans. Details of these data are presented in Appendix 3.

Studies in mice and in rats have shown that caffeine can induce both a protective effect, as well as enhanced toxicity of APAP, respectively. Timing of the dose relative to APAP, pretreatment with microsomal enzyme inducing agents, and in rats, the age and sex of the animals, affected study results (Rainska-Giezek 1995, Jaw 1993, Rainska 1992, Gale 1998, Price 1987, Gale 1987, Gale 1986, Lee 1996, Sato 1985, Sato 1989, Kalhorn 1990, Lee 1991, Lee 1990). When caffeine was co-administered with ASA and APAP in dogs in the same ratio to that of Excedrin,[®] there was no effect on the blood levels of either ASA or APAP (Mueller 1994). Possible explanations for the differences between the species include differences in the relative affinities of APAP and caffeine for hepatic CYP-450 isoenzymes, and differences in composition and proportion of isoenzymes between species.

In light of these preclinical findings, a review of pertinent human clinical data was undertaken. Five human pharmacokinetic studies have been conducted in which caffeine was administered concurrently with APAP in typical doses used in caffeinated analgesics. Four of the 5 studies showed that APAP blood level concentrations were either lower or did not change with concurrent caffeine as compared to APAP alone (Rainska 1992, Wojcicki 1994, Thomas 1972, Battikha 1982). In another study, caffeine did not statistically increase absorption of APAP as compared to APAP alone (Tukker 1986). Only one study showed a 29% increase in AUC, 15% increase in C_{max}, and 32% decrease in total body clearance of APAP when caffeine 60mg and APAP 500mg were given to healthy volunteers (Iqbal 1995). Differences in results between studies may be due to study design, as well as inter-individual differences in metabolism, fasting state, and external caffeine consumption among the study subjects.

Clinically, if concurrent caffeine/APAP ingestion enhanced the toxicity of APAP, one would expect to see hepatotoxicity occurring at doses lower than the 15g APAP typically associated with hepatotoxicity. Based on the spontaneous AE data from BMS, FDA, WHO, and TESS for caffeinated analgesics, this phenomenon does not appear to be evident, despite the limitations in evaluating this data.

In conclusion, human pharmacokinetic studies and spontaneous AE data do not appear to signal a clinically significant interaction between caffeine and APAP.

6.3.3 Hepatotoxicity

Hepatotoxicity is a well-recognized complication of APAP overdose, as discussed earlier. Neither ASA nor caffeine is typically associated with the development of hepatotoxicity, therefore, reports of hepatotoxicity with caffeinated analgesic products, in the absence of other confounding factors, are most likely due to the APAP component of the product.

6.3.3.1 Spontaneous AE Reports of Hepatotoxicity with Caffeinated Analgesics

6.3.3.1.1 BMS AE Database Reports of Hepatotoxicity with Excedrin® Products

Between January 1998-February 2001, BMS received one report possibly suggestive of severe liver injury with Excedrin® Migraine. A consumer reported that her 38 year-old husband took Excedrin® Migraine 2 tablets daily for approximately 6 months for the treatment of chronic headache secondary to previous head trauma. He experienced "unspecific problems relating to his liver and kidneys" which caused him to have an elevated blood alcohol level beyond what was expected based on alcohol consumption. According to the reporter, he sought medical attention, however, the specific problem could not be diagnosed by his physicians. Concomitant medications included sumatriptan and fluticasone. This report was not medically confirmed.

There were no reports of hepatotoxicity with Excedrin® Extra Strength or Aspirin Free Excedrin® during this time period.

6.3.3.1.2 FDA AE Database Reports of Hepatotoxicity with Non-BMS Caffeinated Analgesic Products

Between 1991-2000, the FDA received 2 reports of severe hepatic injury with non-BMS caffeinated analgesic products (ASA/CAF). In both cases, APAP was not a component of the product, however, alcohol was a concomitant drug. Additional information regarding the amount and duration of alcohol consumption, duration of use for the analgesic product, and relevant medical history is not available. Severe liver injury is a well-recognized consequence of chronic alcohol use. A summary of the individual reports is presented below:

**FDA AE Database Reports of Hepatotoxicity with Non-BMS Caffeinated Analgesics
1991 - 2000**

IMAGE ID	AGE	SEX	DRUG: DOSE	CONCOMITANT MEDICATIONS	AE TERMS	OUTCOME
M01527291	47	M	ASA/CAF: 5 GM (Anacin-3)	Alcohol	Abdominal Pain NOS Nausea Hepatic Necrosis Jaundice Cholestatic	Hosp
M01517795	23	F	ASA/CAF: 14.0 GM (Anacin-3)	Alcohol	Jaundice NOS Overdose NOS Liver Function Tests NOS Abnorm Encephalopathy NOS	Hosp

6.3.3.1.3 WHO AE Database Reports of Hepatotoxicity with Caffeinated Analgesics

Between 1995 and March 27, 2001, WHO received 1 report of fatal hepatic failure and encephalopathy with APAP/ASA/CAF in a 30 year-old female. This report originated from a manufacturer in the US and was reported by a health professional. Additional AE terms included in this report were GI hemorrhage, hypertension, and acidosis. No additional information on dose, duration of therapy, relevant medical history, or concomitant medications is available for this report, limiting assessment of this case.

6.3.3.1.4 Summary – Hepatotoxicity

Hepatotoxicity is a well-recognized complication of APAP overdose and is not usually associated with the use of ASA or caffeine. In examining the spontaneous reports for Excedrin,[®] non-BMS caffeinated analgesics, and the WHO data for caffeinated analgesics, there were only 3 reports of severe hepatic injury. Alcohol was a known concurrent drug in 2 of these cases. While the lack of detailed information on these reports limits their meaningful assessment, severe hepatotoxicity appears to be a rare occurrence with caffeinated analgesics.

6.3.4 GI Bleeding

GI bleeding is a known complication of ASA use, as discussed previously. Neither APAP nor caffeine is known to be associated with GI bleeding, therefore, reports of GI bleeding with caffeinated analgesics, in the absence of other confounding factors, are most likely associated with the aspirin component of the product.

6.3.4.1 Spontaneous AE Reports of GI Bleeding with Caffeinated Analgesics

6.3.4.1.1 BMS AE Database Reports of GI Bleeding with Excedrin® Products

Excedrin® Migraine and Excedrin® Extra Strength

Between 1984 -February 2001, BMS received 46 reports with Excedrin® Migraine/Excedrin® Extra Strength describing various clinical presentations of GI bleeding. These reports included the terms, Gastric Ulcer Hemorrhage, Blood in Stool, Hematemesis, Rectal Bleeding, Gastrointestinal Hemorrhage NOS, Hemorrhage NOS, Duodenal Ulcer Hemorrhage, Diarrhea Hemorrhagic, Melena, Esophageal Hemorrhage, Ulcer Hemorrhage NOS, and Upper GI Hemorrhage. Eighteen (18) of these reports were classified as serious. Thirty-nine (39) of these reports were reported spontaneously and 2 originated from BMS Phase IV clinical trials. Of the spontaneous reports, only 4 were medically confirmed. Detailed information on dose, duration, concomitant medications, and past medical history is not available for many of these reports, however, over half the reports described duration of use beyond the labeled recommendation. Where this information is available, 15 reports mentioned previous history of ulcer disease or other GI disorder. In 3 cases, drug dependence was also mentioned as an additional AE. Twenty-one (21) patients were reported to recover and outcome is unknown for the remaining cases.

In the two Phase IV clinical trial reports, Excedrin® was not the study drug, but was considered a suspect drug associated with development of GI bleeding. In the first report, a 77 year-old female was participating in a diabetes trial of metformin versus conventional intervention (Protocol CV 138-002). On the day she received study drug (glyburide 10mg), she was admitted to the hospital with a bleeding gastric ulcer. Six months later she was diagnosed with gastric ulcer, esophageal stricture, and esophageal stenosis by endoscopy. Concomitant drugs included Excedrin®, warfarin, calcium carbonate, and furosemide. The patient had multiple medical conditions, but not a documented history of ulcer disease. In the second report, a female patient (age unknown) was participating in a pravastatin trial (Protocol 800-01-98) and was admitted to the hospital with a bleeding stomach ulcer, diagnosed by endoscopy. Excedrin® and ASA were considered the suspect drugs associated with this event. Concomitant medications included vitamins E and C, and a multivitamin with iron. There was no documented past history of ulcer disease. The patient was subsequently found to have *H. pylori* infection.

Aspirin Free Excedrin®

BMS received 2 reports of GI bleeding with Aspirin Free Excedrin® between January 1998-February 2001. One report described an 82 year-old female who experienced rectal bleeding after receiving Aspirin Free Excedrin®. No additional

information was available. The second report described unspecified "hemorrhage" but contained no additional information.

While GI bleeding is a known complication of ASA use, in the absence of detailed relevant information on these reports, it is not possible to perform a meaningful assessment of the causal relationship between the adverse events and Excedrin.[®]

Details of the Excedrin[®] Extra Strength and Excedrin[®] Migraine reports are presented below:

**BMS AE Database Reports of Gastric Hemorrhage
with Excedrin[®] Migraine and Excedrin[®] Extra Strength
1984 - February 2001**

CASE NO.	AGE	SEX	DOSE	CONCOMITANT MEDS	ADDITIONAL HISTORY	AE TERMS	OUTCOME
9516	48	F	As directed x 5 days	Unk	Unk	Gastric ulcer hemorrhage Hematemesis Syncope Pain abdominal Anemia Tachycardia	Hospitalized Unk
1552181	Unk	Unk	Unk	Unk	Unk	Gastric ulcer hemorrhage	Unk
261907-1	Unk	Unk	Amt. Unk x 20 years	Unk	Unk	Gastric ulcer hemorrhage	Unk
348780-1	Unk	F	Amt. Unk x 3 days	Unk	Unk	Gastric ulcer hemorrhage	Hospitalized Unk
27125-1	53	F	500mg bid x few days	Unk	Unk	GI hemorrhage NOS	Unk
10146819	Unk	Unk	Unk x "quite some time"	Unk	Unk	Gastric ulcer hemorrhage	Hospitalized Unk
10155778	Unk	F	2-4 tabs qd x unk duration	Calan Diuretic Prevacid	Headache Pain NOS Hypertension	Gastric ulcer hemorrhage Upper GI hemorrhage Rectal bleeding Hemoglobin decreased	Hospitalized Recovered
10182095	87	M	Unk dose 1-2 x daily x "many" yrs	Unk	Unk	Gastric ulcer hemorrhage Dizziness Drug dependence	Hospitalized Recovered
10261360	Unk	F	Unk	Unk	Migraine	Gastric ulcer hemorrhage	Hospitalized Unk
10321412	33	F	Unk dose up to qid x yrs	Unk	Ulcer NOS Thyroidectomy	Gastric ulcer hemorrhage	Hospitalized Recovered
M075752	49	F	Unk dose qd x 15 yrs	Tagamet Prilosec	Ulcer NOS Migraine	Gastric ulcer hemorrhage	Hospitalized Unk
M087846*	38	M	Unk dose qid x 10 yrs	Prilosec Tylenol #3	Bleeding ulcer Peptic ulcer Tension headache Alcoholism Toxic shock syndrome NOS	Gastric ulcer hemorrhage Loss of consciousness NEC Nausea Weakness Condition aggravated Hematemesis	Hospitalized Recovered

CASE NO.	AGE	SEX	DOSE	CONCOMITANT MEDS	ADDITIONAL HISTORY	AE TERMS	OUTCOME
						GI hemorrhage NOS Pallor Sweating increased Discomfort NOS Headache NOS Dizziness Cardiovascular disorder NOS Postural hypotension	
M090477*	59	M	9-18 tabs qd x 30 yrs	Buspar Phenergan Remeron Amerge Migranal Prilosec Zoloft Librium Sudafed	Migraines Rebound headaches Depression Anxiety Peptic ulcer disease Tobacco use	Tinnitus Condition aggravated Drug dependence Blindness transient Gastric ulcer hemorrhage Headache NOS Depression NEC Anxiety NEC Photophobia	Disability
M093996	43	F	Unk x "yrs"	Imitrex	Migraines Headaches	Gastric ulcer hemorrhage Drug dependence Drug withdrawal syndrome	Hospitalized Unk
M094565	Unk	F	Unk	Unk	Unk	Gastric ulcer hemorrhage	Hospitalized Unk
M089328	31	F	1 tab 3-4 x weekly x 8 mos	None	Migraines	Urticaria NOS Edema peripheral Diarrhea hemorrhagic Face edema Hematemesis	Recovered
10261352	50	M	Unk x 2 doses	Zantac	Duodenal ulcer w/ vagotomy Gastric ulcer hemorrhage requiring surgery Alcoholism Hypercholester- olemia Appendectomy	Duodenal ulcer hemorrhage	Hospitalized Disability
M073331*	41	M	2 tabs x 1 dose	Unk	Esophageal reflux	Duodenal ulcer hemorrhage	Hospitalized Recovered
10688232	Unk	M	Unk x yrs	Unk	Unk	Gastrointestinal hemorrhage NOS	Hospitalized Unk
M079760	48	F	2 tabs x 3 doses over 2 mos	Prilosec	Migraines Esophageal reflux	Gastrointestinal hemorrhage NOS Hematemesis Syncope	Hospitalized Recovered
M086679	41	F	2 tabs x 1 dose	None	Migraines Gastrointestinal hemorrhage Panic disorder	Gastrointestinal hemorrhage NOS	Recovered
10087203	28	F	17 tabs x 1 day	Unk	Unk	Hematemesis	Recovered
10202034	22	M	Unk	Unk	Unk	Hematemesis Diarrhea NOS Vomiting NOS	Unk
M079354	40	F	2 tabs x 1 dose	Ativan Estradiol	Bipolar disorder Gastric ulcer	Hematemesis Diarrhea NOS	Recovered

CASE NO.	AGE	SEX	DOSE	CONCOMITANT MEDS	ADDITIONAL HISTORY	AE TERMS	OUTCOME
				Pepto-bismol	Colitis Migraines	Abdominal pain NOS Vomiting NOS Malaise Pain NOS	
M087043	47	F	2 tabs q 30 min x 2 doses	Midrin Folate Percocet Claritin	Multiple allergies Sickle cell disease Migraine Joint disorder	Hematemesis Vision blurred Drug ineffective	Recovered
10716546*	Unk	F	Unk x 23 yrs	Unk	Migraines	Esophageal erosions Drug maladministration	Unk
10139608	52	F	Unk	Unk	Irritable bowel syndrome Esophageal reflux Multiple allergies	Epistaxis Ecchymosis Rectal bleeding Dyspepsia	Unk
10197077	Unk	F	Unk x 7 days	Unk	Unk	Rectal bleeding	Unk
10549616	16	F	½ tab x 1 dose	Flexeril	Celiac disease Fibromyalgia	Rectal bleeding	Unk
M077025	37	M	Unk dose x 6 in one day	Unk	Unk	Rectal bleeding Rectal disorder NOS	Unk
M080947	75	M	2 tabs bid x 10 yrs	None	Hemorrhoids Arthritis	Rectal bleeding	Recovered
10118362	Unk	Unk	Unk dose qd x "very long time"	Unk	Unk	Hemorrhage NOS	Unk
10190171	55	M	2 tabs q 4-6 hrs x 2-3 mos	Fiorinal	Migraines Hypertension	Hemorrhage NOS	Hospitalized Recovered
M095651	Unk	F	Unk	Unk	Unk	Hemorrhage NOS	Unk
10335750	Unk	F	Unk x "many" yrs	Unk	Headaches Hypertension	Ulcer hemorrhage NOS	Hospitalized Recovered
10084630	53	F	Unk	Unk	Hypertension	Blood in stool	Unk
10419588	21	M	2 tabs prn x unk duration	Unk	Headaches	Blood in stool	Unk
10467603	Unk	F	1 tab qd x 10 yrs	Unk	Unk	Abdominal pain upper Blood in stool	Unk
M079506	37	F	2 tabs x 1 dose	Prevacid	Esophageal reflux	Blood in stool	Recovered
M079593	45	M	2 tabs x 1 dose	None	Hemorrhoids Headaches Rhinitis	Blood in stool	Recovered
M081453	39	F	2 tabs qd x 3 mos	Imipramine	Depression Migraines	Blood in stool Abdominal pain upper Loose stools	Recovered
M081694	Unk	F	2 tabs x 1 dose	None	Headaches	Diarrhea NOS Vomiting NOS Blood in stool	Recovered
M095252	22	F	2 tabs prn "for awhile"	Loestrin	Headaches Contraception NOS	Blood in stool	Unk
M079804	23	F	Unk dose x 6 weeks	None	Headaches Constipation	Melena	Unk

*Medically confirmed

**BMS Phase IV Clinical Trial Reports of Gastric Ulcer Hemorrhage
January 1998 - February 2001**

CASE NUMBER	AGE	SEX	DOSE	AE TERMS	REPORTER CAUSALITY	OUTCOME
10085017	77	F	6 tabs qd x unk duration	Gastric ulcer hemorrhage Esophageal ulcer Esophageal stenosis	Lik	Rvd
10215457	Unk	M	Unk	Gastric ulcer hemorrhage	Poss	Rws

SOURCE: P – PHASE IV. **CAUSALITY:** LIK – PROBABLY, UNK – UNABLE TO DETERMINE, POSS – POSSIBLY. **OUTCOME:** RVD – RECOVERED/RESOLVED, NRD – NOT RECOVERED/NOT RESOLVED, RWS – RECOVERED/RESOLVED WITH SEQUELAE

6.3.4.1.2 FDA AE Database Reports of GI Bleeding with Non-BMS Caffeinated Analgesic Products

Between 1991-2000, FDA received 20 reports containing a total of 29 events of GI bleeding with non-BMS caffeinated analgesic products, including 18 with ASA/CAF and 2 with APAP/ASA/CAF. Nineteen (19) of these reports were classified as “serious” on the basis of requiring hospitalization. There were no reported deaths. In 10 of the cases, additional NSAID products were also identified as also being suspect, including indomethacin, BC Powder,[®] Trilisate,[®] Orudis,[®] Vioxx,[®] Advil,[®] Celebrex,[®] and ASA. Information on dose, duration of treatment, relevant medical history is not available. The reports in the FDA database are generally similar in nature and severity to those reported to BMS. Reported GI bleeding events, by product, are presented below:

**FDA AE Database Reports of GI Bleeding with Non-BMS Caffeinated Analgesics
1991 - 2000**

AE TERM	COUNT OF GI BLEEDING TERMS		TOTAL COUNT
	ASA/APAP/CAF	ASA/CAF	
Gastrointestinal hemorrhage NOS	2	10	12
Hematemesis	1	7	8
Melena	1	3	4
Rectal hemorrhage	0	2	2
Blood in stool	0	1	1
Upper gastrointestinal hemorrhage	0	1	1
Duodenal ulcer hemorrhage	1	0	1
TOTALS	5	24	29

6.3.4.1.3 WHO AE Database Reports of GI Bleeding with Caffeinated Analgesic Products

Between 1995 and March 27, 2001, WHO received an unknown number of reports describing 46 events of GI bleeding reported with caffeinated analgesic products, 22 events with ASA/CAF and 24 events with APAP/ASA/CAF. Reported GI bleeding events, by product are presented below:

WHO AE Database Reports of GI Bleeding with Caffeinated Analgesics
1995 - March 27, 2001

CRITICAL AE TERM	COUNT OF GI BLEEDING TERMS		TOTAL COUNT
	ASA/CAF	APAP/ASA/CAF	
GI hemorrhage	11	8	19
Melena	6	9	15
Hematemesis	4	4	8
Gastric ulcer hemorrhagic	0	3	3
Hemorrhage rectum	1	0	1
TOTALS	22	24	46

There were 24 reports with a GI bleeding event which contained a WHO Critical Term. Over half of the reports (N=15) originated from the US, however, it is not possible to determine if any of the reports were from BMS. Seven of the reports contain more than 1 AE term for GI bleeding. Where this information is available, 11 patients required hospitalization and 5 patients recovered. There was one death reported which described GI hemorrhage in conjunction with hepatic failure and encephalopathy with APAP/ASA/CAF in a 30 year-old female. This case was previously discussed in the context of hepatotoxicity in Section 6.3.3.1.3. There is no information available regarding total dose, duration of treatment, concomitant drugs, and relevant medical history for any of the cases, therefore it is difficult to assess the causal relationship between the suspect product and the reported adverse events. Based on the available information, these reports appear to be consistent in nature and severity to those reported to BMS and the FDA.

6.3.4.1.4 Summary – GI Bleeding

GI Bleeding is a known complication of ASA use and is not typically associated with the use of APAP or caffeine. Over the period reviewed, BMS, FDA, and WHO received 12, 20, and 46 reports, respectively, of GI bleeding events. Approximately half of the WHO reports originated from the US, however, it was not possible to determine if any of these were duplicates of the BMS reports. Detailed information on dose, duration, concomitant drugs and prior history of ulcer disease is not available for many of these reports, however, in the BMS data, some patients reported long term use of Excedrin[®] and in 4/9 patients, a

history of ulcer disease was noted. In the FDA data, 10/20 cases reported additional suspect drugs which are known to also be associated with GI bleeding. There was one death reported to WHO which also involved hepatic failure and encephalopathy. Despite the limited information available for these reports, cases across the database appear to be similar in nature and severity. The occurrence of GI bleeding appears to be relatively uncommon with caffeinated analgesics when considering the extensive population exposure of these products.

6.3.5 Overdose with Caffeinated Analgesic Products

The early signs of toxicity with caffeinated analgesics are associated with the analgesic ingredients, rather than the caffeine component. For APAP, the minimum acute toxic dose is 5-15gm, with the lethal dose estimated to be 13-25gm. For ASA, acute toxicity is evident at >150mg/kg with severe toxicity evident at >400mg/kg (Drug Facts and Comparisons 2001).

For Excedrin[®] Extra Strength/Excedrin[®] Migraine, ingestion of the following estimated number of tablets may result in a fatal outcome, based on the individual components:

Estimated Number of Tablets of Excedrin[®] Extra Strength or Excedrin[®] Migraine Which May Result in Lethal Ingestion, by Individual Component

	APAP	ASA	Caffeine
# Tablets Required for Lethal Toxicity	20-60	110-120	120-150

6.3.5.1 Spontaneous Reports of Overdose with Caffeinated Analgesic Products

6.3.5.1.1 BMS AE Database Reports of Overdose with Excedrin[®] Products

Historical postmarketing AE data for the period 1984 – April 1997 was reviewed by BMS in preparation for the July 15, 1997 Excedrin[®] Migraine Advisory Committee meeting. During this time period, there were 28 reports of overdose with Excedrin[®] Extra Strength, defined as greater than 5 tablets per dose. Where age was provided (8/28), patients ranged in age from 13-35, with 6 of the 8 between the ages of 13-16 years old. Where dose ingested was known, amounts ranged from 5 tablets to “whole bottle.” In 21 reports, no accompanying symptoms were reported. In the 7 cases who experienced symptoms, reported symptoms included abdominal pain (N=2), nausea (N=2), somnolence (N=1), malaise (N=1), and speech impairment and somnolence (N=1).

For the period January 1998 – February 2001, a total of 25 reports of overdose were received with Excedrin[®] Extra Strength and Excedrin[®] Migraine, including

Overdose NOS, Accidental Overdose, and Non-accidental Overdose. Of these reports, 19 were considered to be serious. One serious report was reported in the literature by a health professional, while the remainder were received from consumers. Age, where provided, ranged from 12 months to 53 years old and doses ranged from "2 tablets with a cappuccino" to 40 tablets in one dose. Accompanying symptoms were generally consistent with the known safety profile of APAP/ASA/CAF combination products.

There were no reports of overdose during this time period with Aspirin Free Excedrin.[®]

The cases are summarized below:

**BMS AE Database Reports of Overdose with
Excedrin[®] Migraine and Excedrin[®] Extra Strength
January 1998 – February 2001**

CASE NUMBER	AGE	SEX	DOSE	CONCOMITANT MEDICATIONS	ADDITIONAL AE TERMS	OUTCOME
M079132	18	F	More than 3	None	Vomiting Diarrhea NOS Sweating increased	Recovered
M081663	53	F	2-3 tabs 6 times daily x 1 week	Atarax Levbid Ibuprofen Albuterol Prozac Meclizine Menest Synthroid Tylenol w/codeine Hydrochlorothiazide	Flushing	Unk
M082233	25	M	10 tabs x 1 dose	None	Diarrhea NOS Nausea	Recovering
M082573	Unk	M	15 tabs x 1 dose	None	Sedation	Recovered
M087434	Unk	M	8 tabs x 1 dose	None	Suicide attempt	Unk
M088720	23 mos	M	15 tabs x 1 dose	None	None	Recovered
M090406	1	F	At least 3 tabs	None	None	Unk
10082550	41	F	2 tabs "with a cappuccino"	Penicillin	Tachycardia Drug ineffective	Recovered
10154821	Unk	F	18 tabs	None	Dizziness Sedation	Unk
10170538	18	F	8 tabs x 1 dose	None	Dizziness Feeling hot Fatigue Abdominal pain upper	Unk
10202539	Unk	F	8 tabs x 1 dose	None	Abdominal pain upper	Unk
10414944	Unk	M	40 tabs	Ethanol	Vomiting NOS	Unk
10518538	Unk	F	30 tabs	None	Unevaluable	Unk

CASE NUMBER	AGE	SEX	DOSE	CONCOMITANT MEDICATIONS	ADDITIONAL AE TERMS	OUTCOME
					reaction	
10538221	16	F	15 tabs	None	Drug ineffective	Unk
10541746	Unk	M	20 tabs	None	None	Unk
10562197	16	F	9 tabs	None	None	Unk
10624591	13	F	12 tabs	None	Nausea	Recovered
10637510	14	F	10 tabs	None	Vision blurred Drug ineffective	Unk
10646677	Unk	M	12 tabs x 1 dose	None	Dizziness	Not resolved
M090172	20 mos	M	17 tabs x 1 dose	None	None	Recovered
M090174	Unk	M	Unk	Tylenol	Speech disorder NEC	Unk
10039287	15 mos	M	Up to 24 tabs x 1 dose	None	None	Recovered
M075936*	37	F	8 tabs x 1 dose	Lysol Advil	Suicide attempt Sore throat NOS Dyspepsia	Recovered
M078374	28	F	13 tabs x 1 dose	None	Dizziness	Not resolved
M085095	15	F	16 tabs x 1 dose	None	Dizziness Nausea Abdominal pain upper	Recovered

*Literature report from health professional. All other reports from consumers and not medically confirmed.

6.3.5.1.2 FDA AE Database Reports of Overdose with Non-BMS Caffeinated Analgesics

Between 1991-2000, the FDA received 6 reports of overdose with non-BMS caffeinated analgesic products (APAP/CAF – 4; ASA/CAF – 2). Additional drugs were also ingested in each of the cases. Where this information is known, three of the overdoses resulted in death and 1 patient was hospitalized. Dose was only reported in one case, which was “14gm” of ASA/CAF. In one report of ASA/CAF overdose, hepatic injury was reported, however, this consumer was also ingesting alcohol. There is no additional information available for these reports. The individual cases are presented below:

FDA Database Reports of Overdose with Non-BMS Caffeinated Analgesics 1991-2000

IMAGE ID	AGE	SEX	SUSPECT DRUG: DOSE	CONCOMITANT MEDICATIONS	AE TERMS	OUTCOME
3618802-8	54	Unk	APAP/CAF: Unk	Suspect: • Advil • Spalt ASS (aspirin)	Overdose NOS Drug abuse	Death
3618756-4	42	Unk	APAP/CAF: Unk	Suspect: • Artane • Fluphenazine	Non-accidental overdose Completed suicide	Death

IMAGE ID	AGE	SEX	SUSPECT DRUG: DOSE	CONCOMITANT MEDICATIONS	AE TERMS	OUTCOME
3618810-7	19	Unk	APAP/CAF: Unk	Suspect: • Robaxin • Oxycodone	Non-accidental overdose Completed suicide	Death
M01517795	23	F	ASA/CAF: 14.0 gm	Concomitant: • Alcohol	Jaundice NOS Overdose NOS Liver function tests NOS abnorm Encephalopathy NOS	Hosp
M01583566	16	F	APAP/CAF: Unk	Suspect: • Aleve	Vomiting NOS Urinary tract infection NOS Nonaccidental overdose Suicide attempt	Other
M01546769	13	F	ASA/CAF: Unk	Suspect: • Aleve	Nonaccidental overdose Headache NOS Suicide attempt	Other

6.3.5.1.3 WHO AE Database Reports of Overdose with Caffeinated Analgesics

In the World Health Organization (WHO) spontaneous AE database, for the period 1995 to March 27, 2001 there was 1 report of Suicide Attempt with a combination product of APAP/ASA/CAF. There is no additional information for this report.

6.3.5.2 Toxic Exposure Surveillance System (TESS) Database of Caffeinated Analgesic Exposures

TESS data was reviewed from 1995-2000 for poison center exposures with caffeinated analgesic combinations of: APAP/CAF, ASA/CAF, and APAP/ASA/CAF. In order to minimize the potential for confounding, these products were examined only for exposures in the absence of concurrent drugs. Amount ingested was not available in the data provided.

All 3 caffeinated analgesic products demonstrate a similar profile with respect to the nature and frequency of clinical events, treatment and medical outcome. The majority of cases resulted in no or minor effects and less than half of the exposures required treatment in a health facility. The most commonly reported clinical effects were those that are commonly associated with the individual ingredients (e.g. vomiting, nausea, agitation/irritability, dizziness, abdominal pain, tachycardia). There were 2 deaths reported with APAP/ASA/CAF, however, there is no information on amount ingested. Considering the extensive exposure to these products over a 5-year period, fatalities associated with overdose of co-formulated analgesics appear to be quite rare.

**Summary of TESS Data for Caffeinated Analgesic Products
Without Concomitant Ingestions
1995 - 2000**

	APAP/CAF	ASA/CAF	APAP/ASA/CAF
Total # Exposures	1208	1,552	16378
Total # Clinical Effects	604	1,210	9405
% Presenting with Clinical Effects	22% w/clinical effects 78% w/o clinical effects	34% w/clinical effects 66% w/o clinical effects	26% w/clinical effects 74% w/o clinical effects
Exposure Classification	68% unintentional 27% intentional	52% unintentional 44% intentional	62% unintentional 34% intentional
Most Frequently Reported Clinical Effects	Vomiting Nausea Agitated/Irritable Dizziness/vertigo Abdominal pain Tachycardia	Vomiting Nausea Tinnitus Abdominal pain Tachycardia Dizziness/vertigo	Vomiting Nausea Abdominal pain Agitated/Irritable Dizziness/vertigo Tachycardia
Treatment	42% treated in health facility <ul style="list-style-type: none"> • 64% released • 23% admitted • 12% lost to f/u or left AMA 	49% treated in health facility <ul style="list-style-type: none"> • 46% released • 38% admitted • 15% lost to f/u or left AMA 	40% treated in health facility <ul style="list-style-type: none"> • 56% released • 27% admitted • 16% lost to f/u or left AMA
Medical Outcome	86% resulted in no or minor clinical effects and no or minimal toxicity	78% resulted in no or minor clinical effects and no or minimal toxicity	84% resulted in no or minor clinical effects and no or minimal toxicity
# Deaths*	0	0	2

* Deaths summarized below. AMA = against medical advice.

**TESS Database Exposures Resulting in Death for Caffeinated Analgesics (APAP/ASA/CAF)
Without Concomitant Ingestions
1995 - 2000**

YEAR	AGE	SEX	REASON	CLINICAL EFFECTS	THERAPIES
1995	58	M	Intentional – misuse	Cardiac arrest Dysrhythmia Hypotension Tachycardia Edema DIC Other coagulopathy Other LFT abnormality PT prolonged Acidosis Alkalosis Bleeding Diaphoresis Electrolyte abnormality Fever/hyperthermia Hyperglycemia Other Confusion Creatinine increased Renal failure Dyspnea Pulmonary edema Respiratory arrest Respiratory depression X-ray findings (+)	Alkalinization IV fluids Hemodialysis Intubation Neuromuscular blocker Oxygen Other Vasopressors Ventilator
1995	23	M	Intentional – suspected suicide	Other Cyanosis Respiratory arrest	None listed

6.3.5.3 Summary – Overdose

In combination analgesic products, severe toxicity will most likely be associated with the analgesic component rather than the caffeine component. For Excedrin® Migraine/Excedrin® Extra Strength (APAP/ASA/CAF), a lethal dose of APAP would require an ingestion of 20-60 tablets, as compared to 110-120 tablets to achieve a lethal dose of ASA, and 120-150 tablets to achieve a lethal dose of caffeine. Therefore, a dose of caffeine 130mg in caffeinated analgesic products is unlikely to be a contributing factor to serious toxicity from these products.

Based on data from the BMS, FDA, WHO, and TESS databases, the majority of caffeine single ingredient and caffeinated analgesic product overdoses were associated with mild to non-existent clinical events and resulted in full recovery, although rare deaths were reported. In the FDA database, which contained 2 reports of fatal overdoses with caffeine single ingredient and 3 reports of fatal overdoses with APAP/CAF, all 5 patients had ingested additional drugs concurrently with the caffeine-containing product, which were also considered suspect drugs by the reporter. The TESS data, in which co-ingestions of additional drugs were excluded from our analysis, showed a generally similar pattern across all products.

6.3.6 Rebound Headache

Rebound headache is a term used to characterize the headache-perpetuating tendency of immediate relief medications when they are used very frequently (Mathew 1997). It can be defined as a self-sustaining headache/medication cycle caused by frequent and excessive use of immediate-relief medications among a susceptible patient population (National Headache Foundation 2000). Other medical phenomena analogous to rebound headache include worsening of nasal congestion by frequent use of nasal decongestants, insomnia aggravated by sleeping pills, chronic constipation due to frequent laxative use, and idiopathic edema caused by diuretics (Mathew 1997).

The International Headache Society (IHS) diagnostic criteria for rebound headache include the following:

- Occurs after use of a high daily dose of a substance for ≥ 3 months
- Occurs within hours after elimination of the substance
- Is relieved by renewed intake of the substance
- Disappears within 14 days after withdrawal of the substance

Rebound headaches can occur after intake of single analgesics, combined analgesics, or specific migraine medications such as ergotamines or triptans. Furthermore, analgesic-induced rebound headache only occurs in patients prone to headache (Mathew 1997, National Headache Foundation 2000). Caffeine-associated rebound headache is associated with ingestion of daily caffeine amounts of at least 15g per month (Feinstein 2000).

The prevalence of rebound headache, a type of chronic daily headache, in the general population is unknown but can be extrapolated from prevalence data on chronic daily headache (CDH). In a study of 1,883 subjects with CDH, it was reported that less than 5% of the general population suffers from CDH and of those, fewer than 2% overused analgesics (Castillo 1999).

The etiology of rebound headache remains unclear. There are no published prospective studies that examine whether the headaches are a cause or a consequence of the daily medical use. In addition, while it appears that those

taking the most medications seem to experience the most pain and it has been hypothesized that rebound headache may be a result of addictive behavior in a small subset of patients, there is no evidence of addictive personality in this group. A small subset of headache patients may exhibit drug-seeking behavior, regardless of the agent involved (Mathew 1997, National Headache Foundation 2000).

There is no evidence that the headache on withdrawal from caffeine-containing analgesics is more severe or problematic than on withdrawal from other headache medications, nor evidence that that rebound headaches occur at a higher incidence than with other analgesics (Feinstein 2000). One study of CDH patients reported that almost 90% of subjects overused single-ingredient NSAIDs, including aspirin and almost 40% overused APAP. Caffeinated analgesics only accounted for about 5% of patients (National Headache Foundation 2000). This finding is supported by data from The Gallup Organization (from 1990-2000), which showed that, among "heavy analgesic users" (>30 or >180 tablets per average 4 weeks), there was no difference in consumption patterns between caffeinated and non-caffeinated analgesics.

6.3.6.1 Spontaneous Reports of Rebound Headache with Caffeinated Analgesic Products

6.3.6.1.1 BMS AE Database Reports of Rebound Headache with Excedrin®

For the period January 1998 through February 2001, BMS received 18 reports of rebound headache with Excedrin® Extra Strength/Excedrin® Migraine. All were initially reported by a consumer; only 2 were subsequently medically confirmed. The typical case presentation was a period of long term Excedrin® use and the inability to discontinue Excedrin® due to rebound headache. Many of these reports were lacking pertinent details such as dose, duration of use, relevant medical history, concomitant medications, treatment measures, and the outcome of the event. There were no reports of rebound headache with Aspirin Free Excedrin®.

**Reports of Rebound Headache in BMS AE Database
With Excedrin® Extra Strength or Excedrin® Migraine
Jan 1998 - Mar 2001**

CASE NO.	AGE	SEX	DOSE	DURATION OF USE	CONCOMITANT MEDICATIONS	OUTCOME
10083418	Unk	M	Unk	Unk	None	Unk
10090454	Unk	M	Unk	30 years	Unk	Unk
10097715	50	M	Unk	Daily for years	Unk	Unk
10097731	55	F	Unk	Daily for years	Unk	Unk
10264570	Unk	F	2 tabs daily	Unk	Unk	Unk
10490068	15	Unk	7-8 tabs daily	8 years	Unk	Unk

CASE NO.	AGE	SEX	DOSE	DURATION OF USE	CONCOMITANT MEDICATIONS	OUTCOME
10517381	75	F	6-8 tabs daily	Unk	Premarin Provera	Unk
M078521*	55	F	4 tabs daily	15-25 years	Maalox	Given tapering regimen, Paxil
M085036	44	F	6-8 tabs daily	24 years	None	Unk
M090477*	59	M	9-18 tabs daily	30 years	Naratriptan Sertraline Omeprazole Librium Buspirone Promethazine Mirtazapine Dihydroergotamine mesylate Pseudoephedrine HCl	Tapering regimen & additional meds for headache pain & depression
M091107	30	F	8-15 tabs daily	6 years	Benazepril	Advised to taper by MD
M092204	Unk	F	1 tab every 2 waking hrs	Unk	Unk	Unk
M092780	48	F	2 tabs daily	1 year	B Complex Calcium/Vit D Furosemide Phenobarbital Potassium Cl Vitamin E	Unk
M094074	Unk	Unk	Regularly	Unk	Unk	Unk
M094131	Unk	F	Unk	Daily for years	Unk	Headache on withdrawal
M094442	63	F	1 as needed	40 years	Unk	Unk
M094620	Unk	F	Daily	Unk	Unk	Resolved on weaning off
M096022	77	M	2 tabs daily	30 years	Quinapril Atenolol Digoxin Vitamin C	Told by MD to discontinue

*Medically confirmed

6.3.6.1.2 FDA and WHO AE Database Reports of Rebound Headache with Caffeinated Analgesics

Due to the lack of a specific AE term for "rebound headache," it was not possible to search the FDA or WHO AE databases for reports of this event.

6.3.6.1.3 Summary – Rebound Headache

Rebound headache is a recognized potential consequence of frequent analgesic use. Based on epidemiologic data, it is believed to be uncommon (<2% in a study of 1,883 subjects with chronic daily headache), and caffeine-containing analgesics are no more likely to be associated with rebound headache than any

other type of analgesic medication. When caffeine-containing analgesics are involved, the consumption level of caffeine associated with rebound headache is greater than 15g per month. The etiology of rebound headache remains unclear, however addictive behavior does not appear to be a factor for the vast majority of analgesic users. Based on this evidence, there is no reason to believe that caffeine doses of 130mg in caffeinated analgesics would result in a greater incidence of rebound headache than caffeine doses of 65mg.

6.3.7 Caffeinated Analgesic Dependence

The issue of whether caffeine should be classified as a drug of dependence has been the subject of considerable controversy among experts in this field. In order to be classified as a drug of dependence, several criteria developed by ICD-10 and DSM-IV must be met.

The following are the criteria that are considered applicable to caffeine (ICD-10, DSM-IV, Heishman 1992):

- Highly controlled or compulsive use
- Psychoactive effects
- Drug-reinforcing behavior
- Tolerance
- Physical dependence

Highly controlled or compulsive behavior describes a habitual pattern of drug self-administration behavior that persists despite a desire to reduce intake or repeated attempts to quit taking a drug. Survey information demonstrates that 92-98% of North American adults consumes coffee on a regular basis. In addition, anecdotal evidence suggests that the majority of coffee users probably consume a cup or two of coffee every morning, which satisfies the criterion of highly controlled or habitual use, although it is difficult to determine whether the extensive use of coffee is due to its centrally mediated stimulus functions, the sensory aspects of hot coffee, or the fact that coffee drinking is such a socially acceptable behavior (Heishman 1992, Fredholm 1999). The compulsive aspect of drug dependence has not been well studied. There appears to be a very small subset of coffee users who use caffeine compulsively to the extent that they develop symptoms of caffeinism. This subset may meet this criteria in that they have difficulty reducing or stopping their intake, but cannot be generalized to the entire population (Heishman 1992).

Psychoactive effects of a drug refers to the CNS-mediated changes in mood or feeling states promoted by the drug. These can be evaluated in terms of subjective effects and the ability to discriminate between a drug and placebo on the basis of the drug's CNS effects. Numerous studies have demonstrated that caffeine produces subjective effects, although there appears to be considerable inter-individual variation in dose response which may in part be related to study design. At low to intermediate doses, most subjects experience positive

subjective effects such as increased alertness and energy and decreased tiredness and fatigue. Between 200mg–800mg, dysphoric effects become more predominant characterized by increases in anxiety, nervousness, and jitteriness (Griffiths 1995). Usually doses above 500mg are associated with caffeine intoxication. When caffeine was compared to d-amphetamine in studies used to measure subjective drug dependence, the results with caffeine were variable, depending on dose, subject population, and experimental conditions. Furthermore, caffeine consistently produced dysphoric effects at high doses. In contrast, d-amphetamine produced a more significant, consistent dose response under a broader range of conditions (Chait 1983).

Humans can discriminate caffeine from placebo, but there appears to be little generalization to dopaminergic agents such as amphetamine or cocaine (Daly 1998). High doses of caffeine are much more easily recognized than low doses, primarily because of the dysphoric effects. Discriminable effects have been documented at doses as low as 10-56mg in non-tolerant individuals. Most experimental evidence indicates that discriminatory effects of caffeine are poorly detected in doses in the range of 50-150mg which are commonly used in OTC analgesic products (Griffiths 1990, Feinstein 2000).

Drugs that produce psychological dependence also increase dopamine in the brain reward system. Caffeine's interaction with dopaminergic system is different from that of typical drugs of abuse such as cocaine and d-amphetamine (Nehlig 1999). In doses equivalent to usual human consumption (200-300mg), caffeine does not act like typical drugs of abuse to increase dopamine release in the shell of the nucleus accumbens. Moreover, caffeine demonstrates a nonspecific effect of widespread increases in cerebral metabolic activity, in contrast to d-amphetamine and cocaine which elicit increases of functional activity only in distinct brain areas (Feinstein 2000).

Drug reinforcing behavior is the specific effect of a drug that increases the likelihood that a person will take it again. Reinforcing effects are inferred when subjects consistently self-administer a drug at a rate greater than or in preference to placebo (Hughes 1992). Caffeine has been shown to exhibit weak reinforcing effects. The reinforcing effects of caffeine have been described as showing an inverted U-shape (Griffiths 1995). Lower doses (up to 50mg) are reinforcing for a small proportion of subjects, increasing in frequency with rising doses, then reaching a plateau between 50-150mg, then decreasing with higher doses of caffeine due to its aversive effects. The effect of prior caffeine use and caffeine tolerance on the level of reinforcement is inconsistent and not fully understood (O'Brien 1996). Furthermore, the level of response is lower in comparison to other dopaminergic drugs of dependence such as cocaine and amphetamine (Daly 1998).

Since most caffeine reinforcement studies were conducted with caffeinated beverages, the extrapolation to caffeinated analgesics is unclear. The choice of

caffeine can be influenced by the desire to avoid withdrawal symptoms or by its positive effects. Moreover, the sensory effects of coffee or other caffeinated beverages is an important aspect of caffeine consumption, demonstrated by studies in which subjects prefer caffeine in beverages to caffeine in capsules (Feinstein 2000).

Tolerance to a drug refers to an acquired change in responsiveness of a subject repeatedly exposed to a drug and can involve two aspects. First, tolerance may indicate that the dose necessary to achieve the desired effects will increase over time, thus leading to the gradual increase in consumption. A second aspect involves the development of tolerance to the aversive effects of high doses of a drug, thereby inciting the consumption of higher doses over time (Nehlig 1999).

In animals, caffeine has been shown to produce tolerance of caffeine-induced locomotor stimulation, cerebral electrical activity, and reinforcement thresholds for electrical brain stimulation. The development of tolerance in animals is rapid, usually insurmountable, and is not associated with cross-tolerance with psychomotor stimulants such as amphetamine and methylphenidate (Nehlig 1999).

In humans, tolerance has been demonstrated for some, but not all the physiological effects of caffeine. Tolerance to cardiovascular and respiratory effects develops within a few days (Daly 1998). Tolerance to subjective effects such as increases in tension/anxiety, jitteriness/nervousness, and activity/stimulation/energy has also been shown to occur. Conversely, there is only limited evidence of tolerance to caffeine-induced alertness and wakefulness. Sleep, which appears to be the physiologic function most sensitive to caffeine, does demonstrate some signs of tolerance although it is unclear whether this is attributable to tolerance or inter-individual sensitivity to caffeine. Poor sleepers are reported to metabolize caffeine at a lower rate, however, heavy coffee drinkers appear to be less sensitive to the caffeine-induced sleep disturbances than light coffee drinkers (Nehlig 1999). Furthermore, mechanisms of tolerance may be overwhelmed by the nonlinear accumulation of caffeine and its major metabolites when caffeine reaches steady-state levels in humans following multiple dosing (Denaro 1990). The development of tolerance to the stimulus effects of drug dependence (positive subjective effects; discriminative stimulus; reinforcing stimulus) has not been studied (Heishman 1992).

Physical dependence, a state of adapting to the effects of a drug, is a corollary to tolerance because physiological adaptation to the presence of a drug produces tolerance. If the drug is withdrawn suddenly, there will be a rebound and re-adaptation of homeostatic systems to compensate for the absence of the drug. The rebound produces a set of systems known as drug withdrawal syndrome. Withdrawal syndrome implies the presence of physical dependence, but is not necessarily "addiction" (O'Brien 1996). Well-known examples of drugs producing

withdrawal syndrome upon sudden cessation, in the absence of addiction, include beta blockers, antidepressants, antipsychotics and caffeine.

Caffeine withdrawal syndrome has been recognized since the 19th century and is associated with the following signs and symptoms (National Headache Foundation 2000):

- Headache
- Sleepiness/drowsiness
- Impaired concentration/lassitude/work difficulty
- Depression
- Anxiety
- Irritability
- Nausea/vomiting
- Muscle aches/stiffness

Typical manifestations of abrupt caffeine withdrawal begin after 12-24 hours, peaking after 20-48 hrs, and sometimes lasting a week (Nehlig 1999). The syndrome is inconsistent in that a person may show symptoms on one occasion of stopping caffeine, but not on another (O'Brien 1996). In addition, it does not appear to be a dose-related phenomenon. In a study of abrupt caffeine withdrawal conducted by Silverman et al. in 62 normal adults with a mean daily caffeine intake of 235mg per day, the incidence of symptoms were: headache (52%), anxiety/depression (8%), fatigue (8%), and use of analgesics (13%). The severity of the withdrawal symptoms was not dose related; some of the patients who had adapted to high doses of caffeine had minimal withdrawal symptoms while some showed significant withdrawal at doses as low as 100mg per day (Silverman 1992).

The frequency of caffeine withdrawal syndrome is unknown, but a recent study suggests that the incidence may be less than previously reported. In 11,000 surveyed subjects, 61% reported daily caffeine consumption but only 11% reported withdrawal symptoms on stopping caffeine, and only 3% claimed their symptoms were severe enough to interfere with their daily activities. When 57 of these subjects who claimed they experienced withdrawal symptoms were studied in a randomized, double-blind study of abrupt and staged cessation, only one-third (33.3%) actually developed symptoms following abrupt withdrawal and none of the subjects developed symptoms after staged withdrawal (Dews 1999).

The majority of studies on caffeine withdrawal were performed with caffeinated beverages, so it not clear if this phenomenon would also occur with caffeinated analgesic products. However, given the time lag of 12 to 24 hours until the occurrence of symptoms following complete deprivation and the ubiquitous nature and easy availability of caffeine in beverages, a withdrawal syndrome resulting solely from discontinuation of caffeine-containing analgesics is unlikely to develop under daily conditions (Feinstein 2000).

6.3.7.1 Spontaneous AE Reports of Dependence, Withdrawal, Tolerance, Abuse with Caffeinated Analgesic Products

6.3.7.1.1 BMS AE Database Reports of Dependence, Withdrawal, Tolerance, Abuse with Excedrin® Products

The BMS AE database was examined for the period January 1998 - February 2001 for reports of AEs with Excedrin® Migraine, Excedrin® Extra Strength, and Aspirin Free Excedrin® that could potentially be associated with caffeine dependence. The following AE terms were searched: Drug Dependence, Drug Withdrawal, Drug Withdrawal Headache, Tolerance, Drug Abuse.

Between January 1998 and February 2001, BMS received 44 reports of drug dependence with Excedrin® Migraine and Excedrin® Extra Strength. Two of these reports also included the term "drug withdrawal syndrome" and 2 reports also included the term "drug withdrawal headache." In 11 reports, "rebound headache" was mentioned in the text and in one report "rebound effect" was mentioned. Of the 44 reports, 41 originated from a consumer; only 3 were medically confirmed by a health professional. 38 of these reports were classified as "serious." and 6 were classified as "nonserious." Where the information was available, the majority of reports were in female adults. Two (2) reports were for teenage children (ages 14 and 15). Many of the consumers reported using Excedrin® within the recommended daily dose range for a period of years to treat various headache disorders. For the cases where this information was available, some of the consumers described a history of stress, anxiety, depression, and obsessive-compulsive disorder. In addition to drug dependence, AEs which were concurrently reported included a variety of events such as headache, gastrointestinal hemorrhagic ulcers, abdominal pain, and tinnitus. In most cases outcome is unknown. Due to the lack of medical confirmation and information regarding past medical history, it is not possible to assess the relationship between these events and the use of Excedrin®.

There were 2 reports of Tolerance during this time period with Excedrin® Migraine and Excedrin® Extra Strength, however, there was no additional information for these reports other than the AE description of "tolerance."

There was only 1 report of Drug Abuse with Aspirin Free Excedrin® which described a female consumer who took 12 tablets (780mg caffeine) daily for 30 years. Aspirin Free Excedrin® was introduced in 1990. This report was not medically confirmed and no additional information was available.

A summary of the individual reports of Drug Dependence with Excedrin® Migraine and Excedrin® Extra Strength are presented below:

**BMS AE Database Reports of Excedrin® Migraine and Excedrin® Extra Strength
Reports of Drug Dependence
January 1, 1998 – February 28, 2001**

CASE NUMBER	AGE	SEX	DOSE	CONCOMITANT MEDICATIONS	ADDITIONAL HISTORY	ADDITIONAL AE TERMS
M076696	66	F	2 tabs qd x 40 yrs	Unk	None	None
M078181	14	M	Unk dose qd x 3 yrs	Unk	Headaches Obsessive-compulsive disorder	None
M078182*	56	M	4-6 tabs qd x 20 yrs	Corgard Desyrel Flexeril	Migraines Back pain	None
M078521*	55	F	4 tabs qd x 25 yrs	Maalox	Headaches Anxiety NEC Depression NEC Abortion NOS Drug allergy	Gastric ulcer Headache NOS
M079027	63	F	2 tabs q 4 hrs x 20 yrs	Estratest Cardizem	Migraines Hypertension Drug allergy	Nausea
M085036	44	F	6-8 tabs qd x 24 yrs	None	Headaches	Abdominal pain upper Headache NOS
M085326	37	F	2 tabs q am & pm x 7 mos	None	Migraines	Drug withdrawal headache Dizziness
M087433	42	M	1-4 tabs qd x 23 yrs	Motrin	Headaches	None
M087435	Unk	F	Unk	Unk	None	Tremor NEC
M087661*	46	F	1 tab qd x 8 yrs	None	Headaches Neck pain Shoulder pain Convulsions Hysterectomy Tonsillectomy	Diarrhea NOS Nausea Abdominal pain NOS Weight decreased Syncope Dizziness Paresthesia NEC Vomiting NOS Flatulence Eruclation Dyspepsia Hypotension NOS Dehydration
M090437	35	F	1-6 tabs qd x 20 yrs	None	Sinus headaches	None
M090477*	59	M	9-18 tabs qd x 30 yrs	Buspar Phenergan Remeron Amerge Migranal Prilosec Zolofl Librium Sudafed	Migraines Rebound headaches Depression Anxiety Peptic ulcer disease Tobacco use	Tinnitus Condition aggravated Deafness NOS Blindness transient Gastric ulcer hemorrhage Headache NOS Depression NEC Anxiety NEC Photophobia
M091107	30	F	8 tabs qd x 6 yrs	Lotensin	Migraines Hypertension	Headache NOS
M092204	Unk	F	1 tab q 2 hrs x unk duration	Unk	Migraines	Headache NOS Pain NOS

CASE NUMBER	AGE	SEX	DOSE	CONCOMITANT MEDICATIONS	ADDITIONAL HISTORY	ADDITIONAL AE TERMS
M092536	50	M	Up to 7 tabs qd x >20 yrs	Unk	None	Tinnitus Tremor NEC Dizziness Euphoric mood Vertigo NEC
M092641	Unk	M	2-4 tabs qd x unk duration	Unk	Headaches	Headache NOS
M093239	56	F	Unk x 18 yrs	Unk	Sinus headaches	None
M093837	51	M	10-15 tabs qd x unk duration	None	Headaches	None
M093996	43	F	Unk x "yrs"	Imitrex	Migraines Headaches	Gastric ulcer hemorrhage Drug withdrawal syndrome
M093998	Unk	F	Up to 10 tabs qd x 18 yrs	Unk	Unk	Drug withdrawal syndrome
M094074	Unk	Unk	Unk	Unk	Unk	Headache NOS
M094130	Unk	F	Unk	Unk	Unk	None
M094131	Unk	F	Unk x "yrs"	Unk	Unk	Headache NOS Drug withdrawal headache
M094660	Unk	F	Unk x 2 yrs	Unk	Unk	None
M094661	59	M	1 tab qd am x >1 yr	Prilosec	Dyspepsia Sinus allergies	None
M096160	59	F	1-2 tabs qd x unk duration	Atrovent Estrogen Humibid LA Miacalcin Synthroid Xalatan	Headaches Bronchiectasis Osteoporosis Glaucoma Thyroid condition Menopause	None
M096389	Unk	F	1 tab qd x 5 yrs	Unk	Unk	None
M096505	31	M	2 tabs bid x 5-6 mos	None	Neck pain Headaches	None
10002798	Unk	F	Unk	Unk	Unk	None
10039352	Unk	F	Unk	Unk	Migraines Caffeine sensitivity Stress	None
10082444	41	F	6-8 tabs qd x unk duration	Paxil	Sinus headaches Stress	None
10083418	Unk	M	Unk	Unk	Headaches Gastric ulcer	Abdominal pain NOS Headache NOS
10093557	Unk	F	Unk	Unk	Unk	None
10097715	50	M	Unk	Unk	Headaches	Headache NOS
10097731	55	F	Unk	Amitriptyline	Headaches Diabetes Fibromyalgia	Headache NOS
10127231	Unk	F	6-10 tabs qd x 15 yrs	Unk	Unk	None
10141893	39	F	3-6 tabs qd x 23 yrs	Unk	Unk	Malaise Dyspepsia
10176477	52	M	1 tab 4-5 x qd x 15 yrs	Unk	Back pain	Abdominal pain NOS

CASE NUMBER	AGE	SEX	DOSE	CONCOMITANT MEDICATIONS	ADDITIONAL HISTORY	ADDITIONAL AE TERMS
10182095	87	M	Unk	Unk	Unk	Gastric ulcer hemorrhage Dizziness
10209427	Unk	F	2-4 tabs qd x 15-20 yrs	Unk	Headaches	Euphoric mood
10209435	41	M	8-10 tabs qd x 5 yrs	Unk	Unk	None
10212447	Unk	F	2 tabs bid x "many yrs"	Unk	Headaches	None
10264570	Unk	Unk	2 tabs qd x unk duration	Unk	Headaches	Headache NOS
10490068	15	Unk	7-8 tabs qd x 8 yrs	Unk	Headaches	Headache NOS Bleeding Time Prolonged

*Medically confirmed

6.3.7.1.2 FDA AE Database Reports of Dependence, Withdrawal, Tolerance, Abuse with Non-BMS Caffeinated Analgesics

Between 1991-2000, FDA received no reports of Drug Dependence, Drug Withdrawal Syndrome, or Tolerance, with non-BMS caffeinated analgesic products. There was one report of Drug Abuse and Overdose in a 54 year-old person with APAP/CAF that resulted in death. There is not enough information available for this report to make a meaningful assessment in the context of drug abuse.

6.3.7.1.3 WHO AE Database of Reports of Dependence, Withdrawal, Tolerance, Abuse with Caffeinated Analgesics

From 1995 –March 27, 2001, WHO received 4 reports of Drug Dependence with APAP/ASA/CAF, 1 report of Drug Abuse with ASA/CAF, and 12 reports of Therapeutic Response Decrease (Tolerance) with APAP/ASA/CAF. There is no additional information provided for the 12 reports of Therapeutic Response Decrease. The only information available for the reports of Drug Dependence and Drug Abuse is a line listing for cases where one of these terms was considered the WHO Critical Term. Minimal information was provided by WHO on these reports, limiting meaningful assessment of these cases. A summary of the information on the individual cases is presented below:

**WHO AE Database Reports of Drug Dependence, Drug Abuse
With Caffeinated Analgesics
1995 - March 27, 2001**

COUNTRY	AGE	SEX	CRITICAL TERM	DRUG NAME	REPORT TYPE	SOURCE	OUTCOME
USA	66y	F	Drug abuse	ASA/CAF	NC:spont	Not spec.	Not spec.
USA		F	Drug dependence	APAP/ASA/CAF	Mf:spont	Other	Rec w seq
USA		M	Drug dependence	APAP/ASA/CAF	Mf:spont	Other	Rec w seq
USA	50y	M	Drug dependence	APAP/ASA/CAF	Mf:spont	Other	Rec w seq
USA		M	Drug dependence	APAP/ASA/CAF	Mf:spont	Other	Not spec.

Rec w seq - Recovered with sequelae Not spec. - Not specified

6.3.7.2 Drug Abuse Warning Network (DAWN) Data

DAWN data obtained from the Substance Abuse and Mental Health Services Administration (SAMHSA), Department of Health and Human Services was examined for the period 1995 to 1999. When compared to single ingredient analgesic products reported over this time period, caffeine accounted for a considerably smaller percentage of Emergency Department drug abuse "episodes" and "mentions" than single ingredient analgesic products. Caffeine-containing analgesic products were not specifically listed in the DAWN data, so further analyses could not be conducted.

DAWN Data Emergency Department Mentions and Episodes 1995 - 1999

	1995		1996		1997	
	Mentions	% of Total Episodes	Mentions	% of Total Episodes	Mentions	% of Total Episodes
APAP	36563	7.12	38265	7.44	35448	6.73
ASA	16729	3.26	15854	3.08	14623	2.77
Butalbital combo	2084	0.41	829	0.16	1454	0.28
Caffeine	3629	0.71	3180	0.62	3151	0.60
Ibuprofen	21250	4.14	16979	3.30	17070	3.24
Naproxen	5253	1.02	4546	0.88	5330	1.01

	1998		1999	
	Mentions	% of Total Episodes	Mentions	% of Total Episodes
APAP	32257	5.95	28258	5.09
ASA	15457	2.85	12815	2.31
Butalbital combo	1298	0.24	845	0.15
Caffeine	2186	0.40	2138	0.39
Ibuprofen	17146	3.16	14400	2.59
Naproxen	5549	1.02	4610	0.83

6.3.7.3 Summary – Dependence

Habitual use of caffeine has been well demonstrated among the millions of daily consumers of coffee, however, true compulsive drug seeking behavior appears to be exceedingly rare and limited to a very small subset of individuals who cannot be generalized to the general population.

The psychoactive effects of caffeine show considerable inter-individual variation, but for most individuals, positive effects are seen at low to intermediate doses with dysphoric effects becoming more prominent as doses exceed 200mg. Doses greater than 500mg are usually associated with caffeine intoxication. These results are in contrast to d-amphetamine, which produces a more significant, consistent dose response under a broader range of conditions, and does not produce a dysphoric effect at high doses. Furthermore, caffeine's effect on the dopaminergic system has been shown to be different from that of typical drugs of abuse such as d-amphetamine and cocaine.

Caffeine has been shown to exhibit weak drug reinforcing effects. The reinforcing effects of caffeine have been described as an inverted U-shape. Lower doses (up to 50mg) are reinforcing for a small proportion of subjects, increasing in frequency with rising doses, then reaching a plateau between 50-150mg, then decreasing with higher doses of caffeine due to its aversive effects.

Tolerance has been demonstrated in animals. The data are less conclusive in humans and may in part be related to differences in inter-individual metabolism of caffeine. Cardiovascular and renal effects appear to exhibit tolerance to caffeine, however, tolerance to some of the central nervous system effects of caffeine appears to be limited and in some instances, incomplete.

Physical dependence, characterized by sudden caffeine withdrawal, has been observed with caffeine, however, it may not be as common as previously believed and symptoms rarely interfere with daily activities. It does not appear to be a dose related phenomenon and occurs inconsistently even within individuals. The majority of data on caffeine withdrawal refers to caffeinated beverages, so it is unclear if this phenomenon would also occur with caffeinated analgesic products. However, given the time lag of 12 to 24 hours until the occurrence of symptoms following complete deprivation and the ubiquitous nature and easy availability of caffeine in beverages, a withdrawal syndrome resulting solely from discontinuation of caffeine-containing analgesics is unlikely to develop under daily conditions.

In examining the spontaneous reports of Drug Dependence, Drug Withdrawal, Drug Withdrawal Headache, Tolerance, and Drug Abuse in the BMS, FDA, and WHO databases for caffeine single ingredient products, there were 5 reports of

Drug Dependence, 8 reports of Drug Withdrawal Headache/Syndrome, 9 reports of Drug Abuse, and 6 reports of Therapeutic Response Decreased (Tolerance). Minimal information was available for most of these reports, however, in the FDA database, all patients reporting Drug Withdrawal Syndrome or Drug Dependence were receiving other medications also reported as suspect drugs and which are known to be associated with drug withdrawal phenomena.

For caffeinated analgesic products, there were 49 reports of Drug Dependence and 2 reports of Drug Abuse, the majority originating from the BMS AE database. There were also 12 reports of Therapeutic Response Decreased (Tolerance) in the WHO database, however, there was no additional information provided for these reports. Most of the reports of dependence and abuse are not medically confirmed and typically described a scenario of long term Excedrin[®] use and the inability to discontinue use. Many of the patients were receiving other medications and had a history of psychiatric conditions. In the absence of detailed medical data regarding dose, duration of use, concurrent medications and illnesses, an assessment of the causal relationship between these events and the use of Excedrin[®] is not possible.

6.4 Conclusion/Safety Assessment of Caffeinated Analgesic Products

OTC caffeinated analgesic products have been used widely for over 40 years. The current formulations of Excedrin[®] Extra Strength/Excedrin[®] Migraine, and Aspirin Free Excedrin[®] have been marketed since 1978 and 1990, respectively, and have been used safely and effectively by more than 200 million consumers in the US alone. BMS clinical trial data in 17,000 subjects and 27 studies across various pain models demonstrate their safety and tolerability in short term studies.

In the postmarketing setting, a comparison of the spontaneous AEs in the BMS, FDA, and WHO databases for these products confirms that their safety profiles are generally consistent in nature and severity with the known pharmacologic profiles of the individual ingredients, despite the frequent lack of medical confirmation and detailed medical information which are necessary to provide a meaningful evaluation of the data. These data do not signal any new or unexpected safety issues with these products.

Human Pharmacokinetic studies and postmarketing AE data do not appear to signal a clinically significant interaction between caffeine and APAP when administered concurrently in doses typically used in caffeinated analgesics.

When examined specifically for AEs of special interest with caffeinated analgesics, *i.e.*, analgesic nephropathy, hepatotoxicity, GI bleeding, overdose, rebound headache, and caffeinated analgesic dependence, the spontaneous AEs across the various databases appear to be consistent with the published literature.

Phenacetin appears to be the only clear risk factor for the development of analgesic nephropathy. Based on spontaneous AE data, analgesic nephropathy does not appear to be a clinically significant issue with caffeinated analgesics. Hepatotoxicity with caffeinated analgesics (due to the APAP component) appears to occur rarely, and based on spontaneous AE data, is not always the sole inciting drug. GI bleeding (associated with the ASA component), while relatively uncommon, is often associated with the presence of additional risk factors for GI bleeding, e.g. history of ulcer disease, concomitant medications also associated with GI bleeding. In overdose settings, severe toxicity will most likely be associated with the analgesic component rather than the caffeine component due to the relative toxicities of each. Most cases of overdose are associated with minimal to no symptoms and result in complete recovery. Rare occurrences of significant toxicity are frequently associated with the ingestion of multiple drugs. Epidemiologic and consumer usage data demonstrate that rebound headache is less common than previously believed and associated with the use of all analgesic products, not specifically caffeinated analgesics. And finally, while caffeine appears to possess some of the attributes of drugs of dependence (*i.e.*, psychoactive effects, drug reinforcing effects, tolerance, physical dependence), these effects are weak, often inconsistently demonstrated in humans, and do not resemble the effects produced by typical drugs of abuse such as d-amphetamine and cocaine. Caffeine and caffeinated analgesics are used safely by the vast majority of users. Rare instances of drug seeking behavior associated with caffeine are usually associated with underlying psychological illness and are frequently associated with abuse of multiple drugs, not just caffeine or caffeinated analgesics.

It is often difficult to assess the postmarketing AE reports due to the paucity of detailed medical information and presence of multiple concomitant medications and illnesses. However, when examined in the context of the extensive use of caffeinated analgesics for over 40 years, these events appear to occur infrequently, are often associated with additional risk factors, and only rarely are they associated with severe morbidity and mortality.

7.0 CONSUMER USAGE PATTERNS OF CAFFEINATED ANALGESIC PRODUCTS

Data obtained from various sources do not show a difference between the use of caffeinated and non-caffeinated analgesic products.

In the US, The Gallup Organization has been measuring oral analgesic consumption since 1984. According to the Gallup tracking study of OTC analgesics (Excedrin[®] Extra Strength, Anacin[®], Aspirin without caffeine, Advil[®], and Tylenol[®] Extra Strength), the mean number of OTC analgesic tablets consumed per average 4-week period per consumer over the past 10 years (1990-2000) ranged from 17.8 – 21.9 (N=50,751). The mean tablet consumption

during this period was no different for caffeinated analgesic products than for non-caffeinated analgesic products. Of the more than 50,000 consumers participating in this poll, there was no meaningful difference in mean consumption between caffeinated and non-caffeinated analgesics. Furthermore, there was no apparent difference in consumption of caffeinated analgesics containing 130mg caffeine (Excedrin®) and those containing 64mg caffeine (Anacin®). These data are summarized in the table below:

Gallup Tracking Data on Oral Analgesic Mean Tablet Consumption per Average 4-Week Period 1990 - 2000

	Excedrin® ES (130mg caffeine per dose)	Anacin®* (64mg caffeine per dose)	Aspirin (w/o caffeine)**	Advil® (ibuprofen)	Tylenol® Extra Strength (excl. PM) (acetaminophen)
No. consumers	3,433	1,492	14,227	10,838	20,761
Mean no. of tablets per average 4-week period	17.8	20.3	21.9	17.9	17.8

*Anacin data was only available for 1990-1997 due to low sales volume post 1997

**Aspirin data post 1997 does not specifically exclude caffeine

A similar usage profile was also observed for "heavy users" of analgesics. There was no meaningful difference between usage of caffeinated and non-caffeinated analgesics when the percentage of consumers who consume 30 or more, or 180 or more pills per average 4- week period (1990-2000) were compared.

Gallup Tracking Data on Percentage of Brand Users of Caffeinated and Non-Caffeinated Analgesics Consuming 30 or More, or 180 or More Pills Per Average 4-Week Period (1990 - 2000)

	Excedrin® ES (130mg caffeine per dose)	Anacin®* (64mg caffeine per dose)	Aspirin** (w/o caffeine)	Advil® (ibuprofen)	Tylenol® Extra Strength (excl. PM) (acetaminophen)
% consumers consuming 30 or more pills	14.8	17.3	19.5	14.4	13.5
% consumers consuming 180 or more pills	0.8	1.1	1.1	1.0	1.1

*Anacin data was only available for 1990-1996 due to low sales volume post 1997

**Aspirin data post 1997 does not specifically exclude caffeine

In a study of analgesic usage among migraine patients in London, England, there was also no meaningful difference in usage between caffeinated and non-caffeinated analgesics (MacGregor 1990).

8.0 DISCUSSION

This review has examined the safety of caffeine in both single ingredient dose forms and in co-formulation with OTC analgesic products in order to address the original questions raised (Section 1.0). This section returns to the four primary questions and discusses the answers in the context of the previously reviewed information.

8.1 Does the addition of caffeine to oral analgesic products negatively impact the safety profile of individual or combination analgesics, such that unique or enhanced toxicities are produced?

Postmarketing experience and research over the past 40 years confirm that caffeinated analgesic products are generally well tolerated and used safely by the vast majority of consumers. However, there are several safety issues that are of potential concern with these products, due to either the individual components or the combination of ingredients. These are discussed below.

- Analgesic Nephropathy
- Hepatotoxicity
- GI Bleeding
- Overdose
- Rebound Headache
- Dependence

Analgesic Nephropathy

The only clear risk factor for analgesic nephropathy identified and agreed upon by experts is previous use of phenacetin-containing analgesics. A recent panel of experts convened by the regulatory authorities of Germany, Austria, and Switzerland, concluded that there is insufficient evidence to conclude that analgesics, in the absence of phenacetin, are causally associated with nephropathy. Similarly, there is no evidence that the addition of caffeine to analgesics is associated with nephropathy.

The data on renal events from the BMS, FDA, and WHO revealed no spontaneous reports suggestive of analgesic nephropathy with caffeinated analgesic products.

Hepatotoxicity

Hepatotoxicity is a well-recognized complication of APAP overdose and is not usually associated with the use of ASA or caffeine. In examining the spontaneous reports for Excedrin,[®] non-BMS caffeinated analgesics, and the WHO data for caffeinated analgesics, there were only 3 reports of severe hepatic injury. Alcohol was a known concurrent drug in 2 of these cases. While the scant information available for these reports limits their meaningful assessment, given the extensive population exposure of caffeinated analgesics consumed

during this time period, severe hepatotoxicity appears to be a rare occurrence with caffeinated analgesics containing APAP.

GI Bleeding

GI Bleeding is a recognized complication of ASA use and is not typically associated with the use of APAP or caffeine. Over the period reviewed, BMS, FDA, and WHO received 12, 20, and 46 reports, respectively, of GI bleeding events. It is not possible to determine if some of the WHO reports are duplicates of the BMS reports. Detailed information on dose, duration, concomitant drugs and prior history of ulcer disease is not available for many of these reports; however, in the BMS data, 9 consumers reported long term use of Excedrin® and in 4 of these consumers, a history of ulcer disease was noted. In the FDA data, 10/20 cases reported additional suspect drugs which are known to also be associated with GI bleeding. Despite the limited information available for these reports, cases across the databases appear to be similar in nature and severity. Furthermore, the occurrence of GI bleeding appears to be relatively uncommon with caffeinated analgesics when considering the widespread use of these products.

Overdose

In combination analgesic products, severe toxicity will most likely be associated with the analgesic component rather than the caffeine component, due to the relative toxicities of the individual ingredients. Therefore, the dose of caffeine, 130mg, in co-formulated analgesic products, is unlikely to be a contributing factor to serious toxicity from these products.

Based on data from the BMS, FDA, WHO, and TESS databases, the majority of caffeine single ingredient and caffeinated analgesic product overdoses were associated with mild to non-existent clinical events and resulted in full recovery, although rare deaths were reported. In the FDA database which contained 2 reports of fatal overdoses with caffeine single ingredient and 3 reports of fatal overdoses with APAP/CAF, all 5 patients had ingested additional drugs concurrently with the caffeine-containing product, which were also considered suspect drugs by the reporter. The TESS data, in which co-ingestions of additional drugs were excluded from our analysis, showed a generally similar profile across all products.

Rebound Headache

Rebound headache is a recognized potential consequence of frequent analgesic use. Based on epidemiologic data, it is believed to be uncommon (<2% in a study of 1,883 subjects with chronic daily headache), and caffeine-containing analgesics are no more likely to be associated with rebound headache than any other type of analgesic medication. When caffeine-containing analgesics are involved, the consumption level of caffeine associated with rebound headache is greater than 15g per month. The etiology of rebound headache remains unclear, however addictive behavior does not appear to be a factor for the vast majority of

analgesic users. Based on this evidence, there is no reason to believe that caffeine doses of 130mg in caffeinated analgesics would result in a greater incidence of rebound headache than caffeine doses of 65mg.

Dependence

Habitual use of caffeine has been well demonstrated among the millions of daily consumers of coffee, however, true compulsive drug seeking behavior appears to be exceedingly rare and limited to a very small subset of individuals.

The psychoactive effects of caffeine show considerable inter-individual variation, but for most individuals, positive effects are seen at low to intermediate doses, with undesirable effects becoming more prominent as doses exceed 200mg. Doses greater than 500mg are usually associated with caffeine intoxication. Moreover, caffeine's effect on the dopaminergic system has been shown to be different from that of drugs of abuse such as d-amphetamine and cocaine.

Caffeine has been shown to exhibit weak drug reinforcing effects. The reinforcing effects of caffeine have been described as an inverted U-shape. Lower doses (up to 50mg) are reinforcing for a small proportion of subjects and increase in frequency as the dose rises. A plateau is reached between 50-150mg, and then the reinforcing effects decrease with higher doses of caffeine, due to its aversive effects.

Tolerance has been demonstrated in animals. The data are less conclusive in humans and may reflect differences in inter-individual metabolism of caffeine.

Physical dependence, characterized by sudden caffeine withdrawal, has been observed with caffeine; however, it may not be as common as previously believed and symptoms rarely interfere with daily activities. It does not appear to be a dose related phenomenon and occurs inconsistently even within individuals. The majority of data on caffeine withdrawal refers to caffeinated beverages, so it is unclear if this phenomenon would also occur with caffeinated analgesic products. However, given the time lag of 12 to 24 hours until the occurrence of symptoms following complete deprivation and the ubiquitous nature and easy availability of caffeine in beverages, a withdrawal syndrome resulting solely from discontinuation of caffeine-containing analgesics is unlikely to develop under daily conditions.

In the spontaneous AE databases for caffeinated analgesic products, there were 49 reports of Drug Dependence and 2 reports of Drug Abuse, the majority originating from the BMS AE database. Most of these reports were not medically confirmed and typically describe a scenario of long term Excedrin[®] use and the inability to discontinue use. Many of the consumers were receiving other medications and had a history of psychiatric conditions. In the absence of detailed medical data regarding dose, duration of use, concurrent medications and illnesses, meaningful assessment of these reports is difficult.

Summary

In summary, while there are reported occurrences of important safety issues with caffeinated analgesic products, these appear to be relatively rare given the long and widespread usage of these products, and are generally associated with other risk factors. No unique toxicities or signals for enhanced toxicities were observed with caffeinated analgesics compared to the individual components.

8.2 Is there a difference in the safety profile between analgesics co-formulated with caffeine 130mg versus 65mg?

Based on the available evidence, it is not possible to differentiate the effects of 130mg versus 65mg of caffeine. Published studies demonstrate that there is considerable inter-individual response, which may in part be due to differences in metabolism of caffeine. Caffeine withdrawal syndrome, less common than previously believed, does not demonstrate a dose response relationship; therefore, the specific amount of caffeine in an analgesic product is unlikely to be a factor.

A comparison of the safety profiles of 65mg and 130mg of caffeine in the BMS Aspirin Free Excedrin[®] trials does not show any meaningful differences in the nature, severity, or frequency of AEs between the products, although head-to-head clinical trials of 65mg versus 130mg have not been conducted.

In the spontaneous AE databases, the majority of non-BMS reports are for Anacin,[®] a combination analgesic containing ASA 800mg and caffeine 64mg per dose. Given the limited information available for the FDA and WHO data and the fact that Excedrin[®] also contains APAP, it is difficult to do more than a gross comparison of AEs reported with analgesic containing caffeine 130mg versus 65mg across databases. However, the AEs reported for both Excedrin[®] and Anacin,[®] including those reported in overdose situations, appear to be generally similar in nature and severity and do not indicate any particular trends or patterns with one product versus the other.

8.3 Is the usage of caffeinated analgesic products different than that of non-caffeinated analgesics?

In the US, The Gallup Organization has been measuring oral analgesic consumption since 1984. According to the Gallup tracking study of several caffeinated and non-caffeinated OTC analgesics, the mean number of OTC analgesic tablets consumed per average 4-week period per consumer over the past 10 years (1990-2000) ranged from 17.8 – 21.9 (N=50,751). The mean tablet consumption during this period was no different for caffeinated analgesic products than for non-caffeinated analgesic products. Furthermore, there was no apparent difference in consumption between caffeinated analgesics

containing 130mg caffeine (Excedrin[®]) and those containing 64mg caffeine (Anacin[®]) (see table below).

**Gallup Tracking Data on Oral Analgesic Mean Tablet Consumption
per Average 4-Week Period
1990-2000**

	Excedrin [®] ES (130mg caffeine per dose)	Anacin ^{®*} (64mg caffeine per dose)	Aspirin (w/o caffeine)**	Advil [®] (ibuprofen)	Tylenol [®] Extra Strength (excl. PM) (acetaminophen)
No. consumers	3,433	1,492	14,227	10,838	20,761
Mean no. of tablets per average 4- week period	17.8	20.3	21.9	17.9	17.8

* Anacin data was available only for 1990-1996 due to low sales volume post 1997.

**Aspirin data post 1997 does not specifically exclude caffeine.

A similar usage profile was also observed for "heavy users" (>30 or >180 pills per average 4-week period) of analgesics.

In a study of analgesic usage among migraine patients in the UK, there was also no difference in usage between caffeinated and non-caffeinated analgesics.

8.4 Does caffeine foster analgesic misuse?

Despite extensive caffeine research over many decades, the weight of the evidence does not support the concern that the addition of caffeine to analgesic products will foster misuse. Further, there are no published experimental studies that clearly implicate caffeine in misuse, nor does consumer use experience demonstrate a misuse problem.

Given the widespread and inexpensive availability of caffeine-containing beverages, it is unlikely that analgesic combinations would be purchased for their caffeine content by those who might be attracted to caffeine's stimulant effect. Indeed, caffeine stimulant tablets (No Doz,[®] Vivarin,[®] etc.) are readily available over-the-counter, and cases of abuse are rare. This conclusion is also supported by caffeine's physiologic profile, which is quite different from drugs of abuse, such as d-amphetamine and cocaine.

Studies in normal subjects show that reinforcement follows an inverted U-shaped function, with reinforcement rising with increased doses until it reaches a plateau between 50-150mg. With higher doses, caffeine's aversive effects discourage misuse. This opinion was corroborated by the FDA Medical Reviewer during the review of the Excedrin[®] Migraine NDA.

The theoretical concern that rebound or withdrawal headache may occur with cessation of caffeinated analgesic use, encouraging additional dosing, is not supported by the evidence. We now know that caffeine has low potential for drug dependence and that dependence is less common than previously thought. We also now understand that rebound headache occurs with all analgesics.

Recognizing the breadth of new data that has emerged in recent years addressing caffeine safety, other drug regulatory bodies have sought to resolve the question of potential misuse of caffeinated analgesics. In January 2000, the drug regulatory authorities of Germany, Switzerland, and Austria convened a committee of international experts to review all the relevant published literature on caffeine and caffeinated analgesics relative to misuse potential. The committee concluded that caffeine's dependence potential is low, and it appears unlikely that withdrawal could play a causative role in stimulating or sustaining analgesic intake. In addition, it concluded that, in the absence of phenacetin, there is insufficient evidence to claim that analgesics co-formulated with caffeine stimulate or sustain overuse or lead to dependence behavior.

9.0 CONCLUSION

Based on this review of the worldwide safety literature, adverse event databases, expert reports and consumer use data that includes both single and multiple dose use, it can be concluded that:

- The safety profiles of analgesics containing 130mg caffeine per dose (ASA 500mg/APAP 500mg/caffeine 130mg, APAP 1000mg/caffeine 130mg) are well characterized and consistent with those of the individual components.
 - No new or enhanced toxicities have been found compared to the individual components.
 - Most adverse events are of a mild and self-limiting nature.
- The potential for caffeinated analgesics to foster analgesic misuse is low.
 - Caffeine has a low potential for drug dependence.
 - Caffeine's U-shaped reinforcement pattern discourages use of high doses due to aversive effects.
 - There are no published experimental studies that clearly implicate caffeine in analgesic misuse.
 - Consumer usage patterns for caffeinated analgesics are similar to those for non-caffeinated analgesics.
- The safety profile of analgesics co-formulated with caffeine at 130mg and 65mg appear to be similar, based on evaluation of the worldwide safety data and consumer usage patterns.
- Caffeine at a 130mg dose is a proven analgesic adjuvant, providing statistical and clinical efficacy improvements to that of the analgesic base alone.
- The Excedrin[®] formulations containing caffeine 130mg have a long history of safe and effective use, and should be included in the Final Monograph.

- Since 1978, more than 47 billion Excedrin® tablets have been used by more than 200 million US consumers.

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Appendix 1

**FDA AE Database Non-BMS Caffeine Single
Ingredient Products and Caffeinated Analgesics**

CAFFEINE	Unknown Caffeine Product
CAFFEINE	PI Gran (Caffeine)
CAFFEINE	Koffein (Caffeine)
CAFFEINE	Caffeine No Dose Form
CAFFEINE	Caffeine Orals
CAFFEINE	Caffeine Powder
CAFFEINE	Caffeine Unknown (Caffeine)
CAFFEINE	Caffeine (Coffee) Liquid
CAFFEINE	Vivarin (Caffeine)
ASA-APAP-CAFF	Anadin Extra (Caffeine, Aspirin, Paracetamol)
ASA-APAP-CAFF	Paracetamol/ASA/Caffeine
ASA-APAP-CAFF	Acetaminophen/Aspirin/Caffeine (Goody's Powders)
ASA-APAP-CAFF	Aspirin, Acetaminophen, Caffeine
ASA-APAP-CAFF	Aspirin/Acetaminophen/Caffeine (Goody's)
ASA-APAP-CAFF	Neuralgin (Acetaminophen/Aspirin/Caffeine)
APAP-CAFF	Anacin Aspirin Free (Acetaminophen, Tablet)
APAP-CAFF	Acetaminophen/Caffeine
APAP-CAFF	Syndol (Paracetamol, Caffeine)
ASA-CAFF	Anacin 3 w/Codeine
ASA-CAFF	Anacin Arthritis Formula
ASA-CAFF	Anacin-3
ASA-CAFF	Anacin Arthritis Pain Formula
ASA-CAFF	ASA + Caffeine
ASA-CAFF	Treo (Acetylsalicylic Acid/Caffeine)
ASA-CAFF	Aspirin w/Caffeine
ASA-CAFF	Acetylsalicylic Acid + Caffeine
ASA-CAFF	Anacin (Aspirin/Caffeine)

Appendix 2

WHO AE Database Caffeine Single Ingredient Products and Caffeinated Analgesics

CAFFEINE	Cafcit
CAFFEINE	Caffeine
CAFFEINE	Vivarin
ASPIRIN+CAFFEINE	Aspirin+Caffeine
ASPIRIN+CAFFEINE	Anadin /Ire/
ASPIRIN+CAFFEINE	Finrexin
ASPIRIN+CAFFEINE	Anacin
ASPIRIN+CAFFEINE	Treo
ASPIRIN+CAFFEINE	Acylicoffin
ASPIRIN+CAFFEINE	Magnecyl-Koffein
ACETAMINOPHEN + CAFFEINE	Azur
ACETAMINOPHEN + CAFFEINE	Prontopyrin Plus
ACETAMINOPHEN + CAFFEINE + ASPIRIN	Excedrin Extra Strength
ACETAMINOPHEN + CAFFEINE + ASPIRIN	Excedrin Migraine
ACETAMINOPHEN + CAFFEINE + ASPIRIN	Contra-Schmerz
ACETAMINOPHEN + CAFFEINE + ASPIRIN	Goodys Powders
ACETAMINOPHEN + CAFFEINE + ASPIRIN	Dolomo T
ACETAMINOPHEN + CAFFEINE + ASPIRIN	Thomapyrin Bei Kopfschmerz
ACETAMINOPHEN + CAFFEINE + ASPIRIN	Neuranidal
ACETAMINOPHEN + CAFFEINE + ASPIRIN	Boxonal
ACETAMINOPHEN + CAFFEINE + ASPIRIN	Thomapyrin N
ACETAMINOPHEN + CAFFEINE + ASPIRIN	Neo-Cibalgina

Appendix 3

Effect of Caffeine on the Biotransformation of APAP

Human Studies

Purpose	Drugs/Doses	Design	Results	Conclusion	Citation
To determine the influence of caffeine on the pharmacokinetics of APAP	Caffeine - 60 mg; APAP - 500 mg	10 healthy, male volunteers were given APAP or a combination of APAP/caffeine in a cross-over design after a 1 week wash-out period; blood samples were drawn and analyzed	Caffeine caused a 29% increase in AUC ($p < 0.01$), a 15% increase in C_{max} ($p < 0.05$) and a 32 % decrease ($p < 0.05$) in total body clearance of APAP	Caffeine taken in doses commonly available can significantly potentiate the therapeutic potential of APAP in man (discussion includes alteration of cycling of acidic metabolites, alteration of APAP disposition, reduction of glutathione depletion, and prevention of hepatotoxicity induced by APAP)	Iqbal, N et al, <i>Biopharmaceutics and Drug Disposition</i> , 15, 481-487 (1995)
To determine the absorption properties of APAP after ingestion of APAP with and without caffeine, to determine the influence of caffeine on absorption of APAP	APAP - 500 mg; Caffeine - 50 mg	7 healthy, male volunteers were given APAP or a combination of APAP/caffeine in a cross-over study	The mean $r(F_u)$ (ratio of fraction of dose excreted in the urine of combo tab and plain APAP tab) did not differ significantly from unity; there were differences among mean absorption times in favor of the combo tab without statistical significance.	No general influence of caffeine on APAP absorption could be established, though there was a slightly positive influence of caffeine on APAP absorption; this influence is not responsible for enhancement of APAP analgesia by caffeine (discussion includes different mechanism for enhancement effect of caffeine on APAP)	Tukker, J. et al, <i>Pharm Weekbl Sci</i> , 8, 239-243 (1986)

Purpose	Drugs/Doses	Design	Results	Conclusion	Citation
				analgesia, 1 st pass metabolism has large intersubject and low intrasubject variability, therefore, likely explanation in pharmacodynamic effect)	
To determine the effect of caffeine on APAP pharmacokinetics in normal subjects	APAP - 1000 mg; Caffeine - 100mg	9 normal subjects were given APAP or a combination of APAP/caffeine in a cross-over study	APAP concentrations after both APAP alone and combo showed slightly lower levels after the combo administration; there were mild differences between the combo and APAP alone	A pharmacokinetic interaction is observed between caffeine and APAP after a single therapeutic dose; this interaction may attenuate liver toxicity	Wojcicki, et al, <i>Acta Med Biol</i> , 42/2, 51-55 (1994)
To determine the effect of caffeine on APAP pharmacokinetics in normal subjects	APAP - 1000 mg; Caffeine - 100mg	Normal subjects were given APAP or a combination of APAP/caffeine in a cross-over study	APAP concentrations after both APAP alone and combo showed slightly lower levels after the combo administration; there were mild differences (27% decrease in Cmax, 22% decrease in AUC, 49% increase in Vd, 20% increase in Tmax, 12 % increase in half-life, 20% increase in clearance) between the combo and APAP alone	A pharmacokinetic interaction is observed between caffeine and APAP after a single therapeutic dose of the combo; this interaction may attenuate liver toxicity	Rainska, T et al, <i>Pol J Pharmacol Pharm</i> , 44, Supplement, 212 (1992) (Poster presentation of above 1994 Wojcicki article)
To determine to effect of caffeine on toxicity and pharmacokinetics of APAP	APAP -1000 mg Caffeine - 100mg	Nine healthy volunteers in randomized, cross-over study twice at 1-week intervals	There was a decrease in APAP levels, smaller AUC changes of APAP levels, and therefore faster elimination of the drug after co-administration with caffeine	A pharmacokinetic interaction between APAP and caffeine was observed; APAP combo may be less toxic than APAP alone	Rainska-Giezek T, <i>Annales Academiae Medicae Stetinensis</i> , 41, 69-85 (1995) (same human data as previously published)
To determine the effect of combining drugs with aspirin, caffeine, and codeine	APCC' - aspirin 453.6mg, phenacetin 324 mg, caffeine 64.8 mg, and codeine 16.2	24 healthy volunteers randomized into 4 groups, APCC', P, AA'CC', and A' and	The changes produced in the metabolism of APAP when it was taken as AA'CC' were minor. No	In this study, when caffeine was given in a combination product, it did not seem to alter	Thomas, BH et al, <i>Clin Pharmacol Ther</i> , 13, 906-909 (1972)

Purpose	Drugs/Doses	Design	Results	Conclusion	Citation
in the same proportions found in a commercially available phenacetin preparation	mg, P = phenacetin 324 mg, AA'CC' – similar to APCC' except that the phenacetin was replaced by 324 mg of APAP (A')	treated in a cross-over trial over a 4 week period	changes in blood or urine were observed with any of the drug treatments	APAP metabolism.	
To study APAP and Caffeine Bioavailability	APAP 500mg/65 mg caffeine – 2 different formulations, APAP 500mg, APAP 325 mg	N = 36 adults, 16 males, 20 females in which each subject tested the 4 meds in one of 4 different order; blood withdrawals were taken at 0,10,20,40,60,120,180, and 240 minutes following scheduled 2 tablet dosing (3 tabs for APAP 325 mg)	The study results do not seem to suggest that caffeine potentiates APAP levels. The Lancet formation F #2252 and current AFE formulation contain similar ingredients other than the APAP excipients (which are different)	Caffeine does not seem to potentiate APAP levels	Battikha JP. Data on file, BMS, 1982
Report of patient overdose	Allegedly consumed 100 capsules of Extra Strength Excedrin (each capsule contains 250 mg APAP, 250 mg ASA, and 65 mg caffeine)	Pt was initially treated 4.5 hr later	No display of significant CNS stimulation (cardiac arrhythmia, muscle spasm, or convulsions) despite the presence of 175mcg of caffeine per mL of serum. APAP was measured at 52 mcg/mL	This patient's clinical course suggests an antagonistic interaction between caffeine and APAP **resulted in mice study	Deng, J. F. et al <i>J. Toxicol:Clin Toxicol</i> , 19 (10), 1031-1043 (1983)

Animal Studies

Mice

Purpose	Drugs/Doses	Design	Results	Conclusion	Citation
To determine to effect of caffeine on toxicity of APAP	APAP - IP Caffeine unknown doses	620 Swiss mice were given drug IP, survival time, number of animal deaths were noted, the degree of hepatic damage was assessed and included histological and histopathological exams	There was a decrease in acute toxicity and hepatotoxic action of APAP administered in combo, as noted in significant decrease in LFT activity and an increase in the concentration of CYP-450 and GSH in the liver which decreased after administration of APAP alone and by limitation or lack of liver necrosis	A pharmacokinetic interaction between APAP and caffeine was observed; APAP combo may be less toxic than APAP alone	Rainska-Giezek T, <i>Annales Academiae Medicae Stetinensis</i> , 41, 69-85 (1995)
To study the effect of caffeine on APAP-induced hepatotoxicity and APAP bioactivation by liver microsomes from uninduced and pretreated mice (pretreated with agents that induce CYP-450)	Caffeine - 0.1, 1, 5mM APAP -0.5, 2, 10 mM	Caffeine was given in different concentrations to uninduced mice and mice pretreated with various agents that induce CYP -450 (agents included phenobarbital, dexamethasone, <i>B</i> -naphthoflavone, and acetone)	Caffeine was a competitive inhibitor of APAP bioactivation in microsomes from BNF- and acetone-treated mice. Caffeine increased APAP bioactivation in microsomes from uninduced, PB-, and DEX-treated mice, but the apparent Km values for APAP were increased by the caffeine. The variable effect of caffeine on APAP hepatotoxicity correlated with the effect of caffeine on APAP bioactivation by liver microsomes, regardless	The results suggest that a murine CYP-450 subfamily similar to the rat P450III _A subfamily may be the candidate in mediating the stimulatory effect of caffeine on APAP bioactivation and APAP-induced hepatotoxicity. The effect of caffeine on APAP bioactivation appears to be P450 isoenzyme selective. (Mention of differences in female S-W mice and male BDF1 mice)	Jaw, S and Jeffery, EH, <i>Biochem Pharmacol</i> , 46/3, 493-501 (1993)

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Purpose	Drugs/Doses	Design	Results	Conclusion	Citation
To study the effect of caffeine on mortality rates and biochemical and histological parameters of liver damage after administration of toxic doses of APAP	Mortality: APAP - 460 and 625 mg/kg IP Caffeine - 10% (by wgt) of the APAP dose or at 100mg/kg IP Hepatotoxicity: APAP - 300mg/kg Caffeine - 30 or 100mg/kg 7 daily IP injections: APAP - 230mg/kg Caffeine - 23 or 100mg/kg	Mortality: 8 treatment groups of 20 mice each after single IP doses Hepatotoxicity: 6 groups of ten mice 3 and 24 hrs after single IP doses, and after 7 daily IP injections	of pretreatment. Caffeine markedly increased the survival rate after administration of a dose of APAP that was lethal to 50% and 100% of mice, reduced liver damage as assessed by SGPT and SGOT, partially prevented the depletion of reduced glutathione and reduced histological changes to the liver accompanying APAP intoxication	The results support the possibility that caffeine might be useful for the treatment of APAP intoxication in humans	Rainska, T et al <i>J Inter Med Res</i> , 20, 331-342 (1992)
To examine the interaction of caffeine with APAP: schedule dependency of the antagonism by caffeine of APAP hepatotoxicity	APAP range of 200 – 300 mg/kg IP Caffeine range of 75– 150 mg/kg IP	Mice were given caffeine 6 hrs prior to a hepatotoxic but non-lethal dose of APAP, given no later than 1 hr after APAP, and given daily for 3 days prior to APAP	Caffeine given 6 hrs before APAP dose significantly antagonized APAP hepatotoxicity as noted by ALT activity. Caffeine given after APAP produced complete antagonism only when caffeine was given no later than 1 hr after APAP. Caffeine given daily for 3 days prior to APAP enhanced APAP toxicity markedly, but little or no toxicity followed when caffeine-pretreated mice received APAP followed immediately by caffeine.	Caffeine and its primary metabolites, theophylline, theobromine, paraxanthine, and trimethyluric acid compete with APAP for biotransformation by the CYP-450 mixed function oxidase system, thereby reducing the rate of formation of the hepatotoxic APAP metabolite	Gale, G and Smith, AB <i>Research Communications in Chemical Pathology and Pharmacology</i> , 59/3, 305-320 (1998)
To examine the effects of caffeine on the pharmacokinetic parameters of APAP metabolism	APAP - 200mg/kg IP Caffeine - 100mg/kg IP	Male mice were given caffeine and APAP IP; urine and blood samples were obtained	Caffeine exerted effects on fractions of APAP metabolites which are formed as a consequence of	It was concluded that the protective effect of caffeine against APAP-induced hepatotoxicity may be explained by a	Price, V and Gale, G <i>Research Communications in Chemical Pathology and Pharmacology</i> ,

Purpose	Drugs/Doses	Design	Results	Conclusion	Citation
			biotransformation via CYP-450 dependent pathways. Following caffeine coadministration with APAP, the apparent rate constants were decreased for the sulfate (35%), mercapturate (56%), cysteine (42%), and methylthio (47%) metabolites of APAP	decreased in the rate of formation of NAPQI, the reactive metabolite of APAP	57/2, 249-260 (1987)
To assess the influence of fasting, effects on serum levels of hepatic enzymes, the role of GSH, and the extent of covalent binding of APAP metabolite when APAP and caffeine are administered singly and concurrently	Acute Toxicity: APAP - 450 mg/kg IP Caffeine - 100mg/kg IP Gross/Microscopic Pathology: APAP - 250mg/kg IP Caffeine - 100mg/kg IP APAP -500mg/kg PO Caffeine - 200mg/kg PO	Acute Toxicity: Fasting male mice were administered drugs IP Gross/Microscopic Pathology: Fasting and Fed Mice were given APAP and caffeine, singly and in combination, both IP and PO.	Caffeine antagonized the acute toxicity of APAP and reduced the severity of APAP-induced hepatic necrosis as assessed grossly and microscopically. Caffeine also attenuated the elevations of serum transaminase levels following APAP administration. Caffeine alone led to a reduction of hepatic GSH concentrations.	The antagonistic action by caffeine of APAP toxicity occurs in spite of markedly depleted hepatic GSH levels when both drugs are administered; this antagonism may occur through competition or interaction between APAP and caffeine at the level of biotransformation by CYP-450 dependent mixed function oxidase system	Gale, G et al <i>Research Communications in Chemical Pathology and Pharmacology</i> , 55/2, 203-225 (1987)

Purpose	Drugs/Doses	Design	Results	Conclusion	Citation
To determine if APAP and caffeine coadministration enhances the hepatotoxicity of APAP	Coadministration of APAP and caffeine - APAP - 400mg/kg IP Caffeine- 50 mg/kg or 100mg/kg IP Pretreatment with caffeine prior to APAP administration - APAP - 300 mg/kg or 400 mg/kg IP Caffeine - 75 mg/kg bid for 3 days IP	Mice were injected with drugs and livers and kidneys were used for histopathological studies	Caffeine abolished the hepatotoxic action of APAP when caffeine was administered immediately after an otherwise hepatotoxic dose of APAP. Pretreatment of mice with caffeine for 3 days followed by APAP enhanced the hepatotoxicity of APAP.	Caffeine interferes with APAP metabolism when administered concurrently, but induces the microsomal mixed function oxidase system when used in a pretreatment regimen, leading to a more rapid rate of formation of the hepatotoxic arylating APAP biotransformation product.	Gale, G et al <i>Research Communications in Chemical Pathology and Pharmacology</i> , 51/3, 337-350 (1986)
To determine whether a decrease in caffeine toxicity could be observed with concomitant administration of APAP, to examine the MOA of this effect	Caffeine-induced seizures: APAP - 100, 150, 300, 450 mg/kg given IP Caffeine - 300-450 mg/kg IP Audiogenic seizures: Caffeine 12.5 to 75 mg/kg IP with and without prior administration of APAP 75mg/kg Biochemical studies: Use of reagents with 1, 75, or 150 mcg/mL of APAP	Mice were injected IP with varying doses of APAP at 2, 5, and 12 min prior to caffeine injections and observed for responses. Mice were injected IP with varying doses of caffeine with and without prior administration of APAP and observed for responses Slices of rat cerebral cortex were used; specific radioactivity of ATP was measured by UV Spectrometry	Approximately 30 % of mice injected with caffeine survived for 4.5 min compared to 10.6 min for 70% of mice. The overall mortality rate for animals receiving no APAP was 44% compared to 21% for mice receiving APAP prior to auditory stimulus. For all animals, the convulsion rate was 58% without APAP versus 21% with APAP. The incidence of audiogenic seizures following caffeine administration was reduced from 50% to 5%. Longer times or higher conc of APAP yielded values equal to or greater than control	The authors conclude that the impact of APAP on cyclic AMP metabolism in the CNS might provide further clues as to the basis of these observations. The mechanism of this interaction between APAP and caffeine might be attributed to pharmacokinetic effects (lowering of caffeine blood levels of APAP), general anticonvulsant activity of APAP regardless of the caffeine presence, or specific interaction of caffeine and APAP, other than a kinetic interaction.	Deng, J. F. et al <i>J. Toxicol: Clin Toxicol</i> , 19/10, 1031-1043 (1983)

Purpose	Drugs/Doses	Design	Results	Conclusion	Citation
			values. Thus APAP has considerable effect on either the transport of ADP or its ultimate transformation to ATP.		
Rats					
To quantitate changes in the formation clearance of NAPQI to assess in vivo the activation and inhibition of NAPQI formation by methylxanthines	APAP - 50 mg and 100 mg/kg IV Caffeine - 100mg/kg IP Theophylline - 93 mg/kg IP	Rats were pretreated with PB (80 mg/kg) daily for 4 days and 3-MC (20 mg/kg) daily for 2 days and control	In PB-treated rats, caffeine increased the formation clearance of NAPQI as previously observed. In 3-MC-induced rats, formation clearance decreased when caffeine was administered, again as previously observed	The authors concluded that these in vivo results agree with the results of their previous studies. Caffeine can activate CYP-450 in vivo and the most likely isoenzyme is CYP11A2.	Lee, CA et al <i>J Phar Exp Ther</i> , 277/1, 287-291 (1996)
To study the effect of caffeine on APAP hepatotoxicity	APAP - 0.5g/kg IP Caffeine - 0.1g/kg IP	4 groups of SD rats fasted for 18 hours; given APAP alone (11), Caffeine alone (6), Combo (8), and Control (6)	24 hours after treatment, SGOT, SGPT were not significantly altered by APAP not caffeine injection alone; however, combo treatment significantly increased enzyme activities; APAP - induced hepatic necrosis was significantly increased by co-administration of caffeine (histology results from liver samples); caffeine alone did not produce any hepatic necrosis	Careful observations on hepatotoxicity are suggested when APAP and caffeine are prescribed simultaneously (discussion of CYP-450 enzyme system - APAP and CYP-448 - caffeine; competitive inhibition of APAP biotransformation)	Sato, C et al, <i>Toxicology</i> , 34, 95-101 (1985)
To study the mechanism of increased hepatotoxicity of APAP by the co-administration of caffeine	APAP - 0.5g/kg IP Caffeine - 0.1g/kg IP	4 groups of SD rats fasted for 18 hours; given APAP alone, Caffeine alone, Combo, and Control	Caffeine enhanced APAP-induced GSH depletion and potentiated covalent binding of the reactive metabolite to cellular	Caffeine appears to potentiate APAP-induced hepatotoxicity mainly by enhancing the production of a reactive metabolite of APAP by	Sato, C et al <i>J Pharm Exp Ther</i> , 248/3, 1243-1247 (1989)

Purpose	Drugs/Doses	Design	Results	Conclusion	Citation
			proteins. Caffeine potentiated the decrease in the extracellular release of GSH + oxidized glutathione. In the cells, the production of APAP-GSH conjugate was increased in the presence of caffeine, while that of glucuronide conjugate was decreased.	mixed function oxidases; to what extent caffeine-induced GSH depletion plays a role needs clarification	
To evaluate the effect of methylxanthines on APAP hepatotoxicity in various induction states	Caffeine 200mg/kg Theophylline 186 mg/kg Theobromine 186 mg/kg APAP 250, 300, and 500 mg/kg All drugs were administered IP	Rats were pretreated with 3 methylcholanthrene (3-MC)(20mg/kg) daily for 2 days or phenobarbital (80mg/kg) daily for 4 days	In 3-MC -induced rats, each methylxanthine afforded protection in varying degrees against APAP-induced hepatotoxicity (as reflected by ALT and liver histopathology) . In PB-induced rats, caffeine and theophylline substantially potentiated the APAP toxicity; theobromine had no effect. Caffeine depleted hepatic GSH in uninduced and PB-induced rats, but not in 3-MD-induced rats.	The results suggest that the induction state of the species may account for the difference in caffeine's effect on the biotransformation of APAP in the liver	Kalhorn, TF et al <i>J Phar Exp Ther</i> , 252, 112-116 (1990)
To study the CYP-450 forms involved in APAP hepatotoxicity in rats	APAP - 1 to 10mM Caffeine - 0 to 5mM	Rat liver microsomes, prepared after pretreatment with various inducers, were used to examine the effect of caffeine on N-acetyl-p-benzoquinoneimine	There was a 43% decrease in NAPQI formation at caffeine conc. of 0 to 0.5mM; NAPQI formation was accelerated at caffeine conc greater than 2.5mM. In	The results suggest that CYP-450III _{A2} , the adult male constitutive form, is the predominant form activated by caffeine; CYP-450III _{A1} may be activated to a lesser extent.	Lee, C et al <i>Drug Metab Dispos</i> , 19/2, 348-353 (1991)

Purpose	Drugs/Doses	Design	Results	Conclusion	Citation
		(NAPQI) formation	uninduced and PB-induced adult rat microsomes, there was a 3 to 4-fold acceleration of NAPQI formation with no evidence of inhibition. Caffeine caused a 3 to 4-fold increase in NAPQI formation by juvenile male and female rat microsomes, but no activation was observed in adult female rat microsomes; caffeine activated a member of the CYP-450IIA subfamily	Protection in induced rats may be due to competitive inhibition of CYP-P450IAI	
To determine the mechanism of inhibition of NAPQI formation by CYP-450IA1	Caffeine - up to 5nM	Adult male and female rat liver microsomes	Caffeine competitively inhibited formation of NAPQI by CYP-450IA1. Caffeine accelerated the formation of NAPQI from APAP in PB-exposed rat liver microsomes and in adult uninduced male, but not female microsomes. Caffeine led to activation of APAP turnover.	Caffeine appears to activate NAPQI formation by the CYP-450IIIA family and appears to be relatively selective for IIIA2.	Lee, CA, et al <i>Pharm Res</i> , 7/9, Supplement, S268 (1990) (May be precursor to previous publication, 1991)
To assess the role of caffeine in the modulation of APAP hepatotoxicity in different induction states in rats	APAP - 250 -300 mg/kg Caffeine - 93 mg/kg	Rats were induced with 3-methylcholanthrene and PB, administered APAP alone, and also given caffeine; the level of hepatic necrosis and serum ALTs were measured	Caffeine afforded protection from APAP toxicity in the pretreated 3-MC animals; caffeine administration to PB-induced rats elicited APAP toxicity	In PB-induced microsomes, APAP-3GSH increased with caffeine concentration. In 3-MC-induced microsomes, caffeine caused a progressive inhibition of APAP-3GSH up to 1 mM, but at higher caffeine	Lee, CA, et al <i>Pharm Res</i> , 6/9, Supplement, S205 (1989)

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				concentrations, the APAP-3GSH conjugate rose such that at 5mM, the levels were similar to control	
To determine effects of caffeine on the absorption and analgesic efficacy of APAP in rats	APAP – 200 mg/kg Caffeine - 10,50, or 100 mg/kg	Oral doses of caffeine were given to rats together with APAP	Caffeine given to rats with APAP inhibited APAP absorption and decreased serum conc of APAP. The caffeine action was dose dependent. APAP analgesia was not decreased by caffeine, which, given alone at 50 and 100mg/kg, increased the pain threshold in rats. The lowest caffeine dose reduced APAP analgesia significantly.	Delayed stomach emptying was cited as probably the main cause for the diminished absorption of orally given drugs in the presence of caffeine	Siegers, CP <i>Pharmacology</i> , 10/1, 19-27 (1973)
Mice/Rat					
To study the effect of caffeine on APAP/ glutathione conjugate in rat and mouse liver microsomes	Use of incubation mixture of buffer, 1.0mm glutathione, 0.4mm NADPH, and various conc of APAP (0.2,0.5,1,2,4,8) with and without various amounts of caffeine (1,0.1,0.4,2,10,20)	Rat and mouse liver microsomes	In the presence of caffeine, glutathione conjugate production in rat microsomes was enhanced; in mouse microsomes were not significantly affected	The data may partly explain the species difference in the effects of caffeine on APAP hepatotoxicity	Lui, J, et al <i>Xenobiotica</i> , 22/4, 433-437 (1992)
Canine					
To evaluate the effects of caffeine on blood levels of ASA and APAP when the 3 drugs are co-administered.	ASA – 30 mg/kg APAP – 30 mg/kg Caffeine – 8 mg/kg	12 beagles were randomized into a 4-way crossover design, separated by a minimum 1-week washout period, so that each animal received each treatment over the	The addition of caffeine to ASA and APAP did not significantly affect the bioavailability of either component to dosing that component alone.	In this dog model, the addition of caffeine to the combination of ASA and APAP at the same ratio as that of Excedrin, does not appear to affect the blood levels of either APAP or ASA	Mueller, F and T. Re, Data on file, BMS, 1994

Purpose	Drugs/Doses	Design	Results	Conclusion	Citation
		course of the study. Blood samples were drawn at baseline, and at 10,20,40,60, and 90 minutes after treatment	** There were missing APAP conc and the terminal portion of individual conc-time curves was inadequately define; all APAP drug profile parameter estimates were affected by missing values. Therefore, analysis results should be viewed with caution.		