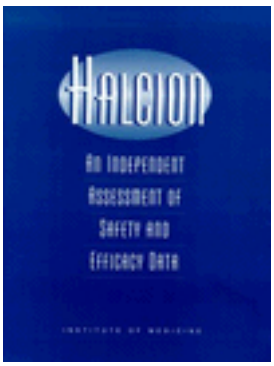

Halcion: An Independent Assessment of Safety and Efficacy Data

Committee on Halcion: An Assessment of Data Adequacy and Confidence, Division of Health Sciences Policy, Institute of Medicine

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An Independent Assessment of Safety and Efficacy Data

Committee on Halcion: An Assessment of Data Adequacy and Confidence
Division of Health Sciences Policy
Division of Neuroscience and Behavioral Health
INSTITUTE OF MEDICINE

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COMMITTEE ON HALCION: AN ASSESSMENT OF DATA ADEQUACY AND CONFIDENCE

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Preface

The "sleeping pill" Halcion (triazolam) has a long and controversial history in terms of its approval and surveillance and the attention that it has received in the media. The safety and efficacy of Halcion as a drug for promoting sleep have been extensively reviewed by a number of regulatory agencies including those in the United States and United Kingdom. A review of the data, however, suggests that the results of these analyses are inconsistent and, at times, conflicting. In the United Kingdom, for example, Halcion has been removed from the market (following Upjohn's announcement in 1991 that "errors had been identified" in one of the clinical trials). Attempts in the United Kingdom to overturn this decision by committees and panels endorsing the drug have thus far been unsuccessful. In the United States, some scientists were concerned about the drug's safety and efficacy but have not convinced the U.S. Food and Drug Administration (FDA) to withdraw it. Neither proponents nor critics of the drug are completely satisfied with the present status, partly due to the awareness that scientific reviews and determinations may have been subject to political and other external influences.

It is appropriate, then, that these issues concerning Halcion be brought to the Institute of Medicine (IOM). As part of the National Academy of Sciences, IOM occupies a special niche in the science policy arena as an independent adviser to the federal government and others on matters pertaining to public health. IOM provides unique advantages in situations such as this one in which both high-quality science and independent Perspective are important.

In addressing its task, the committee was faced with reviewing, assessing, and evaluating a huge amount of information in a short amount of time. The committee met three times in 3 months to review data and testimony from FDA, Public Citizen, Pharmacia and Upjohn, and Canadian and British government agencies. More than 20 years' worth of clinical trials, postmarketing reports, published literature, statistical analyses, expert opinion, and meeting transcripts were reviewed (see Appendix E). In addition to providing the committee with copies of the New Drag Application for Halcion, FDA was helpful in arranging for committee members to interview and meet with various FDA Staff members who were intimately involved with and highly knowledgeable about the issues. The committee interviewed individuals in the Office of Epidemiology and Biostatistics, the Division of

Neuropharmacological Drug Products, and the Division of Drug Evaluation I, including individuals who worked directly with the evaluation of the safety and efficacy of Halcion and the Spontaneous Reporting System

In addition, the IOM committee heard reports from Public Citizen, a consumer advocacy group that filed a petition requesting FDA to remove Halcion from the U.S. market. Dr. Sidney Wolfe, representing Public Citizen, discussed the issues with the committee at their first meeting. Copies of the petition and all supporting documents were provided to the committee and reviewed. Public Citizen also hosted an additional meeting with Dr. Anthony Kales, a sleep researcher who has been prominent in the Halcion debate, and Dr. Edward Bixler, a professor of psychiatry, both of whom are from Pennsylvania State University College of Medicine, Hershey, Pennsylvania, and have published extensively on the subject of Halcion. Drs. Wolfe, Kales, and Bixler were helpful in providing details about certain aspects of the science, approval process, and safety issues.

The committee requested, received, and reviewed a large amount of detailed information from Pharmacia and Upjohn, including copies of original protocols, case report forms, and final reports from more than 40 studies that the committee considered important. Upjohn additionally provided the committee with integrated summaries of the safety and effectiveness of Halcion and data for subjects withdrawing from Halcion drug trials, and filled numerous requests from the committee for additional data. Upjohn also agreed to disclose all the relevant documents from proprietary files so that the committee could review them as public information (see Appendix F).

Although the database was enormous, the specific task was a narrowly focused one, primarily, to assess the adequacy of study designs and the quantity and quality of the available data related to the safety and efficacy of Halcion taken at different doses and for different durations, including those described in the current labeling. It was not part of our charge to review and evaluate specific concerns of the Public Citizen petition or any other criticisms that have been raised about Halcion. These concerns, however, do relate to the committee's charge, were of great interest to the committee, and have been addressed in our report. Similarly, we were not appointed to second-guess the United Kingdom or any other countries that removed Halcion from the market, but we hope that our report will be of interest to them.

One of the unique aspects of this activity that needs to be highlighted is that the committee performed its own reanalyses of key components of the data. Thus, in addition to examining the clinical trials and other dam to make an independent assessment of their quality, the committee's conclusions are also based on some newly generated data analyses.

Although our task was fairly narrow, the committee was inescapably drawn by the data to an area of broader concern that is addressed in some detail in the report and that became apparent to the committee in the course of assessing the current patterns of Halcion use. As is described in various other reports, including the 1996 FDA task force report, Halcion is often prescribed and used in a manner that far exceeds the recommended labeling with respect to close and duration. This has direct and broad implications for the safety and possible efficacy of Halcion, but is also an issue for other drugs and products on the market. Moreover, only limited data on the actual use of drugs are available, and in the committee's opinion, insufficient effort appears to be directed toward assessing reported adverse events and responding effectively to these issues.

Lastly, this has been a truly interesting and challenging experience. The issues were complex and controversial, and the data were limited in some areas; however, the potential ramifications were large. Because of this, debate among the members was often vigorous. But the purpose was always clear: an objective analysis of the data. It would have been an insurmountable task, however, if not for the support, cooperation, and assistance from all parties involved. Most importantly, it was the vigor, critical insight, and dedication of both the committee and the supporting IOM staff that made this a successful activity.

William E. Bunney
Chair

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Executive Summary

Recent estimates indicate that there is a 10 percent prevalence of chronic insomnia in the adult population of the United States, with an associated annual cost of $90 billion to $107 billion. Since its approval in 1982 for use in the treatment of insomnia, an estimated 11 billion prescriptions for Halcion[1] (triazolam) have been filled worldwide. Its widespread use is attributed, at least in part, to the fact that as a benzodiazepine, Halcion was considered safer in terms of overdose, drug interactions, and addictive potential than the barbiturates and other hypnotic drugs that were often previously used for this purpose. In addition, Halcion had a relatively short plasma elimination half-life that afforded it the additional benefit of less morning grogginess compared to that from the use of other, longer half-life benzodiazepings.

Concerns about the safety of Halcion began to emerge when a Dutch physician reported a possible link between this drug and a syndrome that included depression, amnesia, hallucinations, and anxiety. In the United Kingdom, a decision to evaluate the safety of Halcion was made in response to a report from the manufacturer, Upjohn, in 1991 that "errors had been identified in a report of one of the clinical studies included in the original" application for approval. Since that time and for various reasons, the United Kingdom, Brazil, Argentina, Norway, and Denmark have removed Halcion from the market; Upjohn withdrew Halcion from the market in The Netherlands. Other countries, including the United States and Canada, modified the labeling to reduce the recommended dose and duration of treatment and to heighten awareness regarding possible side effects affecting behavior and cognition. The labeling changes raised questions regarding the hypnotic effectiveness of these lower doses of Halcion.

[1] "Halcion" refers to the actual product that is manufactured and marketed by Upjohn. "Triazolam" is the generic name of the pure active ingredient in Halcion. The committee uses the term "Halcion" in the text when it discusses clinical trials or events involving the actual product; otherwise, the committee uses the term "triazolam."

In 1996, a U.S. Food and Drug Administration (FDA) task force looking into the medical, procedural, and legal aspects of the drug's approval process concluded that Halcion was "safe when prescribed according to current labeling" and "effective in the treatment of insomnia at doses and durations currently recommended in the labeling." The task force also recommended that a separate reassessment of the safety and efficacy of Halcion be conducted by a panel of experts. To that end FDA requested that the Institute of Medicine (IOM) assess the following:

- the adequacy of the study designs and quantitative endpoints used in the major clinical trials of Halcion;
- the quality and quantity of postmarketing data with respect to adverse drug reactions;
- the overall confidence in the data on the effectiveness, adverse events, and side effects of Halcion at different doses and for different durations, including those specified in the current product labeling; and
- the need for additional studies to clarify and characterize the risk and efficacy profiles of Halcion.

THE DATA

The committee evaluated numerous sources of data to provide a broad perspective on the efficacy and safety of Halcion. These sources are listed in detail in Appendix. E. An abbreviated list appears in Box 1.

BOX 1 RESOURCES REVIEWED BY THE COMMITTEE

Premarketing clinical trial data (from the New Drug Application)
Information from FDA Psychopharmacological Drug Advisory Committee meetings
International data
Integrated summaries of safety and efficacy
Postmarketing surveillance data
Spontaneous report data
Published literature
Use, sales, and prescription data

ASSESSMENT OF EFFICACY DATA

The primary purpose of a hypnotic agent is to improve the quality of sleep. The efficacies of hypnotic agents are assessed through subjective evaluations that involve the use of questionnaires or interviews and also through objective (polysomnographic) measurement of endpoints that include time to onset of sleep, duration of sleep, and number of awakenings.

Because there is ample evidence of Halcion's efficacy at 0.5 mg, and because this is no longer a recommended dose level, the committee focused much of its attention on data related to the efficacies of the 0.25- and 0.125-mg doses, including the possibility of the development of tolerance over time.[2] The committee examined the study designs from premarketing and postmarketing clinical trials and, having judged the study designs to be sufficient to produce reliable data, used statistical methods and analyses to evaluate the data across studies, grouping them by those that measured polysomnographic endpoints and those that measured subjective endpoints. The committee also reviewed the published literature.

Conclusions and Recommendations

The following conclusions and recommendations are based on the committee's review and analysis of various types of data, including randomized, controlled (dose and duration) clinical trials, spontaneous reports of adverse events, and survey data.[3] The postmarketing trials met current standards for a well-controlled clinical trial; the premarketing trials were adequate for the time and were sufficient to provide data of adequate quality to judge the effects of the drug. A statistical reanalysis of the data from trials using questionnaires to evaluate the subjects' sleep clearly supports the previous analyses that Halcion positively affects the quality of sleep. Polysomnographic data did not exhibit evidence of tolerance over time. Additionally, the committee found that a dose-response relationship does exist, and the literature generally supports the claim that the drug is efficacious.

Data Adequacy

Based on review of the original studies, FDA's reanalysis, and the IOM committee's own reanalysis of 20 studies, the questionnaire and polysomnographic dam are adequate to support the conclusion that Halcion is effective in achieving the defined endpoints in the general adult population with insomnia when used as directed (in the current labeling) at doses of 0.25 mg for up to 7-10 days. In addition, polysomnographic data from clinical trials support the efficacy of Halcion at 0.25 mg in non-geriatric adults for 2 Weeks or more.

The questionnaire data are limited but adequate to support the conclusion that Halcion is effective in achieving the defined endpoints at the 0.125-mg dose in the geriatric population. Two studies (one for 2 days' duration; one for 7 days' duration) support this conclusion; one

[2] Tolerance is the pharmacological term indicating a waning effect with the continuing use of the same dose of a drug, or the ability to endure or be less responsive to a stimulus, especially over a period of continued exposure. See Appendix C.

[3] It is important to note that the conclusions and recommendations are based on a review of publicly available information. The committee did not review original, raw data or case reports but, rather, reviewed the data that were summarized in the New Drag Application and other sources and data that have been reviewed by FDA. The committee's analyses were based on these publicly available summary data.

study in the literature did not. Although there are no polysomnographic clinical trials in the New Drug Application for the 0.125-mg dose in geriatric subjects, nor in the postmarketing clinical trials or published literature for this dose in geriatric subjects with insomnia beyond 3 days of treatment, the committee's reanalysis of the combined data clearly shows statistically significant drug-related effects at the 0.125-mg dose in the geriatric population.

Although analysis of the questionnaire data supports the efficacy of Halcion at a dose of 0.125 mg in the geriatric population, inadequate data are available to establish the effect of this dose on sleep architecture in the elderly insomniac.

***Recommendation 1: Improve Confidence in Lowest Dose*. Definitive short-, intermediate-, and long-term polysomnographic studies are needed in a geriatric population to determine the sleep architecture of elderly insomniacs using the 0.125-mg dose.**

Clinical Trial Design

The study designs and quantitative endpoints (i.e., sleep latency, duration, awakenings, and global assessment) used in the major clinical trials of Halcion in the past are of sufficient quality to yield adequate and reliable data for the determination of efficacy. The modem standards for the conduct of clinical trials have become more rigorous.

***Recommendation 2: Update Guidelines*. FDA should revise and update its *Guidelines for the Clinical Evaluation of Hypnotic Drugs* (U.S. Department of Health, Education, and Welfare, 1977) to include clinical trials on the intermediate- and long-term efficacies of hypnotic drugs. Future studies comparing Halcion with other drugs should use multiple doses of both Halcion and the comparator drugs to permit the determination of relative clinical potency.**

***Recommendation 3: Improve Outcomes Measures*. Research is needed to identify the most valid and reliable endpoints for determination of the clinical efficacies of hypnotic agents. Most importantly, this should include endpoints that are nested in a 24-hour day-night cycle (e.g., to evaluate amnesia and daytime sedation). This should also include better integration of the subjective and objective (polysomnographic) response measures.**

Tolerance

The committee's analysis of questionnaire data from studies of the efficacy of Halcion taken for up to 43 days indicates that there is no evidence to support the development of tolerance to the hypnotic effects of Halcion; that is, the difference in the effects between drug versus placebo was consistent over time (0.5 mg for 43 days, 0.25 mg for 28 days, 0.125 mg for 8 days, and 0.25 nag for 12 weeks). In addition, polysomnographic data from clinical trials

do not provide evidence of tolerance. In contrast to the clinical trial data, the polysomnographic literature suggests that tolerance may develop. However, available data suggests that tens of thousands of prescriptions are being obtained by patients for much longer periods of time (e.g., the Evaluation of Medications for Insomnia in Canada study reports a mean duration of 1.7 years of use in Canada). No data indicating the efficacy (or safety) of such long-term use of Halcion for chronic insomnia exist.

***Recommendation 4: Determine Tolerance*. Controlled clinical trials of a duration of Halcion use beyond that recommended in the current labeling are needed to determine whether tolerance to Halcion develops with long-term use.**

ASSESSMENT OF SAFETY DATA

The committee also considered the quality and the adequacy of the data (e.g., clinical trial data and spontaneous reports of adverse events) with regard to the safety of Halcion, particularly the concerns that the drug (1) produces a unique profile or syndrome of adverse events, and (2) produces adverse effects that are qualitatively similar to but quantitatively more frequent or severe than the adverse effects associated with drugs in the benzodiazepine class of drugs or drugs with benzodiazepine-like activity.

Conclusions and Recommendations

The data from premarketing clinical trials, postmarketing studies, and the published literature do not support clearly the existence of a unique profile or syndrome of adverse events associated with Halcion relative to those associated with other drugs of its type. Furthermore, reanalysis of 25 parallel-group, placebo-controlled studies and a review of the published literature did not provide clear evidence of a greater risk of adverse events associated with Halcion relative to the risk of adverse events associated with comparator drugs of its class.

On the other hand, there are some gaps in the data regarding safety. For example, despite reports of amnesia, no study has been conducted to evaluate rigorously the effects of Halcion on autobiographical memory. Studies addressing this shortcoming would be an important addition to the understanding of the effects of triazolam. Also, because it is clear that Halcion is frequently used at higher doses and for longer durations than those recommended by FDA, studies of the long-term use of high-dose Halcion should be considered.

Clinical Trials and Surveillance

The committee is confident in the quality and adequacy of the data from the clinical trials (pre- and postmarketing) supporting the safety of using Halcion within the current labeling guidelines. The committee recognizes, however, that the lack of significant adverse

events reported from clinical trials appear to conflict with the numbers and types of adverse events (e.g., anterograde amnesia and confusion) that have appeared in the Spontaneous Reporting System of FDA and in some case reports in the literature. Many factors contribute to this apparent conflict, including the nature and design of clinical trials and external events that can affect the reporting of adverse events.

It is important to note that the statistical power to detect rare events is necessarily limited in controlled clinical trials because such trials include a small number of subjects compared with the number of patients using the drug in the postmarketing period, and subjects admitted to the trials must conform to carefully defined inclusion and exclusion criteria, narrowing the likely range of adverse events; rare events are unlikely to be detected in sample populations of a few hundred subjects. In addition, the treatment regimens in these trials are purposely chosen to avoid untoward or adverse events that might be expected to occur with higher doses or with dose dependent or duration-dependent use.

With respect to surveillance and reports of adverse events, the committee notes that apparent inconsistencies in the data from clinical trials and spontaneous reports are likely to occur for the reasons stated above, and concludes the following:

- The popularity and consequent widespread use of Halcion produced large at-risk populations from which spontaneous reports of adverse events emerged.
- Many people take Halcion (and other hypnotic drugs) for more than a year and at dosages above those recommended in the labeling.
- In general, the types and frequencies of reported adverse events are subject to many external influences, including media attention, marketing, litigation, differential reporting rates, ability to connect drug use to a health event, and other factors, all of which affect the accuracy of interpreting the results.

***Recommendation 5: Improve Surveillance, Analysis, and Integration of Findings*. The committee recommends that FDA develop improved methods for integrating the findings of clinical trials and postmarketing surveillance, and for resolving discrepancies in the interpretation of data from spontaneous reports, clinical case reports, and controlled clinical trials. This would include the reestablishment of a biostatistics and epidemiology advisory committee (in addition to having biostatistics and epidemiology expertise on the other advisory committees) that would be charged with the rapid and thorough assessment of the potential health risks suggested by reports of adverse events, identification and resolution of conflicts that may arise in the review of clinical trial and surveillance data, and the provision of expert advice on the maintenance and operation of effective postmarketing surveillance systems.**

BROADER IMPLICATIONS

During the course of the study, the IOM committee was led by the data and other information to consider some important, broader implications of its findings. The committee's

concluding remarks in this report therefore address, first, the need for additional research to expand and improve the fundamental understanding of sleep and the related condition of insomnia. Second, but not less important, is an issue that arose from information that was collected in an attempt to reconcile the apparent discrepancy between the clinical trial data and the reports of adverse events related to the use of Halcion. It seemed that at least some of the adverse events that were being reported through the Spontaneous Reporting System of FDA were similar to those that had been reported in some of the early clinical trials with higher doses and longer durations of use of Halcion. This, combined with survey data that indicate that many people use hypnotic agents for very long periods of time (the Evaluation of Medications for Insomnia in Canada reported average use of 1.7 years), led the committee to consider the possibility that the adverse events that were being reported for Halcion might be due, at least in part, to the use of Halcion for longer periods of time and at higher doses than those currently recommended in the labeling.

The committee believes that this type of use may be a problem common to all hypnotic medications and is complicated by incomplete understanding of insomnia and its clinical management. Although prescription of hypnotic drugs at higher doses and for longer durations than those recommended in the product labeling may provide benefit to some patients, the magnitude of Halcion use at higher doses and for longer durations than those that are recommended also suggests that alternatives (e.g., other medications or diagnoses) are not being fully explored, to the potential detriment of patients.

Spontaneous reporting of adverse events provides a "signal" to FDA of the possibility of serious unintended threats to the health of the patient. The pharmacoepidemiolgist, among others, then has the task of deciding which signals should be followed up and which can be ignored. The severity of the events, the size of the at-risk population (and the potential for larger numbers of adverse events), and information concerning use at higher doses or for longer durations than those that are recommended are all important factors in the decision to pursue the spontaneous report(s) further.

Postmarketing surveillance requires the collection and assessment of at least two very different types of information: (1) data from controlled trials, and (2) data from spontaneous reports of adverse events. These two types of data vary significantly in their quality, and, thus, their interpretation as a body can be quite complicated. This was true for Halcion, because some of the clinically significant adverse events (e.g., memory impairment, nervousness) were detected not in the clinical trials but only in the spontaneous reports. In such circumstances and in those instances in which adverse events are difficult to detect—but are clinically significant in terms of the health and well-being of the patient—the need for objective, critical assessments, better methods for detecting behavioral or psychological adverse events, and integrated evaluations of the entire body of information is critical.

Recommendation 6: Improve Postmarketing Data Collection and Analysis **. The committee recommends that additional effort be dedicated to the postmarketing surveillance and monitoring of hypnotic agents and other drug products and that this effort include objective and critical evaluations of integrated sets of data on adverse events, on actual patient use, and from clinical trials. Special emphasis should be placed on developing improved methods for (1) collecting and**

integrating evaluations of patient use data and Clinically significant adverse events, and (2) responding effectively when there appear in the spontaneous reports signals that correlate with data indicating patient use at higher doses and for longer durations than those that are recommended.

***Recommendation 7: Educate Health Care Providers*. The committee recommends that FDA establish an independent task force with the charge of reviewing and developing mechanisms for improving prescribing practices and patient use of hypnotic medications. This task force should pay special attention to issues raised by the actual use of these agents and, for physicians, to the issues of appropriate differential diagnosis when addressing the problem of insomnia in their patients. It would be useful to provide physicians with efficacy and adverse effects dose-response curves for durations comparable to those being used in practice, even if they are greater than those recommended in the labeling.**

In addition, the committee recommends that professional societies of primary care and other health providers increase their members' attention to the need for caution in prescribing hypnotic drugs at higher doses and for longer durations than those that are recommended. Efforts in this area should include increased attention to this issue in medical education and in residency programs, including the addition of questions about the use of hypnotic drugs on medical specialty examinations.

FDA should identify ways to disseminate information on the diagnosis and management of insomnia more effectively to medical students and in training programs for primary care physicians.

Table 1 presents the individual tasks that were addressed by the Committee and a summary of the relevant conclusions and recommendations.

TABLE 1 Committee Tasks and Summary of Relevant Conclusions and Recommendations

Task	Conclusions and Recommendations
The adequacy of the study designs and quantitative endpoints used in the major clinical trials of Halcion.	Clinical trials are of sufficient quality to yield adequate and reliable data for the determination of safety and efficacy. **Recommendations 2 and 3: Update guidelines and improve outcomes measures** .
The quality and quantity of postmarketing data with respect to adverse drug reactions.	Postmarketing clinical trials meet current standards for well-controlled clinical trials. Inconsistencies in the data from clinical trials and spontaneous reports are likely to occur. **Recommendation 5: Improve surveillance, analysis, and integration of findings**. **Recommendation 6: Improve postmarketing data collection and analysis.**
The overall confidence in the data on the effectiveness of, adverse events from, and side effects of Halcion at different doses and for different durations, including those specified in the current product labeling.	The committee is confident in the quality and adequacy of the pre-and postmarketing data as it relates to a determination of safety and efficacy within current labeling guidelines. Many people use Halcion, other hypnotic drugs, and other drug products for longer periods of time, and at higher doses than are recommended in labeling guidelines.
The need for additional studies to clarify and characterize the risk and efficacy profiles of Halcion.	**Recommendation 1: Improving confidence in lowest dose**. **Recommendation 3: Improve outcomes measures**. **Recommendation 4: Determine tolerance**. **Recommendation 7: Educate health care providers**.

NOTE: Recommendation numbers correspond to those in the body of the report.

1

Introduction

The definition of insomnia remains somewhat unsettled both in clinical practice and in research. Several definitions currently exist, including those in the International Classification of Sleep Disorders. Insomnia is usually defined as a subjective complaint of poor, insufficient, or nonrestorative sleep. The duration of symptoms is important in the evaluation of a complaint of insomnia. Transient or short-term insomnia is common in otherwise healthy people who have acute stress; who are bereaved, jet lagged, or admitted to a hospital; or who have an intercurrent illness. Long-term insomnia, usually defined as at least 2 or 3 weeks in duration, is often associated with chronic medical conditions. Chronic insomnia is often multifaceted and has multiple determinants. In the clinical evaluation of the insomniac patient, clinicians often try to identify predisposing, precipitating, and perpetuating factors.

Insomnia is a common symptom of many disorders; about one third of the adult population experiences insomnia each year. By most recent estimates, there appears to be approximately a 10 percent prevalence of chronic insomnia in adults in the United States (Mellinger et al., 1985). It is also estimated that the annual cost of treatment of insomnia is between $92.5 billion and $107 billion in the United States (Staller, 1994). Reports of insomnia tend to increase with age and are more prevalent among women. Furthermore, people who are divorced, widowed, or separated have chronic insomnia more often than married individuals. Finally, insomnia is persistent and recurrent in both clinical populations and community-based samples of the population (Balter and Uhlenhuth, 1992).

Given the need to treat chronic insomnia, the treatment approach has generally been use of sedative-hypnotic medication. It is estimated that such forms of medication are used by 5 percent of the population in a year's time and over the course of a year are used regularly by 0.5 percent of the population in the United States (Mellinger et al., 1985; Baltex and Uhlenhuth, 1992). Despite the widespread use of pharmacotherapy in the treatment of insomnia, the optimal role of medication is still poorly defined (Bliwise, 1991). Attempts to provide educational and behavioral interventions are receiving increasing attention from the medical

community. Various types of educational efforts and behavioral intervention, including stimulus control therapy, sleep restriction therapy, and improved sleep hygiene, have been shown to provide considerable benefit (Kupfer and Reynolds, 1997).

HISTORICAL OVERVIEW OF HALCION

Upjohn,[1] a company that manufactures pharmaceutical products including hypnotic drags, submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for its sleep-inducing drug, triazolam, in May 1976. Subsequently marketed under the trade name Halcion,[2] triazolam was a new compound in the benzodiazepine group—a category of sedative-hypnotic agents (see Table 1-1). Benzodiazepines represented a great improvement over barbiturates in terms of both efficacy and safety. Additionally, triazolam appeared to be an improvement over other benzodiazepines because of its short half-life. Because the body eliminated it rapidly, triazolam did not induce the hangover effect associated with other benzodiazepines. (Box 1-1 further describes the pharmacology of triazolam.) As a consequence of these advantages, physicians prescribed Halcion widely, and the drug became one of Upjohn's best-selling pharmaceuticals (U.S. Food and Drug Administration, 1996).

TABLE 1-1 Common Benzodiazepines and Their Trade Names

Compound	Trade Name
alprazolam	Xanax
diazepam	Valium
flurazepam	Dalmane
lorazepam	Ativan
midazolam	Versed
oxazepam	Serepax
zolpidem	Ambien
temazepam	Restoril
triazolam	Halcion

Before Halcion reached the U.S. market, however, it had undergone an eventful approval process (see Box 1-2 for a detailed time line). Upon reviewing the NDA, the chief medical review officer expressed concern about both efficacy and safety, including (1) high rates of amnesia, incoordination, confusion, and other central nervous system-related side effects associated with Halcion (0.5 to 1.0 mg) compared with those associated with either

[1] Pharmacia and Upjohn merged in October 1995. This report refers to the company as "Upjohn."

[2] "Halcion" refers to the actual product that is manufactured and marketed by Upjohn. "Triazolam" is the generic name of the pure active ingredient in Halcion. The committee uses the term "Halcion" in the text when it discusses clinical trials or events involving the actual product; otherwise, the committee uses the term "triazolam."

flurazepam or placebo; (2) possible diminished effectiveness with repeated administration; (3) "rebound insomnia" during withdrawal; and (4) possible unique safety or efficacy profiles uncharacteristic of those for other benzodiazepines. These concerns were not sufficient, however, to prevent an FDA Psychopharmacologic Agents Advisory Committee (now named the Psychopharmacologic Drugs Advisory Committee [PDAC]) from recommending in 1977 that Halcion be approved for clinical use. The approval was delayed, however, by a request from the Division of Neuropharmacological Drug Products for additional preclinical animal studies and human bioavailability data. When FDA approved Halcion for clinical use in November 1982, reports of possible problems with the drug were already starting to appear in Europe.

BOX 1-1 PHARMACOLOGY OF TRIAZOLAM

Triazolam (Halcion) is known for its rapid onset of action when given orally, for its short duration of action, and for its ability to produce a sleeplike state (sedation). This profile makes it a candidate for effective therapeutic use in patients with sleep disorders. Other benzodiazepines that have been used therapeutically include chlordiazepoxide, clonazepam, clorazepate, diazepam, flurazepam, lorazepam, quazepam, and temazepam. The profile of activity of the benzodiazepines includes muscle relaxation, sedation, anxiolytic activity, anticonvulsant activity, and induction of amnesia. All types of activities can be demonstrated among the benzodiazepines, with one or more attributes dominating and being characteristic for each compound. Each drug is further characterized by the time of onset of activity and the duration of the effects. The duration of action of each drug is characterized by its rate of metabolism and clearance from the body, by the possible generation of active metabolites, and by excretory mechanisms. Importantly, triazolam is metabolized by cytochrome P-450 3A4, an enzyme with activity that is both inducible and inhibitable by a large number of other drugs and even grapefruit juice.

Overseas Events

Halcion was approved for use at a dose of 1.0 mg in The Netherlands in 1977. Two years later, a Dutch psychiatrist, C. van der Kroef, published an article (1979) detailing a series of adverse events in his patients that he described as a syndrome. The syndrome included symptoms of depression, amnesia, hallucinations, and anxiety. Although van der Kroef never disclosed his source records, The Netherlands' regulatory body suspended Halcion from its market and began negotiations with Upjohn to change the labeling, restrict its use, and require further studies. In February 1980, Upjohn withdrew Halcion from the Dutch market rather than comply with the possible restrictions.

In the United Kingdom, a decision to review the safety of Halcion was made in response to a report from Upjohn that "errors had been identified in a report of one of the clinical studies included in the original" application for approval (U.S. Food and Drug Administration, 1996, p. 1). The summary tables for a tolerability study with prisoners (Study 321) did not reflect all of the adverse events reported by the participants. Upon learning this,

many governments around the world reassessed the safety of the drug, and most made changes in the labeling. This included the Committee on Proprietary Medicinal Products (CPMP) of the European Union. CPMP released two position papers (in October and December 1991) that dealt specifically with Halcion. In both papers, CPMP concluded that the drug was safe as labeled, but warned that the use of Halcion should precisely follow the labeling in terms of the maximum dose (0.25 mg) and the length of use (not more than 10 days). Additionally, CPMP formed an ad hoc group in 1993 to assess Halcion, along with six other short-acting hypnotic drugs, at the request of France and The Netherlands. This group saw a risk of dependence on these drugs and felt that these drugs should be used only for short periods of time and only for severe circumstances. The use of Halcion, specifically, should be limited to a few days with a maximum of 2 weeks. The United Kingdom took the additional step of suspending Upjohn licenses to market the drug and, after further review, revoked them permanently in 1993.

FDA Activity

FDA approved Halcion for use in 1982 and since then has monitored its safety through postmarketing surveillance, a large part of which was through the Spontaneous Reporting System (SRS), the system that FDA uses to track adverse events reported by physicians and patients. [3] FDA also reassessed the data from the NDA, and, in 1994, formed a task force to examine various related issues.

Halcion had been associated with a large number of these spontaneous reports of adverse events from the time of its approval. Indeed, there was sufficient concern about the safety of the drug to cause Public Citizen, a consumer advocacy group, to submit petitions in 1991 and 1992 requesting that FDA remove Halcion from the U.S. market. [4]

Spontaneous Reports

Interpretation of the spontaneous reports was a matter of some debate within FDA. The FDA's Office of Epidemiology and Biostatistics identified a signal from the SRS data; that is, there appeared to be a heightened number of reports of adverse events associated with Halcion within the first six years of the drug's marketing. For example, in that period, there were 174 spontaneous reports of amnesia by people taking Halcion whereas there were only 3 for temazepam (Restoril), another benzodiazepine hypnotic drug. Even though there were approximately 10 million more prescriptions for Halcion in the compared time frames, the data suggested an increased rate of adverse events for Halcion (Tsong, 1992). In addition, Wysowski and Barash (1991) reported that psychiatric adverse reactions were up to 56 times higher (amnesia) with Halcion than with temazepam (see Chapter 3, Table 3-14).

[3] The current system for monitoring and reporting adverse events is called Med Watch, the FDA Medical Products Reporting Program.

[4] FDA denied this petition in August 1997.

The FDA Division of Neuropharmacological Drug Products, however, questioned the reliability and interpretation of the SRS data, suggesting that the large number of reports reflected a general tendency to overreport adverse events, particularly following adverse media attention, rather than a greater incidence in the actual occurrence of adverse events. An analysis performed by Tsong (1992) used statistical methods to adjust for many factors, including publicity, variability in rate ratios, manufacturers' reporting practices, and trends in overall reporting rates, among others. This analysis resulted in reduced overall risk ratios (e.g., 8 to 1 relative risk for depression and 26 to 1 relative risk for amnesia). Note, however, the rate ratio for seizures, an unlikely adverse event for a benzodiazepine, was as high as 26 to 1, and mortality was 3 to 1. In 1992, PDAC assessed these data and concluded that action was not required on the part of FDA.

FDA Reassessment

In addition to tracking the postmarketing data, FDA reassessed the information from the original application, which Upjohn had reentered into a new database, and requested that Upjohn undertake an integrated summary of safety. FDA also investigated Upjohn "for adherence to applicable laws and regulations in generating clinical safety and efficacy data for Halcion," an effort that was subsequently handed over to the U.S. Department of Justice. Finally, PDAC reviewed the data in May 1992. That committee judged the numbers from the new database to be valid and Halcion to be safe and effective, but at a lower dose: 0.25 mg for the general population and 0.125 mg for the elderly population. In response to a request by PDAC, Upjohn initiated two new dose-response studies (Protocols M/2100/0366 and M/2100/0373) and one large insomnia treatment study (Protocol M/2100/0235) comparing the safety and efficacy of Halcion compared with those of temazepam.

FDA Task Force

In 1994 FDA formed a task force to investigate scientific questions, regulatory concerns, and possible misconduct or impropriety by both Upjohn and FDA in the Halcion approval process. The FDA task force made recommendations related to improving the drug approval process and improving the investigation of suspected misconduct. It concluded that Upjohn's actions should have been considered material[5]—but that this in and of itself does not constitute a violation of the law.

With respect to safety and efficacy, the task force concluded that Halcion was "safe when prescribed according to current labeling" and "effective in the treatment of insomnia at doses and durations currently recommended in the labeling" (U.S. Food and Drug

[5] "*Materiality* is one element of a criminal violation of the U.S. Code, 18 U.S.C. § 1001, which makes it a crime to knowingly and willfully falsify, conceal, or cover up a material fact, or make false, fictitious, or fraudulent statements, to a Federal Agency" (U.S. Food and Drug Administration, 1996, p. ii).

Administration, 1996, p. iii). The task force also recommended that a separate reassessment of the safety and efficacy of Halcion be conducted by a panel of independent experts. To that end FDA requested the present study by the Institute of Medicine (IOM).

CHARGE TO THE IOM COMMITTEE

FDA asked IOM to perform an independent assessment of the publicly available data on Halcion and to prepare a report. This was to include an assessment of the following:

- the adequacy of the study designs and quantitative endpoints used in the major clinical trials of Halcion;
- the quality and quantity of postmarketing data with respect to adverse drug reactions;
- the overall confidence in the data on the effectiveness, adverse events, and side effects of Halcion at different doses and for different durations, including those specified in the current product labeling; and
- the need for additional studies to clarify and characterize the risk and efficacy profiles of Halcion.

If additional studies were deemed necessary to help clarify and characterize the risk and efficacy profiles of Halcion, the committee was instructed to describe what specific types of studies would be needed.

ORGANIZATION OF THE REPORT

The remainder of this report is organized into sections that address issues related to the quality and adequacy of the data regarding effigy (Chapter 2) and safety (Chapter 3). The final chapter (Chapter 4) presents concluding remarks regarding broader implications. Several appendixes (A-G) are included, as follows: Appendix A, FDA safety tables; Appendix B, summary tables of literature reviewed for safety of Halcion; Appendix C, glossary; Appendix D, acronyms; Appendix E, resources reviewed by the committee; Appendix F, Upjohn consent to disclosure; and Appendix G, committee and staff biographies.

BOX 1-2 TIME LINE OF SIGNIFICANT EVENTS IN HALCION'S HISTORY

INVESTIGATIONAL NEW DRUG AND NEW DRUG APPLICATION PERIOD: 1976-1982

1970	
September	Upjohn files Investigational New Drug Application in the United States
1976	
May	NDA submitted. The NDA included pivotal studies (Protocols 6024, 6041, and 6045) and Protocol 321
1977	
January	FDA medical officer review: • initial comprehensive review • safety was not demonstrated • amnesia and frequency of adverse reactions need to be investigated
February	Group leader review
March	Psychopharmacologic Agents Advisory Committee (PAAC) meeting, where PAAC recommended approval but did not specify dose
November	Division of Neuropharmacological Drug Products issues a not approvable letter because of inadequate preclinical and bioavailability data Halcion approved for clinical use at a dose of 1.0 mg in The Netherlands
1978	
August	FDA Division of Neuropharmacological Drug Products issues a not approvable letter because of deficiencies in animal studies
September	United Kingdom approves Halcion for clinical use
1979	
July	C. van der Kroef reports a "syndrome"
August	The Netherlands suspends Halcion from its market

1980	
February	Upjohn withdraws Halcion from Dutch market
March	Review and evaluation by FDA of clinical data on the basis of data from adverse events reports in The Netherlands
June	NDA resubmission
1981	
February	FDA's "not approvable" letter because of deficiencies in bioavailability studies
April	NDA resubmission
October	FDA medical officer review: review of resubmission
1982	
February	First "approvable" letter
August	FDA medical officer review: adverse events reports from Europe
October	Second approvable letter
November	Approval letter Summary basis of approval at doses of 0.25 and 0.5 mg
December	FDA disqualifies data from one investigator because of an unrelated incident
POSTAPPROVAL PERIOD: 1983-1991	
1983	
April	Upjohn introduces 0.125-mg tablet
1987	
February	France withdraws 0.5-mg tablet from French market
June	FDA medical officer's review: reduction of adult dose from 0.5 to 0.25 mg

October	FDA medical officer review: label changes and *Dear Doctor* letter
1988	
March	Upjohn discontinues production of 0.5-mg tablet
1989	
June	FDA medical officer review: label changes regarding withdrawal and dependence
September	PDAC meeting: Halcion judged to be safe and effective FDA medical officer review: label changes reflecting possibility of abuse and dependence
1990	
April	FDA medical officer review: label changes reflecting possibility of amnesia
POSTAPPROVAL PERIOD: 1991 to PRESENT	
1991	
June	Upjohn discloses discrepancies in reporting in Study 321
August	Upjohn revises medical events analysis for Study 321
October	United Kingdom suspends Halcion from its market
November	Four major changes to the Halcion labeling, all with regard to short-term nature of prescriptions
December	FDA (Clinical Investigations Branch) begins investigation of Upjohn Public Citizen submits first petition to remove FDA approval
1992	
February	Reentry of original data into a new database
March	FDA investigation of Upjohn suspended

May	FDA ad hoc committee meets to discuss criminal investigation of Upjohn PDAC meeting: Halcion is judged to be safe and effective (0.25- and 0.125-mg doses)
June	FDA reviews safety on the basis of data in the new database • new database numbers judged to be valid • Halcion judged to be safe
July	United Kingdom announces intention to revoke licenses for Halcion Public Citizen submits final petition to remove FDA approval
December	FDA investigation of Upjohn terminated
1993	
June	United Kingdom revokes licenses for Halcion
1994	
April	FDA medical officer review: labeling and packaging changes FDA commissioner requests formation of an FDA task force on Halcion to examine criminal misconduct, scientific questions, and regulatory concerns
1996	
May	FDA task force on Halcion issues its report
1997	
April	FDA contracts Institute of Medicine to assess data quality
August	FDA denies Public Citizen petition to remove approval of Halcion
November	IOM report *Halcion: An Independent Assessment of Safety and Efficacy Data*

2

Assessment of Efficacy Data

The U.S. Food and Drug Administration (FDA) originally approved the hypnotic drug Halcion (triazolam) for use at a dose of 0.5 mg for the purpose of improving the quality of sleep in 1982. In 1987, however, concerns about the drug's safety caused FDA to lower the recommended starting dose in the labeling to 0.25 mg for adults and 0.125 mg for the geriatric population (data are available demonstrating that elderly subjects clear triazolam from the blood at half the rate of younger subjects [Greenblatt et al., 1991]). This, in turn, raised questions about efficacy at the lower doses. For that reason, the Institute of Medicine (IOM) committee focused on these two lower doses, specifically examining the data for evidence of (1) improvement in certain endpoints over those from use of the placebo or the comparability of endpoints from the use of Halcion and a positive comparator drug and (2) tolerance to the drug's effects over time.[1]

To assess the quality and quantity of the available data regarding the efficacy of Halcion, the committee first examined the indications for the use of hypnotic drugs and the means of evaluating the efficacies of these types of drugs, including the requirements for approval by FDA. The committee then assessed the quality of the protocols and the designs of the pre- and postmarketing clinical trials investigating the efficacy of Halcion. To analyze the data from those trials, the committee reviewed several statistical methods and then reanalyzed the data across studies. Finally, the committee summarized the available literature pertinent to the efficacy of Halcion, and from all of this information, the committee drew the conclusions presented at the end of this chapter.

[1] Specifically, the 7-10 consecutive nights of use as described in the current labeling (package insert).

PURPOSE AND EVALUATION OF HYPNOTIC DRUGS

The process of assessing the efficacies of hypnotic drugs requires a statement of the purpose for the drug's use. The primary indication for use of a hypnotic agent is to improve the quality or quantity of sleep. A secondary purpose is to improve the quality of life throughout the 24-hour day. One useful distinction is-between the need for sleep improvement on a short-term (acute) versus a long-term (chronic) basis. Virtually anyone can suffer an acute sleep problem due to a variety of circumstances, including jet lag and acute situational stress. On the other hand, individuals can experience a persistent reduced quality of sleep for a variety of reasons, and this population will be quite heterogeneous. Separating people with chronic insomnia from those who suffer from acute insomnia is useful in evaluating the efficacy of a hypnotic agent.

The study populations used to study the efficacies of hypnotic drugs ideally should be heterogeneous. The exclusion criteria should be such that large segments of the population who will be treated in good clinical practice will not be eliminated. However, because impairment of sleep can be a clinical symptom associated with psychotic disorders, the standard of care is treatment of the psychotic disorder rather than prolonged use of hypnotic agents, and the exclusion of psychotic patients in clinical trials of an hypnotic agent is justified and appropriate.

Evaluating Efficacy

There are two approaches to the evaluation of sleep quality: subjective and objective. The subjective evaluation of sleep involves the use of questionnaires or interviews. The subjects indicate their evaluation of the endpoint, for example, onset of sleep, duration, awakenings, and quality. The objective approach involves the use of polysomnographic studies. In these electroencephalographic (EEG) studies the exact length of time to the onset of sleep can be measured precisely, as can sleep duration and number of awakenings. Obviously, the evaluation of the quality of the sleep is still determined by the subject. Having obtained precise sleep parameters from the polysomnograph, one can compare people with and without subjective sleep problems. Interestingly, the differences in objective sleep measurements between these two groups are relatively small. It can therefore be argued that many people who complain of sleep disturbances actually sleep quite well in an objective sense. This approach fails to recognize, however, that the experience of satisfaction is, by definition, subjective. The length of time required to fall asleep that is or is not satisfying to an individual is subjective. A statistically small reduction in sleep latency may be experienced by the subject as very valuable and desirable. Telling insomniacs that their sleep latency is actually within one standard deviation of the mean is not likely to improve their satisfaction.

In the clinical setting, the insomniac patient and the clinician are seeking increased subjective improvement in sleep. In the sleep laboratory, however, subjective measures may not coincide with objective measures. For example, tolerance to benefits from hypnotic agents often occurs in objective measures despite continued improvement with subjective questionnaires. Since the reasons for the discrepancy between subjective and objective sleep

measures are obscure, it is premature to rely solely on subjective measures in the evaluation of hypnotic agents.

Although it is important to try to develop methods that allow for a more precise analysis of sleep parameters, researchers must continue to recognize the inherent subjectivity of the evaluation of the endpoints by the individual. It follows, then, that the subjective evaluation of the endpoints is more appropriate in the sense that it is patient satisfaction that is the principal goal of the pharmacologic intervention.

The committee is not aware of studies designed specifically to compare the two methods of hypnotic evaluation. Indeed, although not a specific objective, in a study comparing the effects of nefazodone and fluexetine on mood and polysomnographic data for depressed patients complaining of insomnia, the patients and clinicians reported nearly equal improvement in subjective sleep measures for both days, whereas polysomnographic data showed a progressive deterioration of some measures for fluexetine (Gillin et al., 1997). Finally, the nature of polysomnographic studies restricts them to small numbers of subjects who are unlikely to be a representative subset of the population at large.

In assessing efficacy, the question of the duration of time between taking the hypnotic agent and actually going to bed has been raised. The point of an efficacy study is not to assess the absorption time of the compound or to have sleep onset occur during the period of absorption. Taking the active and comparator compounds at a specified interval before going to bed is an appropriate method of eliminating the measurement error incurred by adding absorption time to sleep onset.

FDA Efficacy Requirements

Approval of a New Drug Application (NDA) by FDA usually requires two well-controlled trials. The sponsor developing a new drug uses Phase I studies to determine dose and drug levels in plasma, tolerability, pharmacokinetics, and pharmacodynamic data when possible. The next step is the initiation of studies performed to determine the appropriate dose and dosing schedule to establish efficacy and safety in patients for whom the drug is intended. Using this information, the sponsor undertakes two or more clinical trials with a large enough number of subjects to provide sufficient statistical power to establish that the drug is effective for its intended use. These latter trials are referred to as the "pivotal trials"; that is, the proof of efficacy pivots on these studies as being of vital or central importance. Supporting data from other trials are also used in the regulatory approval process. Approval of a drug for marketing, however, hinges on a determination not only of efficacy but on a risk-benefit analysis.

Available Efficacy Data on Halcion

Upjohn's NDA (NDA 17=892) for the treatment of insomnia with triazolam (Halcion) was approved in 1982 by FDA on the basis of the results of efficacy studies with a 0.5-mg dose. In response to concerns about the safety of this and a larger dose (van der Kroef, 1979;

Medicines Control Agency, 1992), FDA lowered the dose recommended in the labeling to 0.25 mg for the general adult population and 0.125 mg for the geriatric population. Because the lower doses were not part of the studies performed during original NDA approval process, this change raises the question of whether there are adequate data to support this recommendation and whether the lowest effective dose has been established.

To attempt to answer these dose-related efficacy questions and to evaluate the quality of the data on which FDA based its decision that Halcion was effective at the lower doses (Marticello, 1992), the committee undertook an evaluation and reanalysis of the available data[2] using a statistical method different from that used by FDA.

From a list of all protocols in the NDA (U.S. Food and Drug Administration, 1996, Appendix C), the committee selected those that appeared by their descriptions to define well-controlled studies. These studies had adequate numbers of subjects to suggest that they constituted a sample large enough to provide adequate statistical power. The goal was to determine whether Halcion differed from the placebo in the achievement of the primary efficacy endpoints or was comparable to a positive comparator drug in achieving these endpoints. A list of the protocols examining the low dose (<0.5 mg), including a summary of some demographic data and other aspects of these protocols, is presented in Table 2-1. The committee also reviewed a final report of a study that FDA used in making its decision concerning the approval of Halcion at lower doses but that was not part of the Upjohn NDA (Lee, 1990).

QUALITY OF PROTOCOLS AND STUDY DESIGN

Before undertaking its review, the committee familiarized itself with the FDA publication *Guidelines for the Clinical Evaluation of Hypnotic Drugs* (U.S. Department of Health, Education, and Welfare, 1977). The initial step in the review was to evaluate the quality of the protocols and the study designs. The committee was especially interested in the specificities of the primary endpoints, the method(s) used to quantify those endpoints, and the characteristics of the study population, as well as other items required for a well-controlled study. A checklist was devised and was used to evaluate each protocol. The major categories of the variables and the criteria used to evaluate the protocol review form are as follows:

- Objective(s)
- Inclusion and exclusion criteria
- Study design and procedures
- Outcome variables (endpoints)
- Concomitant drugs
- Statistical methods

[2] The committee did not review the source data (i.e., the raw data) or the case report forms for accuracy. The committee's review was limited to the data presented in the NDA and other sources cited in the text. FDA did find some discrepancies in the data from a few investigators (U.S. Food and Drug Administration, 1996, Appendix F), but it did not use these data in its analyses, nor did this committee include these data in its review.

TABLE 2-1 Low-Dose Premarketing Studies Reviewed by IOM Committee for Efficacy of Halcion (less than 0.5 mg)

Protocol Number	Investigator	Study Design and Focus	Planned Duration	Schedule	Treatment Group (dose [mg])	No. of Patients	Age (yr)			Gender (no.)	
							Mean	Min.	Max.	Male	Female
2401	Cohn and Fabre	Controlled, DB, randomized, parallel, adjustable-dose efficacy/ safety study with outpatients with anxiety, neurosis, and insomnia	1 wk Pbo washout; 1 wk Tx	Triazolam 0.25; diazepam 5; Pbo; HS dosing: after 3 days, dose could be increased to 2 capsules HS	Triazolam (0.25) Diazepam (5) Placebo	39 43 44	41 34 34	20 20 19	62 61 56	24 21 23	15 22 21
6010	Sunshine	Controlled, DB, randomized, crossover efficacy/ safety study with patients with insomnia	28 days—1 wk on each treatment	HS dosing	Triazolam (0.3) Triazolam (0.6) Flurazepam (15) Flurazepam (30)	42 39 41 41	32 32 23 32	19 19 19 19	60 60 60 60	Data not available	
6014 IV	Kramer	Experiment IV: study to evaluate the EEG and hypnotic effects of triazolam with patients with insomnia; drug nights compared to Pbo baseline and withdrawal	7 nights	HS dosing	Triazolam (0.25)	6	21	18	24	6	0

6020	Vogel	Study in patients with insomnia in sleep lab to study EEG and hypnotic effects; drug nights compared to Pbo baseline and withdrawal	7 nights	HS dosing	Triazolam (0.25) Triazolam (0.5) Triazolam (1.0)	3 6 3	Data not available				
6033	Edmondson	Controlled, DB, randomized, crossover efficacy/ safety study with patients with insomnia	5 nights of Tx	HS dosing	Triazolam (0.25) Triazolam (0.5) Diazepam (10) Diazepam (5) Placebo	30 31 31 31 31	49 49 49 49 49	26 26 26 26 26	58 58 58 58 58	30 31 31 31 31	0 0 0 0 0
6034	Knapp	Controlled, DB, randomized, crossover efficacy/ safety study with inpatients with insomnia	5 nights; 1 night each Tx	HS dosing	Triazolam (0.25) Triazolam (0.5) Diazepam (10) Diazepam (5) Placebo	30 30 30 30 30	Data not available				
6035	Kramer	Controlled, DB, randomized, crossover efficacy/ safety study with geriatric inpatients with insomnia	5 nights	HS dosing	Triazolam (0.25) Triazolam (0.5) Chloral hydrate (250) Chloral hydrate (500) Placebo	34 32 32 35 34	70 70 70 70 70	52 52 52 52 52	94 94 94 94 94	33 31 31 34 33	1 1 1 1 1
6056	Kramer	Controlled, DB, randomized, crossover performance study with healthy subjects	6 weeks; 2 nights on each Tx followed by 5 night washout	HS dosing	Triazolam (0.25) Triazolam (0.5) Flurazepam (15) Flurazepam (30) Secobarbital (100) Placebo	12 12 12 12 12 12	23 23 23 23 23 23	20 20 20 20 20 20	26 26 26 26 26 26	12 12 12 12 12 12	0 0 0 0 0 0

Protocol Number	Investigator	Study Design and Focus	Planned Duration	Schedule	Treatment Group (dose [mg])	No. of Patients	Age (yr)			Gender (no.)	
							Mean	Min.	Max.	Male	Female
6060	Albert et al.	Controlled, DB, randomized, crossover, preference efficacy/ safety study with geriatric patients with insomnia	2 nights	HS dosing	Triazolam (0.25)	101	69	59	84	21	80
					Placebo	100	69	59	84	21	79
6060 A	Lipani	Controlled, DB, randomized, crossover, preference efficacy/ safety study with geriatric patients with insomnia	2 nights	HS dosing	Triazolam (0.125)	42	76	62	90	7	35
					Placebo	41	76	62	90	7	34
6061	Cohen	Controlled, DB, randomized, parallel efficacy/safety study with geriatric patients with insomnia	7 nights	HS dosing	Triazolam (0.25)	31	73	61	89	14	17
					Placebo	28	70	61	81	9	19
6062	Okawa	Controlled, DB, randomized, parallel efficacy/safety study with geriatric patients with insomnia	7 nights	HS dosing	Triazolam (0.25)	36	69	63	84	8	28
					Flurazepam (15)	35	67	61	81	18	17
6063	Beber	Controlled, DB, randomized, parallel efficacy/safety study with geriatric patients with insomnia	14 consecutive nights	HS dosing	Triazolam (0.25)	18	82	73	90	6	12
					Placebo	20	83	70	93	6	14

6064	Cole	Controlled, DB, randomized, parallel efficacy/safety study with geriatric patients with insomnia	14 consecutive nights	HS dosing	Triazolam (0.25) Flurazepam (15)	20 23	68 70	61 61	75 91	8 8	12 15
6065	Reeves	Controlled, DB, randomized, parallel efficacy/safety study with geriatric patients with insomnia	28 nights	HS dosing	Triazolam (0.25) Flurazepam (15) Placebo	14 13 14	69 70 71	63 61 61	78 83 81	3 5 6	11 8 8
6401	Wiscombe and Okawa	Controlled, DB, randomized, parallel efficacy/safety study with patients with insomnia	7 nights	HS dosing	Triazolam (0.25) Placebo	35 35	50 48	30 29	60 60	7 9	28 26
6402	Pickering and Holvey	Controlled, DB, randomized, parallel efficacy/safety study with outpatients with insomnia; also evaluated tolerance development potential and withdrawal effects	28 consecutive nights, followed by 7 on Pbo	2/3 received triazolam; 1/3 received flurazepam; HS dosing	Triazolam (0.25) Flurazepam (30)	54 27	49 46	28 24	71 68	23 12	31 15

Protocol Number	Investigator	Study Design and Focus	Planned Duration	Schedule	Treatment Group (dose [mg])	No. of Patients	Age (yr)			Gender (no.)	
							Mean	Min.	Max.	Male	Female
6403	Fabre and DuPree	Controlled, DB, randomized, cross-over, parallel efficacy/safety study with outpatients with insomnia	7 nights; 2 nights crossover, then parallel	HS dosing	Triazolam (0.25)	96	40	19	66	62	34
					Flurazepam (30)	93	40	19	66	59	34
6414	Vogel	Controlled, DB, crossover, (period 1: Pbo; periods 2-4: 3-way crossover with active treatment) efficacy/safety study with patients with middle-of-the night insomnia; performance was also evaluated	26 days	HS dosing	Triazolam (0.125)	9	49	33	61	2	7
					Triazolam (0.25)	9	49	33	61	2	7
					Flurazepam (15)	9	49	33	61	2	7
					Placebo	9	49	33	61	2	7
6417	Lipani and Bowen	Controlled, randomized, DB, parallel, tolerance efficacy/safety study with geriatrics patients with insomnia	7 nights	HS dosing	Triazolam (0.125)	46	72	60	88	11	35
					Placebo	44	72	59	84	5	39

NOTE: Abbreviations: DB, double blind; Pbo, placebo; HS, bedtime; EEG, electroencephalogram; Tx, treatment.
SOURCE: U:S. Food and Drug Administration (1996, Appendix C).

Study Design

In reviewing the quality of the protocols and the study design, the committee was cognizant of the fact that the majority of the studies were designed and performed in the 1970s and were not performed with the level of detail and sophistication that is commonly expected today. For example, the protocols listed multiple objectives and endpoints without defining a priori which ones were primary and which ones were secondary. Patient selection criteria did not include body weight, a factor that might affect the levels of a drug in the blood of subjects receiving the same dose. Analyses of statistical power, which are required to determine the appropriate number of subjects to be enrolled in the study (which requires identification of the minimal detectable difference), were not recorded in the protocols. Similarly, the statistical methods and the analysis plan are not presented in the protocols, and several items were not specified at the level of detail considered appropriate today.

Other inadequacies in the study methods could lead to bias or statistical imprecision. Inadequate attention was paid to the instructions to be given to subjects. For example, although drug and alcohol abusers were excluded from participation in the studies, instructions prohibiting participants from consuming alcohol during the study were not given. Sleep latency could well be influenced by the effect of ethanol on gastric emptying (Pikaar et at., 1988), and acute ingestion of ethanol induces drowsiness, at least initially. In some protocols the amount of water to be ingested when taking the drug was not defined, but sleep latency could be influenced by the volume of fluid in the stomach. Instructions regarding other confounding factors such as caffeine ingestion and naps were also not given.

Although only cursory knowledge about the hepatic cytochrome P-450 isozymes existed when the protocols were written, it was already known that these microsomal drug-metabolizing enzymes could be inhibited or induced by other drugs. Yet, the only restrictions on the use of concomitant medication related to the use of psychoactive drugs. The committee also could find no data demonstrating that the blinding procedures did not change the bioavailabilities of the different dosage forms used in these clinical trials.

Many of these observations also relate to the few polysomnographic studies that were performed. Additional weaknesses of polysomnographic studies are their small sample sizes, and the sample is likely to be unrepresentative of the total population of people with insomnia.

The three more recent postmarketing protocols (Protocols M/2100/0366, M/2100/0235, and M/2100/0373) were more explicit and contained much more of the information and safeguards expected in a quality protocol written today. A summary of the evaluation of the protocols is presented in Table 2-2.

Endpoints

In general, the protocols listed three or more primary endpoints (e.g., sleep latency, total duration of sleep, and number of nocturnal awakenings). The protocols, however, did not define the criteria needed to establish whether efficacy required one, two, or all of the endpoints, which one(s), or how much improvement was relevant. Thus, the manner in which multiple primary endpoints should be used statistically was not specified.

TABLE 2-2 Results of IOM Committee Review of Low-Dose Protocols, Pivotal Protocols, and Postmarketing Protocols

			No. of Protocols Meeting the Criterion/Total No. of Protocols			
			Low-Dose	Pivotal	Postmarketing	
Group	Parameter	Result	Protocols	Protocols	Protocols	Total
Objectives	Clear	Yes	15/20	2/3	2/3	19/26
		No	5/20	1/3	1/3	7/26
Criteria	Psychiatric	Yes	18/20	1/3	1/3	20/26
		No	2/20	2/3	2/3	6/26
	Appropriateness	Yes	20/20	1/3	2/3	23/26
		No	0/20	2/3	1/3	3/26
Design	Design	Parallel	6/20	2/3	2/3	10/26
		Crossover	7/20	0/3	0/3	7/26
		Other	7/20	2/3	0/3	9/26
	Blinding	Yes	20/20	3/3	3/3	26/26
	Comparator	Placebo	8/20	3/3	3/3	14/26
		Drug	3/20	0/3	0/3	3/26
		Both	9/20	0/3	0/3	9/26
		Neither	0/20	0/3	0/3	0/26
	Pharmacokinetics	No	20/20	3/3	3/3	26/26
	Dose	No	20/20	3/3	3/3	26/26
	Fluid	Yes	15/20	1/3	1/3	17/26
		No	5/20	2/3	2/3	9/26
	Endpoints	Yes	20/20	3/3	3/3	26/26
	Determination	EEG	4/20	1/3	2/3	7/26
		Observer	2/20	1/3	0/3	3/26
		Questionnaire	18/20	2/3	1/3	21/26
		Other	5/20	0/3	0/3	5/26
	EEG evaluation	Human	4/20	1/3	2/3	7/26
		Computer	0/20	0/3	0/3	0/26
		Validated	0/20	0/3	0/3	0/26
		Not validated	0/20	0/3	0/3	0/26

			No. of Protocols Meeting the Criterion/Total No. of Protocols			
			Low-Dose	Pivotal	Postmarketing	
Group	Parameter	Result	Protocols	Protocols	Protocols	Total
Design	Levels in Blood	Yes	0/20	0/3	2/3	2/26
		appropriate	0/20	0/3	2/3	2/26
		inappropriate	0/20	0/3	0/3	0/26
		No	20/20	3/3	1/3	24/26
	Dropouts	Yes	20/20	3/3	3/3	26/26
Concomitant substances	Alcohol	Yes	7/20	0/3	0/3	7/26
		No	13/20	3/3	3/3	19/26
	Tobacco	Yes	20/20	3/3	3/3	26/26
	Medication	Yes	20/20	3/3	3/3	26/26
	CNS	Yes	20/20	3/3	3/3	26/26
	Recorded	Yes	20/20	3/3	3/3	26/26
Statistics	Power	Yes	0/20	0/3	1/3	1/26
		No	20/20	3/3	2/3	25/26
	Methods	Yes	0/20	0/3	2/3	2/26
		No	20/20	3/3	1/3	24/26
	Significant	No	20/20	3/3	3/3	26/26
General	Adequate	Yes	20/20	3/3	3/3	26/26
		No	0/20	0/3	0/3	0/26

NOTE: Not included in this table are written comments and responses to the following: a description of the primary and secondary objectives, the duration of the study, methods for blinding, how compliance was determined, and other comments. Low-dose protocols included Protocols 2401, 6010, 6014 IV, 6020, 6033, 6034, 6035, 6056, 6060, 6060A, 6061, 6062, 6063, 6064, 6065, 6401, 6402, 6403, 6414, and 6417. Pivotal protocols included Protocols 6024, 6041, and 6045. Postmarketing protocols included Protocols M/2100/3066, M/2100/0373, and M/2100/0235. Abbreviations: EEG, enectroencephalogram; CNS, central nervous system.

Polysomnographic Studies

A review of the polysomnographic protocols for a 0.25-mg dose was also undertaken. Data from a very limited number of studies, each with few subjects, were available. Although the objectives and endpoints of these protocols were clear, a number of issues were not always well specified. Statistical analyses were usually appropriate, but often the small number of subjects precluded the use of statistical procedures and limited generalizability. It could not be determined whether scoring of EEG records was performed in a double-blind fashion.

The committee reviewed three protocols in which the 0.25-mg dose Was used (Protocols 6014, 6020, and N/2100/0232). In all studies the primary efficacy variables were polysomnographic sleep latency, total sleep time, and number of awakenings during the night. Subject self-evaluation questionnaires were also routinely used.

In Protocol 6014, six male subjects were studied for 14 consecutive nights and received active drug for a mean of 7 nights (range, 5 to 11 nights). Four conditions were examined: baseline, early period of drug therapy (nights 5 to 7), late period of drug therapy (nights 9 to 11), and recovery. It was found that sleep latency was affected more in the early nights of administration and that a reduction in the amount of wakefulness was primarily a function of reduced sleep latency. Analysis of the data reveals that during the early period of drug therapy, sleep latency was significantly different from the baseline sleep latency; however, sleep latency during the late period of drug therapy was not statistically different from that either at the baseline or during the early period of drug therapy. The absence of an effect in the late period of drug therapy may be due to the small sample size.

In Protocol 6020, the protocol was similar to that in Protocol 6014, with 7 nights of treatment with active drug. However, only three subjects receiving the 0.25-mg dose were studied, which precluded statistical analysis and which allowed for only a descriptive interpretation. Thus, it would appear that the effects of the 0.25-mg dose on total sleep time are similar to those of the 0.5-mg dose.

Protocol M/2100/0232 was a multicenter, randomized, double-blind, placebo-controlled trial with patients with chronic insomnia. Thirty-three women and 19 men (age range, 23 to 63 years) were enrolled in the study. These patients had (1) a complaint of chronic insomnia, that is, total sleep time of 6 hours or less or sleep latency of greater than 45 minutes on the majority of nights for the previous 2 months, and (2) confirmed objective polysomnographic insomnia on 1 of 2 screening-recording nights, that is, sleep latency of greater than 30 minutes or total sleep time of 6.5 hours or less. The patients enrolled underwent 2 nights of baseline polysomnography, followed by randomization to treatment with either Halcion (0.25 mg) or placebo nightly for 2 weeks (study days 1 to 14). A posttreatment period consisted of 2 nights of placebo substitution (all patients, single-blind, days 15 to 16). Patients were evaluated in a sleep laboratory on the 2 screening nights, on the 2 baseline nights, and on nights 1 and 2 and 13 and 16 of the study; they spent nights 3 to 12 at home.

Data for 24 patients in the placebo group and 26 patients in the Halcion group were used for the efficacy analysis, The primary endpoint variables were polysomnographic sleep latency and total sleep time. For sleep latency, Halcion was significantly more effective than placebo at both the beginning and the end of the treatment period ($p = 0.015$ and <0.01, respectively). For total sleep time, the changes for the Halcion group did not reach statistical

significance. The magnitudes of the sleep latency changes are considered to be clinically significant. Neither polysonmnographic sleep latency nor total sleep time was significantly different from the baseline level during the posttreatment period.

The findings on sleep latency are subject to different interpretations because of a baseline sleep latency imbalance at one of the three study sites. FDA's reanalyses of the sleep data except for those from one protocol or the creation of three strata on the basis of baseline sleep latency measurements are supportive oft he sleep latency improvement for patients receiving the active drug (Marticello, 1992). Statistical differences between the drug and the placebo groups were not achieved for the nighttime awakening measures. Finally, the results of the three polysomnographic studies reviewed (Table 2-3) suggest that tolerances did not develop under the study conditions. Despite small sample sizes and few studies, the findings are supportive of the questionnaire findings that sleep latency and total sleep time are affected by the 0.25-mg Halcion dose. There are no polysomnographic data (in the NDA) for subjects receiving Halcion at the 0.125-mg level.

TABLE 2-3 Polysomnographic Data Results for Tolerance for 0.25-mg Dose in Controlled Clinical Trials

	Difference	
Protocol and Periods of Comparison	Total Sleep Time (min)[a]	Sleep Latency (min)
6014 (n = 6)		
Baseline to early drug treatment period (5-7)[b]	-19.4	-22.9
Baseline to late drug treatment period (9-11)	-12.6	-11.8
Late drug treatment period to posttreatment period	17.7	20.0
6020 (n = 3)		
Baseline to early drug treatment period (5-11)	17.8	-4.1
Drug treatment period to posttreatment period	-30.5	-0.1
M/2100/0232 (n = 26)		
Baseline to early drug treatment period (1-2)	45.0	-23.9
Baseline to late drug treatment period (13-14)	30.1	-24.7
Late drug treatment period to posttreatment period	-43.4	25.4

[a] Total sleep time represents awake time before sleep for Protocol 6014.
[b] Values in parentheses are days of drug treatment.

REVIEW OF STATISTICAL METHODS USED BY UPJOHN AND FDA TO EVALUATE EFFICACY DATA

As stated previously, in performing an evaluation of the data analyses that were done by Upjohn and FDA, it is important to acknowledge that much of the original work was done more than 20 years ago. In the time since then, many changes and improvements have occurred—both in study design and in statistical analysis methods. Nonetheless, the statistical methods used to analyze these data were often quite limited. The analyses presented in the original reports were typically based only on data for the subjects completing the protocols, and those data may have been quite dissimilar from those for the original randomized sample. In FDA reanalyses of these data, attempts were often made to rectify such sources of bias by carrying the last observation forward (i.e., an endpoint or intent-to-treat analysis). This is a better choice, but it still ignores the majority of the available longitudinal data. Better approaches to the analysis of longitudinal data are now available and are widely used (see Gibbous et al. [1993] for a review in the context of psychiatric research).

In terms of the analyses themselves, it was most common to compare the ordinal measures of efficacy (i.e., global ratings, onset of sleep, duration of sleep, and number of awakenings; see Box 2-1) by chi-square statistics applied to the $k \times 2$ contingency table, where k is the number of rating categories (e.g., $k = 4$ for the global ratings of none, a little, quite a bit, and a lot of help). This approach ignores the ordering of rating categories and requires an additional 3 degrees of freedom for the test statistic (i.e., for the example of four categories). On the one hand, this approach limits statistical power (i.e., a 3-degree-of-freedom test versus a more powerful 1-degree-of-freedom test); on the other hand, the test may be sensitive to differences that are restricted to an intermediate rating category (e.g., helps a little), even though no difference in the more important lowest (i.e., no help) or highest (i.e., helps a lot) rating categories may be present. Other tests for comparison of ordinal response measures were available and would have been appropriate to use. In some cases the categorical nature of the response measures were simply ignored, and either analyses of variance or *t*-tests were used in analyses of the data, but these ignore the possible effects on inferences due to nonnormality and the discontinuous scale of measurement of these qualitative response measures.

It is important to note that probability values for tests of hypotheses (e.g., dose, duration, and differential drug effects) alone are insufficient to fully characterize the effect of a given drug. In addition, it is of critical importance to characterize the magnitude of both expected and observed effects (e.g., the size of the mean difference in overall sleep time between the Halcion and placebo groups divided by a pooled estimate of the standard deviation). Unlike probability estimates, "effect sizes" are not dependent on sample size, and therefore, effect sizes provide a view of the absolute magnitude of the difference. The optimal approach is to design studies based on a statistical analysis with an appropriate statistical power that leads to the specification of a sample size that can reliably detect a clinically significant difference that is specified a priori by the investigator.

Statistical Reanalysis and Evaluation of Clinical Trial Efficacy Data

To determine the efficacy of low-dose Halcion (i.e., 0.25 mg in the general population and 0.125 mg in the geriatric population), data from the pivotal protocols from the randomized controlled clinical trials involving these smaller dosages and placebo controls were reanalyzed by the committee (see below). To this end, the committee compiled data from the protocols listed in Tables 2-1 and 2-4.[3] These protocols were selected because (1) they were the pivotal studies conducted with the 0.5-mg dose (see Table 2-4), (2) they contained data for subjects receiving low doses for sufficient durations and had sufficient sample sizes, and (3) they provided summary data that could be compiled for the four primary endpoints obtained from questionnaires. The committee used the rating categories described in Box 2-1.

For a subset of the protocols, the global endpoint had an additional rating category of "terrific," which was combined with the "a lot" category. In addition, the same subset of protocols rated onset in terms of time to sleep, but this could not be combined with data reported in the onset item described above.

BOX 2-1 FOUR PRIMARY ENDPOINTS AND THEIR RESPECTIVE RATING CATEGORIES USED IN THE QUESTIONNAIRES

1. Patient global rating: Did the medication help you sleep?

0 = No
1 = A little
2 = Quite a bit
3 = A lot

2. Onset (sleep latency)

0 = Slower than usual
1 = The same
2 = Faster than usual

3. Duration (hours of sleep)

0 = <5 hours
1 = 5-6 hours
2 = 6.1-7 hours
3 = 7.1-8 hours
4 = >8 hours

4. Number of awakenings

0 = >6
1 = 4-5
2 = 2-3
3 = 1
4 = 0

[3] The 20 low-dose protocols analyzed were 2401, 6010, 6014 IV, 6020, 6033, 6034, 6035, 6056, 6060, 6060 A, 6061, 6062, 6063, 6064, 6065, 6401, 6402, 6403, 6414, and 6417. The protocols using a 0.5-mg dose were 6024, 6041, and 6045.

TABLE 2-4 Pivotal Premarketing Studies Reviewed by IOM Committee for Efficacy of Halcion

							Age (yr)			Gender (no.)	
Protocol Number	Investigator	Study Design and Focus	Planned Duration	Schedule	Treatment Groups (dose [mg])	No. of Patients	Mean	Min.	Max.	Male	Female
6024	Kales	Study with patients with insomnia in sleep lab; evaluated EEG and hypnotic effects; drug nights compared to Pbo baseline and withdrawal	14 days	HS dosing	Triazolam (05.)	7	Data not available				
6041	Hawkins et al.	Controlled, DB, randomized, parallel efficacy/ safety study with patients with insomnia	7 nights	HS dosing	Triazolam (0.5)	70	44	19	72	17	53
Placebo	73	44	20	71	28	45					
6045	Simson et al.	Controlled, DB, randomized, parallel efficacy/ safety study with patients with insomnia	28 nights	HS dosing	Triazolam (0.5)	31	52	35	60	13	18
Placebo	31	51	23	60	15	16					

NOTE: Abbreviations: EEG, electroencephalogram; Pbo, placebo; HS, bedtime; DB, double blind.
SOURCE: U.S. Food and Drug Administration (1996, Appendix C).

Random-Effect Regression Models

To provide an assessment and synthesis of the information contained in these studies, the committee performed a random-effect ordinal probit regression analysis (Gibbons et al., 1994; Hedeker and Gibbons, 1994) using the MIXOR computer program (Hedeker and Gibbons, 1996) in which the random effect was the study and the fixed effects included treatment (i.e., 0.25-mg dose versus placebo and 0.125-mg dose versus placebo in geriatric subjects), study duration, age (i.e., geriatric versus non-geriatric), and the associated interactions (i.e., treatment by age and treatment by duration). Two general analyses were performed. First, all available data for subjects receiving the 0.25-mg dose were compared with data for subjects receiving placebo. Second, data for a geriatric population receiving the 0.125-mg dose were compared with data for a geriatric population receiving placebo. The second analysis was limited to two available protocols (Protocols 6417 and 6060A), which is insufficient to estimate precisely a random effect. Therefore, analysis of these two protocols was done as a fixed-effect analysis, and the main effect of the study and the study-by-treatment interaction were combined in the general model.

In evaluating each of the endpoints separately at the 5 percent level, it should be noted that the committee did not adjust for the effects of multiple comparisons. Also, the committee did not have baseline data for individual subjects and assumed that randomization satisfactorily balanced the means of the baseline variables among the groups.[4]

Results of Reanalysis

Analysis of these data revealed the following. For the 0.25-mg dose, there were no significant interactions among age, duration, and treatment. As such, the committee concludes that the relative difference between the 0.25-mg dose and placebo was comparable in geriatric and non-geriatric subjects and studies of short and long duration (i.e., a range of 2 to 43 days). In terms of treatment-related effects, the 0.25-mg dose produced significant improvement relative to that from placebo for all four endpoints (global rating, $p < 0{,}0001$; onset, $p < 0.01$; duration, $p < 0.0001$; and awakenings, $p < 0.05$). Table 2-5 displays the observed proportions of subjects for each endpoint category and treatment group over all studies. For example, among the subjects treated with 0.25 mg of Halcion, 30 percent reported that they received "a lot" of help from the drug, whereas only 10 percent of the subjects receiving placebo reported this level of help. By contrast, only 17 percent of the subjects receiving Halcion reported no help from the drug, whereas 51 percent of the subjects receiving placebo reported no help from the drug. For onset, 64 percent of the subjects treated with 0.25 mg of Halcion reported "quicker sleep onset," whereas only 27 percent of the subjects receiving placebo reported such an effect.

[4] The committee is aware that FDA found inequality in one study.

TABLE 2-5 Observed Proportions of Four Primary Endpoints for Subjects Who Received 0.25 mg of Halcion Versus Those for Subjects Who Received Placebo

		Proportion for the Following Effect Category:				
Endpoint	Treatment	1	2	3	4	
		None	A little	Quite a bit	A lot	
Did the medication help you sleep?	Placebo	0.51	0.21	0.18	0.10	
(global rating)	Halcion	0.17	0.18	0.35	0.30	
		Slower	Same	Quicker		
Time to onset (sleep latency)	Placebo	0.14	0.59	0.27		
	Halcion	0.07	0.30	0.64		
		<5 h	5-6 h	6.1-7 h	7.1-8 h	>8 h
Duration (hours of sleep)	Placebo	0.25	0.29	0.22	0.15	0.08
	Halcion	0.10	0.17	0.26	0.31	0.16
		>6	4-5	2-3	1	0
Number of awakenings	Placebo	0.05	0.17	0.41	0.19	0.17
	Halcion	0.02	0.07	0.29	0.36	0.26

For the 0.125-mg dose groups versus the placebo groups of geriatric subjects, combination of the data from the two studies revealed significant treatment-related effects for global rating ($p < 0.003$), onset ($p < 0.002$), and duration ($p < 0.003$) but not for the number of awakenings ($p < 0.69$). The main effects of the study and study-by-treatment interaction were not significant. Table 2-6 displays the observed proportions for each condition. The results are quite similar to those for the 0.25-mg dose for the total sample, with onset exhibiting the most pronounced effect and number of awakenings exhibiting the smallest effect (in this case the drug's effect on the number of awakenings was nonsignificant).

In summary, reanalysis of the efficacy data obtained by questionnaire supports the earlier findings of FDA that demonstrated the efficacy of 0.25 mg of Halcion for the general adult population and 0.125 mg of Halcion for the geriatric population.

Dose Response

To evaluate whether a dose-response relation exists for subjective efficacy ratings, data from the pivotal studies (Table 2-4) conducted with the 0.5-mg dose were included in the previous set of data from the low-dose studies (Table 2-1). The combined data set was tested for a linear dose-response relationship for each of the four endpoints by using the random-

effect probit regression model. The observed frequencies as a function of dose are presented in Figure 2-1, which reveals the visual impression of linear dose-response relations toward improving global sleep quality ratings (a), sleep duration (c), and number of awakenings (d). Sleep latency (b) is improved for subjects receiving the 0.25- and 0.5-mg doses relative to that for subjects receiving placebo; however, the observed proportions for 0.25 and 0.5 mg of Halcion are identical. The results of the statistical analysis reveal significant linear dose-response relationships for global ratings ($p < 0.0001$) and number of awakenings ($p < 0.002$), with the results for sleep duration being in the same direction but not reaching conventional levels of statistical significance ($p < 0.15$). The statistical test for linear dose-response relation for sleep latency was not significant given the equivalence of the effect of Halcion at the 0.25-and 0.5-mg doses.

LITERATURE REVIEW

The committee also reviewed the published literature on well-controlled clinical trials evaluating the effectiveness of Halcion or triazolam at doses of 0.25 or 0.125 mg.

TABLE 2-6 Observed Proportions of Four Primary Endpoints for Geriatric Subjects Who Received 0.125 mg of Halcion Versus Those for Subjects Who Received Placebo

		Proportion for the Following Effect Category:				
Endpoint	Treatment	1	2	3	4	
Did the medication help you sleep? (global rating)		None	A little	Quite a bit	A lot	
	Placebo	0.52	0.24	0.14	0.10	
	Halcion	0.28	0.22	0.27	0.23	
Time to onset (sleep latency)		Slower	Same	Quicker		
	Placebo	0.12	0.62	0.26		
	Halcion	0.00	0.43	0.57		
Duration (hours of sleep)		≤5 h	5-6 h	6.1-7 h	7.1-8 h	≥8 h
	Placebo	0.26	0.32	0.26	0.10	0.06
	Halcion	0.09	0.31	0.23	0.22	0.14
Number of awakenings		≥6	4-5	2-3	1	0
	Placebo	0.06	0.20	0.44	0.23	0.07
	Halcion	0.03	0.15	0.47	0.27	0.08

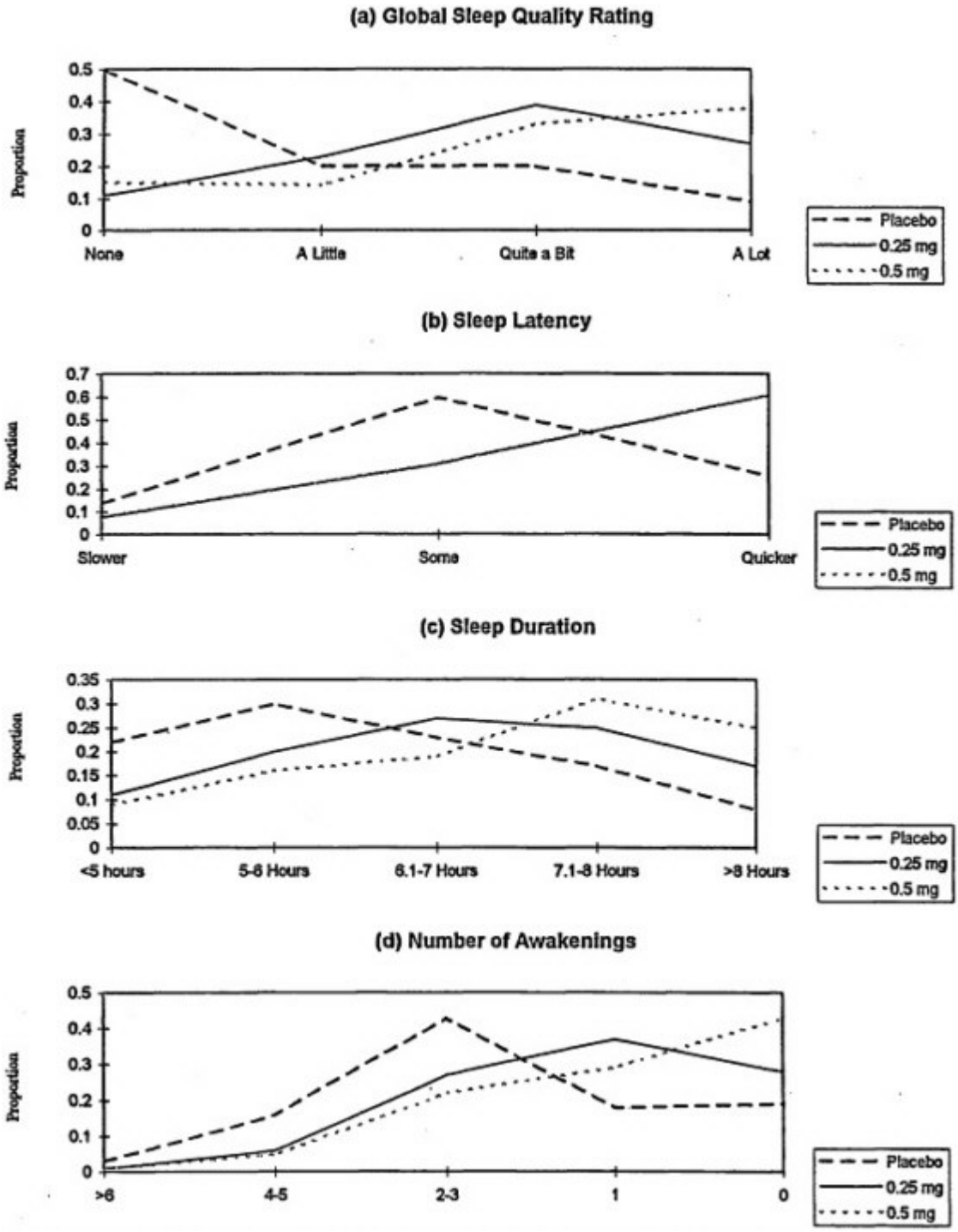

Figure 2-1
Observed dose-response relations for efficacy measures: placebo and Halcion at 0.25 and 0.5 mg in non-geriatric subjects. In panel b, the 0.25- and 0.5-mg dose-response lines are superimposed on each other.

In a study by Leppik and colleagues (1997), 335 elderly male and female subjects (ages, 60 to 85 years) with a 3-month history of subjective insomnia were studied in a double-blind, randomized, four-parallel-treatment-arm study. The dose of Halcion in that study was 0.125 mg; zolpidem (5 mg), temazepam (15 mg), and placebo were used in the other three arms. Following a 1-week period of treatment with placebo, clinical trial materials were administered daily at bedtime for 4 weeks, followed by a 4-day period of treatment with placebo to evaluate rebound insomnia. The investigators defined the primary outcome variables as a change in the subjective determination of sleep latency and total sleep time. Secondary outcome variables were items on a morning questionnaire and the subjects' global clinical assessment. Halcion improved sleep latency and the duration of sleep compared with those for subjects receiving placebo, but not to a statistically significant degree. Subjects did not categorize Halcion at this dose to be better than placebo on the global clinical assessment, whereas they did for the other two hypnotic agents.

A study by Hajak and colleagues (1994) is particularly interesting because it is the only study that the committee found in which the investigators defined responders a priori (e.g., clinically meaningful efficacy). Their definition states that a responder is someone who has a shortening of sleep latency by 15 minutes, prolongation of total sleep time by at least 20 percent, or a reduction of nocturnal awakenings to three or less and a fresh feeling in the morning as well as a lack of impairment in daytime well-being as a result of tiredness or anxiety. A total of 1,507 subjects from a group of practicing physicians was randomized to four treatment arms: zopiclone (7.5 mg), Halcion (0.25 mg), flunitrazepam (1 mg), and placebo at a ratio of 2:1:1:1, respectively. The rates of response to Halcion were most pronounced in those patients with a history of insomnia for 1 year or longer, although the number of responders in the Halcion group was not statistically different from that in the placebo group (32.2 Versus 26.8 percent).

In another study, Rosenberg and Ahlstrom (1994) compared 0.25 mg of Halcion with 10 mg of zolpidem in 178 outpatients (ages, 18 to 80 years) with at least a 1-week history of insomnia. The study involved double-blind, randomized parallel groups with patients treated nightly for 14 days. The investigators observed no difference from baseline values between the two drags in terms of improvements in duration of sleep, number of awakenings, or quality of sleep. Unfortunately, that study did not include a placebo control group.

In a study by Roger et al. (1993), 5 or 10 mg of zolpidem was compared with 0.25 mg of Halcion in a 3-week trial with 221 hospitalized elderly patients (ages, 60 to 90 years) with insomnia requiring medication for at least 3 weeks. A 3-day washout period to eliminate previous hypnotic medication preceded the administration of active drug for 3 weeks and was followed by a 7-day period of treatment with placebo to evaluate rebound insomnia. The efficacy variables were responses to a questionnaire regarding ease of sleep onset; estimated duration of sleep; and number, time, and duration of nocturnal awakenings. Visual analog scales were used to evaluate sleep quality and quality of awakenings. A clinical global impressions rating scale and use of rescue hypnotic medication were considered secondary endpoints. All measures of efficacy improved significantly for each parameter on the questionnaire, visual analog scales, and clinical global impression scale for all three groups. On day 31 all measures of efficacy had declined, although they still remained improved over the baseline measurements.

The hypnotic effects of zolpidem (10 mg), Halcion (0.25 mg), and placebo on hospitalized patients the night before surgery were studied in a well-controlled trial in six Canadian hospitals (Morgan et al., 1997). Three hundred fifty-seven patients (ages, 19 to 71 years) were administered a drug or placebo at bedtime and were allowed to sleep for 8 hours. Analysis of subjective outcome measures provided evidence that the results for groups receiving active drug were significantly different ($p < 0.001$) from those for the group receiving placebo; that is, sleep latency was shorter, total sleep time was longer, patients fell asleep more easily, and the number of patients awake 2 hours after drug administration was lower. Among none of the groups were there differences in somnolence or ability to concentrate the next morning. Both active drugs were well tolerated, with adverse event incidence rates for the groups receiving active drag being nearly identical to those for the group receiving placebo.

Thus, two of the three studies provide support for the efficacy of Halcion at 0.25 mg in the general population, including elderly subjects. Halcion was not statistically better than a placebo in the third study (at 0.25 mg), which defined responders. The one study with elderly patients with a 0.125-mg dose (Leppik et al., 1997) does not support efficacy in that population.

Polysomnographic Studies of Halcion in the Published Literature

Polysomnographic studies provide the most detailed and quantitative measures of physiologic sleep. These measures include sleep latency, total sleep time, sleep efficiency, number of awakenings, wake time after sleep onset (WASO), and mount of time spent in each of the stages of non-REM and REM sleep. These so-called objective sleep measures do not always coincide with the so-called subjective measures of sleep, in which the patient estimates sleep latency, total sleep time, and so forth, with questionnaires. When comparing reported and recorded sleep, unmedicated patients with chronic insomnia typically overestimate sleep latency and WASO, and underestimate total sleep time and sleep efficiency. Since publication of the 1977 FDA guidelines (U.S. Department of Health, Education, and Welfare, 1977), both subjective and polysomnographic sleep studies have been suggested in the evaluation of hypnotic drugs.

The committee reviewed data from 15 polysomnographic sleep laboratory studies in patients with insomnia: 5 studies of Halcion at 0.5 mg given to adults (duration of treatment, 5 to 35 nights), 5 studies of Halcion at 0.25 mg in adults (5 to 28 nights), 2 studies of Halcion at 0.25 mg given to geriatric subjects (3 to 15 nights), 1 study of Halcion given at 0.125 mg to general adults (14 nights), and 2 studies of Halcion at 0.125 mg given to geriatric subjects (3 nights to 12 weeks) (Table 2-7). In addition, the committee reviewed two polysomnographic studies in which normal subjects underwent a phase shift of the sleep-wake cycle. In most studies conducted with insomniacs, subjects had chronic insomnia that was rated as severe by both subjective and objective (polysomnographic) measures. In all studies, a placebo was administered before and after the active treatment phase. Additionally, 5 of these 15 studies with insomnia subjects also included a parallel group that received placebo for the active study period. With three exceptions (Salem et al., 1994; Mendelson, 1995; Ware et al., 1997), the number of subjects in each limb of these polysomnographic studies was small (ten or fewer) for studies lasting more than 1 week.

In all but one study of subjects with insomnia, the three doses of Halcion (0.125, 0.25, and 0.5 mg) significantly improved various objective parameters of sleep on the first 1 to 3 nights compared with those for the baseline, placebo-controlled nights. In the study by Kales and colleagues (1986), which did not report improvement, the baseline values for Halcion and placebo were markedly different for latency, raising a question regarding the validity of these results. For the 0.5-mg dose in general adults, statistically significant efficacy for one or more objective measures of sleep was. maintained through 2 weeks of treatment compared with the baseline condition in the studies with data at the end of the 2 weeks (Mitler et al., 1984; Monti et al., 1994; Ware et al., 1997). With increasing duration of treatment, however, several but not all studies indicated that statistically significant benefits for these measures were lost. Interestingly, in the three studies using a parallel placebo group, statistically significant differences between Halcion (0.5 mg) and placebo disappeared by 3 to 4 weeks of treatment, due in part to the sleep improvement of patients receiving placebo compared with baseline, and in part to the less pronounced sleep improvement over time of patients on Halcion as compared with the baseline condition (Mitler et a1., 1984; Monti et al., 1994; Ware et al., 1997).

In the adult subjects with insomnia who initially benefited with Halcion at 0.25 mg, evidence for clinical efficacy was mixed starting at the end of the first week. Although no tolerance was reported in a study measuring efficacy at 14 nights (Scharf et al., 1990), in one of the two studies lasting 28 nights, return to baseline measures was evident at the end of the study, but was not measured at 2 weeks (Salem et al., 1994). In the other study, objective improvement was noted throughout each of the 4 weeks of treatment (Mendelson et al., 1995.) Interestingly, subjective improvements showed tolerance for sleep latency and sleep quality.

In two studies with elderly subjects using Halcion at 0.25 mg for 2 weeks, the sleep of subjects given Halcion showed statistical improvement over baseline when measured at the end of the study and compared to the sleep of subjects receiving placebo (Mouret et al., 1990; Scharf et al., 1990).

The committee found only two polysomnographic studies that used Halcion at 0.125 mg for more than a few days. In a study with adult subjects with insomnia, tolerance to 0.125 mg—but not 0.25 mg—developed at 2 weeks compared with initial benefits or temazepam administered in a parallel group (Scharf et al., 1990). In a study in elderly patients with chronic insomnia associated with periodic limb movements of sleep (PLMS), Halcion at 0.125 mg was statistically significantly better at 12 weeks than at baseline (Bonnet and Arandt, 1991). The committee was unable to locate any polysomnographic sleep studies in with more typical elderly insomniac patients treated with triazolam at 0.125 mg for more than a few consecutive nights.

TABLE 2-7 Selected Polysomnographic Sleep Studios Evaluating Triazolam (Halcion) for Insomnia

Investigators	Study Design	Planned Treatment Duration	Treatment Groups	Results and Comments
Fernandez-Guardiola and Jurado (1981)	Double-blind crossover, placebo control; subjective insomnia; ages 24-36 (mean age, 30)	5 nights	Halcion at 0.25 mg and 0.5 mg (n = 8)	At night 5, Halcion at 0.5 mg increased TST; Halcion at 0.25 mg decreased number of awakenings
Mitler et al. (1984)	Double-blind, randomized, parallel placebo group S + O; ages 38-45 for different groups	35 nights	Halcion at 0.5 mg; flurazepam at 30 mg; placebo (n = 7 in each group)	Tolerance developed within and between groups at end of 2 weeks for Halcion group and 3 weeks for flurazepam group; rebound for Halcion group
Mamelak et al. (1985)	Double-blind, randomized, placebo controlled S + O; ages 32-56 (mean age, 45)	14 nights	Quazepam at 30 mg; Halcion at 0.5 mg (n = 6 in each group)	Both drugs effective with no tolerance; rebound insomnia for Halcion group
Kales et al. (1986)	Double-blind, randomized placebo control; S + O; ages 19-65 (mean age, 41 ± 5)	14 nights	Halcion at 0.25 mg, quazepam at 15 mg (n = 6 in each group)	Halcion: no major effect, tolerance, and withdrawal insomnia; Quazepam: persistent improvement
Seidel et al. (1986)	Double-blind, parallel placebo group; normal controls (180° shift of sleep period); ages 24-26	3-day shifted sleep periods (1200-2000 h)	Experiment I: Halcion at 0.5 mg, flurazepam at 30 mg, and placebo Experiment 11: Halcion at 0.25 mg, flurazepam at 15 mg and placebo	Halcion at 0.25 mg no better than placebo on sleep; Halcion at 0.5 mg and flurazepam better than placebo; hangover effects greater with flurazepam
Bonnet and Arand (1990)	Double-blind crossover placebo control; S + O associated with PLMS; mean age, 65 years	3 nights	Halcion at 0.125 and 0.25 me, placebo (n = 15	Halcion better than placebo for TST plus percent SE
Mouret et al. (1990)	Double-blind, randomized placebo control; elderly subjects	15 nights	Halcion at 0.25 mg, zopiclone at 75 mg (n = 10)	Both drugs improved sleep
Scharf et al. (1990)	Double-blind, randomized placebo control; S + O; ages, 21-55 (mean age, 34 ± 9)	14 nights.	Halcion at 0.125 mg (n = 7), Halcion at 0.25 mg (n = 7), temazepam at 15 and 30 mg (n = 9)	Halcion at 0.25 mg generally more effective than Halcion at 0.125 mg; subjects receiving Halcion at 0.125 mg showed tolerance from nights 1-3 to nights 13-14; groups receiving both doses showed greater rebound Insomnia than the group receiving flurazepam

Investigators	Study Design	Planned Treatment Duration	Treatment Groups	Results and Comments
Bonnet and Arand (1991)	Double-blind, placebo control; ages 55-79; O + S associated with PLMS	12 weeks	Halcion at 0.125 mg (2 baseline and 2 placebo 5 nights after active drug)	Increased TST, increased SE, increased daytime alertness, no rebound insomnia
Schweitzer et al. (1991)	Double-blind, parallel placebo, normal controls (180° shift); ages 18-31 (mean, 24)	3-day shift sleep periods (1200-2000 h)	Halcion at 0.25 mg, estazolam at 2 mg	Halcion did not change TST on shifted schedule, although estazolam improved TST significantly
Monti et al. (1994)	Double-blind, randomized, parallel placebo; subjective insomnia; ages 20-65 (mean, 45-49)	27 nights	Halcion at 0.5 mg; zolpidem at 10 mg; placebo (n = 8 in each group)	Both drugs were effective initially, but tolerance developed with Halcion group; rebound in Halcion group but not zolpidem group
Saletu et al. (1994)	Double-blind, randomized, generalized anxiety disorder	28 nights	Halcion at 0.25-0.5 mg (median = 0.25 mg) (n = 18); quazepam at 15-30 mg (median =15 mg) (n = 20)	Quazepam decreased SL; both quazepam and Halcion increased SE initially but tolerance developed in Halcion group, who also showed rebound
Mendelson (1995)	Double-blind, parallel placebo control; S; mean age 38 ± 3	4 weeks, weekly psg	Halcion 0.25 mg (n = 15)	Increased total sleep time, decreased sleep latency, decreased wake time, increased sleep efficiency; no objective tolerance; subjective SL showed tolerance
Ware et al. (1997)	Double-blind, randomized parallel placebo control; S + O; ages 21-55	28 nights	Halcion at 0.5 mg (n = 34); zolpidem at 10 mg (n = 30); placebo (n = 35)	Nights I-2, increased SE and decreased SL for all 3 groups; at nights 27 + 28, increased SE for placebo and Halcion groups compared with baseline. For Halcion group, increased SL, increased awake time, and decreased SE on first withdrawal night but not subjectively. Halcion group showed rebound.

NOTE: Abbreviations: O, objective (polysomnographic) insomnia; PLMS, periodic limb movements of sleep; TST, total sleep time; PSG, polysomnography; Q, questionnaire; S, subjective insomnia; SE, sleep efficiency; SL, sleep latency, Z, zolpidem (Ambien).

[a] $p < 0.05$

In contrast to Halcion, many of the other hypnotic agents that have been compared in parallel research designs have maintained efficacy for longer periods of treatment. These include flurazepam (Mitler et al., 1984), quazepam (Saletu et al., 1994), and zolpidem (Monti et al., 1997; Ware et al., 1997). Finally, the majority of laboratory sleep studies indicate that rebound insomnia develops after the administration of Halcion (clearly with the 0.5 mg dose and probably with the 0.25 mg dose, depending on the duration of treatment and other factors).

The committee's review and analysis of the questionnaire data generally supported the efficacy of the 0.25-mg dose in the non-geriatric population for 7-10 days, which is the current FDA recommendation. In addition, the polysomnographic laboratory sleep studies in the published literature generally justify the current recommended guidelines for Halcion at the 0.25 mg dose for the non-geriatric population. In addition, the committee found the questionnaire data for the 0.125-mg dose in the geriatric population to be supportive but weak. Except for the study with elderly patients with PLMS, the committee found no polysomnographic data for the 0.125-mg dose of the geriatric population for 7 to 10 nights of treatment.

CONCLUSIONS AND RECOMMENDATIONS

In summary, the IOM committee reviewed the protocols and study designs of clinical trials used to evaluate the efficacy of Halcion.[5] The postmarketing trials met current standards for a well-controlled clinical trial; the premarketing trials were adequate for the time and were sufficient to provide data of adequate quality to judge the effects of the drug. A statistical reanalysis of the data from trials using questionnaires to evaluate the subjects' sleep clearly supports the previous analyses that Halcion positively affects the quality of sleep. Polysomnographic data did not exhibit evidence of tolerance over time. Additionally, the committee found that a dose-response relationship does exist, and the literature generally supports the claim that the drug is efficacious.

Data Adequacy

Based on review of the original studies, FDA's reanalysis, and the IOM committee's own reanalysis of 20 studies, the questionnaire and polysomnographic data are adequate to support the conclusion that Halcion is effective in achieving the defined endpoints in the general adult population with insomnia when used as directed (in the current labeling) at doses of 0.25 mg for up to 7-10 days. In addition, polysomnographic data from clinical trials

[5] It is important to note that the conclusions and recommendations are based on a review of publicly available information. Various types of data were reviewed and evaluated, including randomized, controlled (dose and duration) clinical trials, spontaneous reports of adverse events, and survey data. The committee did not review original, raw data or case reports but, rather, the data that were summarized in the NDA and other sources and that data have been reviewed by FDA. The committee's analyses were based on these summary data.

support the efficacy of Halcion at 0.25 mg in non-geriatric adults for 2 weeks or more.

The questionnaire data are limited but adequate to support the conclusion that Halcion is effective in achieving the defined endpoints at the 0.125-mg dose in the geriatric population. Two studies (one for 2 days' duration; one for 7 days' duration) support this conclusion; one study in the literature did not. Although there are no polysomnographic clinical trials in the New Drug Application for the 0.125-mg dose in geriatric subjects, nor in the postmarketing clinical trials or published literature for this dose in geriatric subjects with insomnia beyond 3 days of treatment, the committee's reanalysis of the combined data clearly shows statistically significant drug-related effects at the 0.125-mg dose in the geriatric population.

Although analysis of the questionnaire data supports the efficacy of Halcion at a dose of 0.125 mg in the geriatric population, inadequate data are available to establish the effect of this dose on sleep architecture in the elderly insomniac.

***Recommendation 1: Improve Confidence in Lowest Dose*. Definitive short-, intermediate-, and long-term polysomnographic studies are needed in a geriatric population to determine the sleep architecture of elderly insomniacs using the 0.125-mg dose**.

Clinical Trial Design

The study designs and quantitative endpoints (i.e., sleep latency, duration, awakenings, and global assessment) used in the major clinical trials of Halcion in the past are of sufficient quality to yield adequate and reliable data for the determination of efficacy. The modem standards for the conduct of clinical trials have become more rigorous.

***Recommendation 2: Update Guidelines*. FDA should revise and update its *Guidelines for the Clinical Evaluation of Hypnotic Drugs* (U.S. Department of Health, Education, and Welfare, 1977) to include clinical trials on the intermediate-and long-term efficacies of hypnotic drugs. Future studies comparing Halcion with other drugs should use multiple doses of both Halcion and the comparator drugs to permit the determination of relative clinical potency**.

***Recommendation 3: Improve Outcomes Measures*. Research is needed to identify the most valid and reliable endpoints for determination of the clinical efficacies of hypnotic agents. Most importantly, this should include endpoints that are nested in a 24-hour day-night cycle (e.g., to evaluate amnesia and daytime sedation). This should also include better integration of the subjective and objective (polysomnographic) response measures**.

Tolerance

The committee's analysis of questionnaire data from studies of the efficacy of Halcion

taken for up to 43 days indicates that there is no evidence to support the development of tolerance to the hypnotic effects of Halcion; that is, the difference in the effects between drag versus placebo was consistent over time (0.5 mg for 43 days, 0.25 mg for 28 days, 0.125 mg for 8 days, and 0.25 mg for 16 weeks). In addition, polysomnographic data from clinical trials do not provide evidence of tolerance, but the polysomnographic literature suggests that tolerance may develop.

Available data suggest, however, that tens of thousands of prescriptions for much longer periods of time are being obtained by patients for much longer periods of time (e.g., the Evaluation of Medications for Insomnia in Canada study reports a mean duration of 1.7 years of use in Canada [Mariano and Gardner, 1988]; see Chapter 3). No data indicating the efficacy (or safety) of long-term use of Halcion for chronic insomnia exist.

***Recommendation 4: Determine Tolerance*. Controlled clinical trials of a duration of Halcion use beyond that recommended in the current labeling would be needed to determine whether tolerance to Halcion develops with long-term use**.

3

Assessment of Safety Data

Concerns about the safety of the hypnotic drug Halcion (triazolam) have existed since C. van der Kroef reported a syndrome of adverse reactions to the drug in 1979 (van der Kroef, 1979)[1]. Many changes in the labeling guidelines have been made since then, but concerns have persisted and are described most succinctly in the 1992 Public Citizen petition to remove Halcion from the U.S. market. In its investigation of these and other concerns, the Institute of Medicine (IOM) committee reviewed and assessed the relevant data from Upjohn's New Drug Application (NDA; NDA 17-892) and other sources, including the published literature, as they pertain to whether triazolam (1) produces a unique profile or syndrome of adverse events and (2) produces adverse effects that are qualitatively similar but quantitatively different from those associated with other benzodiazepine hypnotic agents.

More specifically, the committee reviewed and evaluated (1) protocols and data from well-controlled pre- and postmarketing clinical trials; (2) data from studies performed in countries other than the United States, including data from a cohort study; (3) spontaneous reports of adverse events; and (4) data from the published literature. This chapter is organized according to these sources of data and their analyses. The committee then presents its conclusions and recommendations at the end of the chapter.

WELL-CONTROLLED PREMARKETING CLINICAL TRIALS

In assessing the data from well-controlled premarketing clinical trials, the IOM committee reviewed and performed independent statistical reanalyses of two comprehensive summaries of the safety data: Upjohn's Integrated Summary of Safety (ISS) (The Upjohn Company, 1991) and the reconstructed tabular data of adverse events analyzed by the U.S.

[1] An English text description of the Dutch experience is available (Meyboom, 1992).

Food and Drug Administration (FDA) (Laughren and Lee, 1992); both had been presented at a May 1992 meeting of the FDA Psychopharmacologic Drugs Advisory Committee (PDAC). The committee first analyzed the frequency of adverse events and then examined the frequency and nature of adverse events that led to the withdrawal of subjects from the trials (i.e., dropouts).

Adverse Events

In 1992 Upjohn created a new database of safety information by reentering the data from the case-report forms for the 116 clinical trials in the NDA. FDA oversaw this effort and verified that "there was a highly accurate transfer of pertinent data" from the case reports to the new database (Laughren and Lee, 1992, p. 9). Upjohn also developed an ISS using results from 79 studies (from among the 116 studies from the NDA, but without the Phase I studies and including the available postmarketing clinical trials) comparing approximately 4,000 subjects treated with Halcion (0.1 to 1.0 mg), 1,300 subjects treated with flurazepam (Dalmane; 15 to 30 mg), and 2,100 subjects treated with placebo.

A subset of the 116 studies was selected specifically to compare Halcion with placebo and another benzodiazepine hypnotic drug. That subset consisted of the 25 studies that (1) involved subjects with insomnia, (2) had a parallel-group design, (3) were at least 1 week in duration, and (4) involved placebo or flurazepam as the comparator drug. Upjohn used this subset of 25 studies in its comparative analysis in the ISS, and FDA used this subset in its analysis of dropouts. The IOM committee first examined Upjohn's comparative analysis of the frequency of adverse events as described in the ISS.

Integrated Summary of Safety

Table 3-1 indicates the frequency of adverse events involving the central nervous system (CNS) from the 79 clinical trials in the ISS. Tables 3-2 through 3-5 present tabular summaries of the data from the subset of 25 studies using the following classifications: adult and geriatric insomniac populations, low and high doses, and shorter and longer durations. In reviewing these data, the committee made the following three observations.

Observation 1: Comparable Safety Profile

Halcion at the currently recommended doses (0.125 and 0.25 mg) and for the shortest durations of use (1 to 7 days) has a safety profile comparable to those of both placebo and the lowest dose of flurazepam (15 mg), even for those undesirable events associated with the pharmacologic activity of benzodiazepines, namely, restlessness, nervousness, drowsiness, impaired coordination, light-headedness, and dizziness (Tables 3-2, 3-4, and 3-5). Rates of response for the most frequently occurring CNS-related adverse event (sedation or drowsiness) were 16.7, 23.5, and 11.3 percent for the three groups (Halcion, flurazepam, and placebo), respectively (see Table 3-1), Dizziness and headache were second and third most common adverse events. Other events of interest described in the tabulated summaries were impaired memory (at rates of 0.7, 0.5, and 0.2 percent, respectively) and impaired coordination (at rates of 3.4, 4.6, and 1.5 percent, respectively).

TABLE 3-1 Number (percent) of Subjects Reporting CNS-Related Adverse Events in Adequate and Well-Controlled Phase II/III Studies () with a Duration of Treatment of 1 to 92 days

Medical Event	Halcion (n = 3,982)	Flurazepam (n = 1,295)	Placebo (n = 2,151)	Other[a] (n = 1,098)
Drowsiness/sedation	664 (16.7)	304 (23.5)	244 (11.3)	178 (16.2)
Dizziness	350 (8.8)	68 (5.3)	132 (6.1)	80 (7.3)
Headache	307 (7.7)	110 (8.5)	175 (8.1)	41 (3.7)
Tiredness	183 (4.6)	77 (5.9)	171 (7.9)	122 (1.1)
Nervousness	164 (4.1)	61 (4.7)	117 (5.4)	19 (1.7)
Impaired coordination	136 (3.4)	60 (4.6)	33 (1.5)	3 (0.3)
Depression	100 (2.5)	47 (3.6)	81 (3.8)	1 (0.1)
Insomnia	73 (1.8)	28 (2.2)	98 (4.6)	9 (0.8)
Confusion	53 (1.3)	14 (1.1)	50 (2.3)	1 (0.1)
Excitement	49 (1.2)	1 (0.1)	52 (2.4)	0
Euphoria	38 (1.0)	25 (1.9)	26 (1.2)	2 (0.2)
Memory impairment	27 (0.7)	7 (0.5)	5 (0.2)	0
Tremor	22 (0.6)	5 (0.4)	24 (1.1)	1 (0.1)
Concentration difficulty	21 (0.5)	15 (1.2)	16 (0.7)	5 (0.5)
Vasomotor disturbances	21 (0.5)	5 (0.4)	8 (0.4)	0

[a] Pentobarbital, secobarbital, chloral hydrate, methaqualone, diazepam, and oxazepam.
SOURCE: The Upjohn Company (1992).

TABLE 3-2 CNS-Related Medical Events for Adult Insomniac Subjects, 1 to 2 Weeks of Treatment

	Triazolam 0.25 mg (n = 35) vs. Placebo (n = 35)[a]		Triazolam 0.25-0.5 mg (n = 121) vs. Flurazepam 15-30 mg (n = 52) and Placebo (n = 77)[b]			Triazolam 0.5 mg (n = 418) vs. Flurazepam 30 mg (n = 216) Flurazepam 30 mg (n = 216)[c]		
Medical Event	TZ	PBO	TZ	FLU	PBO	TZ	FLU	PBO
Drowsiness/ sedation	3 (8.6)	4 (11.4)	55 (45.5)	11 (21.2)	47 (61.0)	107 (25.6)	68 (31.5)	29 (13.7)
Headache	9 (25.7)	6 (17.1)	12 (9.9)	4 (7.7)	2 (2.6)	65 (15.6)	24 (11.1)	36 (17.0)
Dizziness	5 (14.3)	0	25 (20.7)	1 (1.9)	21 (27.3)	39 (9.3)	15 (6.9)	10 (4.7)
Nervousness	1 (2.9)	1 (2.9)	6 (5.0)	2 (3.8)	1 (1.3)	27 (6.5)	11 (5.1)	9 (4.2)
Tiredness	0	0	46 (38.0)	1 (1.9)	59 (76.6)	13 (3.1)	6 (2.8)	2 (0.9)
Paresthesia	3 (8.6)	0	0	0	0	2 (0.5)	0	0
Dysesthesia	1 (2.9)	0	0	0	1 (1.3)	1(0.2)	0	0
Insomnia	1 (2.9)	0	0	0	0	2 (0.5)	3(1.4)	3 (1.4)
Impaired coordination	0	0	2 (1.7)	2 (3.8)	0	22 (5.3)	7 (3.2)	6 (2.8)
Memory impairment	0	0	0	0	0	2 (0.5)	1 (0.5)	0
Confusion	0	0	0	0	0	2 (0.5)	0	1 (0.5)
Disorientation	0	0	0	0	0	1 (0.2)	0	0
Vasomotor disturbances	0	0	3 (2.5)	1 (1.9)	0	3 (0.7)	0	0
Derealization	0	0	1 (0.8)	0	0	0	1 (0.5)	0
Dream abnormalities	0	0	1 (0.8)	0	0	1 (0.2)	2 (0.9)	1 (0.5)
Euphoria	0	0	I (0.8)	0	0	1 (0.2)	0	0
Fear	0	0	1 (0.8)	0	0	1 (0.2)	0	0
Intellectual impairment	0	0	1 (0.8)	0	0	1 (0.2)	0	0
Irritability	0	0	1 (0.8)	0	2 (2.6)	2 (0.5)	3 (1.4)	3 (1.4)
Shakiness	0	0	1 (0.8)	0	0	0	0	0
Depression	0	0	0	0	0	7 (1.7)	4 (1.9)	3 (1.4)

	Triazolam 0.25 mg (n = 35) vs. Placebo (n = 35)[a]		Triazolam 0.25-0.5 mg (n = 121) vs. Flurazepam 15-30 mg (n = 52) and Placebo (n = 77)[b]			Triazolam 0.5 mg (n = 418) vs. Flurazepam 30 mg (n = 216) Flurazepam 30 mg (n = 216)[c]		
Medical Event	TZ	PBO	TZ	FLU	PBO	TZ	FLU	PBO
Intoxicated/ inebrious state	0	0	0	0	0	2 (0.5)	0	0
Concentration difficulty	0	0	0	0	0	1 (0.2)	2 (0.9)	0
Muscle tone disorders	0	0	0	0	0	1 (0.2)	1 (0.5)	1 (0.5)
Syncope	0	0	0	0	0	1 (0.2)	0	0

NOTE: Abbreviations: n, number of subjects in the treatment group; TZ, triazolam; FLU, flurazepam; PBO, placebo.
[a] Includes Protocol 6401.
[b] Includes flexible-dose Protocols 6400 and 2401.
[c] Includes Protocols 6004, 6016, 6042, 6043, and 6044.
SOURCE: The Upjohn Company (1992).

TABLE 3-3 CNS-related Medical Events for Adult Insomniac Subjects, 4 to 6 and 12 to 13 Weeks of Treatment

	4-6 Weeks' Duration					12-13 Weeks' Duration	
	Triazolam 0.25 mg (n = 54) vs Flurazepam 30 mg (n = 27)[a]		Triazolam 0.5 mg (n = 220) vs Flurazepam 30 mg (n = 121) and Placebo (n = 96)[b]			Triazolam 0.5 or 0.6 mg (n = 119) vs Flurazepam 30 mg (n = 97)[c]	
Medical Event	TZ	FLU	TZ	FLU	PBO	TZ	FLU
Drowsiness/ sedation	14 (25.9)	15 (55.6)	62 (28.2)	33 (27.3)	10 (10.4)	38 (31.9)	40 (41.2)
Headache	5 (9.3)	4 (14.8)	38 (17.3)	10 (8.3)	12 (12.5)	31 (26.1)	20 (20.6)
Dizziness	7 (13.0)	7 (25.9)	49 (21.8)	10 (3.3)	3 (3.1)	9 (7.6)	5 (5.2)
Impaired coordination	6 (11.1)	8 (29.6)	17 (7.7)	8 (6.6)	0	9 (7.6)	7 (7.2)
Tiredness	4 (7.4)	1 (3.7)	4 (1.8)	5 (4.1)	2 (2.1)	2 (1.7)	7 (7.2)
Insomnia	3 (5.6)	1 (3.7)	2 (0.9)	0	2 (2.1)	2 (1.7)	1 (l.0)
Depression	2 (3.7)	0	3 (1.4)	3 (2.5)	0	6 (5.0)	5 (5.2)
Memory impairment	0	0	2 (0.9)	0	0	11 (9.2)	1 (1.0)
Confusion	1 (1.9)	0	0	0	0	3 (2.5)	0
Disorientation	0	0	2 (0.9)	0	0	1 (0.8)	1 (1.0)
Paresthesia	0	0	1 (0.5)	0	0	0	1 (1.0)
Dysesthesia	0	0	1 (0.5)	0	1 (1.0)	1 (0.8)	0
Vasomotor disturbances	1 (1.9)	0	2 (0.9)	0	0	3 (2.5)	2 (2.1)
Derealization	0	0	1 (0.5)	0	0	0	0
Dream abnormalities	0	0	1 (0.5)	0	1 (1.0)	2 (1.7)	2 (2.1)
Increased motor activity	0	0	0	0	0	1 (0.8)	0
Intellectual impairment	5 (9.3)	0	0	0	0	2 (1.7)	0

	4-6 Weeks' Duration					12-13 Weeks' Duration	
	Triazolam 0.25 mg (n = 54) vs Flurazepam 30 mg (n = 27)[a]		Triazolam 0.5 mg (n = 220) vs Flurazepam 30 mg (n = 121) and Placebo (n = 96)[b]			Triazolam 0.5 or 0.6 mg (n = 119) vs Flurazepam 30 mg (n = 97)[c]	
Medical Event	TZ	FLU	TZ	FLU	PBO	TZ	FLU
Irritability	0	1 (3.7)	1 (0.5)	0	0	1 (0.8)	0
Shakiness	1 (1.9)	0	0	0	1 (1.0)	1 (0.8)	0
Excitement	0	0	0	0	0	1 (0.8)	0
Mood changes	0	0	2 (0.9)	0	0	1 (0.8)	0
Apathy	1 (1.9)	0	1 (0.5)	0	0	0	0
Drug withdrawal symptoms	1 (1.9)	0	0	0	0	0	0
Personality changes	0	0	1 (0.5)	0	0	0	0
Hallucinations	0	0	0	0	0	2 (1.7)	0
Concentration difficulty	0	0	0	0	0	1 (0.8)	0
Drug abuse	0	0	0	0	0	1 (0.8)	0
Agitation	0	0	0	0	0	1 (0.8)	0

NOTE: Abbreviations: n, number of subjects in the treatment group; TZ, triazolam; FLU, flurazepam; PBO, placebo.
[a] Includes Protocol 6401.
[b] Includes flexible-dose Protocols 6400 and 2401.
[c] Includes Protocols 6004, 6016, 6042, 6043, and 6044.
SOURCE: The Upjohn Company (1992).

TABLE 3-4 CNS-Related Medical Events for Geriatric Subjects, 1 Week of Treatment

	Triazolam 0.25 mg (n = 46) vs Placebo (n = 44)[a]		Triazolam 0.125-0.25 mg (n = 18) vs Placebo (n = 19)[b]	
Medical Event	TZ	PBO	TZ	PBO
Drowsiness/sedation	5 (10.9)	4 (9.1)	2 (11.1)	1 (5.3)
Headache	4 (8.7)	3 (6.8)	0	1 (5.3)
Dizziness	2 (4.3)	2 (4.5)	0	1 (5.3)
Tiredness	1 (2.2)	0	0	1 (5.3)
Nervousness	1 (2.2)	4 (9.1)	0	3 (15.8)
Memory impairment	1 (2.2)	0	0	0

NOTE: Abbreviations: n, number of subjects in the treatment group; TZ, triazolam; PBO, placebo.
[a] Includes Protocol 6401.
[b] Includes flexible-dose Protocols 6400 and 2401.
SOURCE: The Upjohn Company (1992).

TABLE 3-5 CNS-Related Medical Events for Geriatric Subjects, 1 to 2 and 4 Weeks of Treatment

	1-2 Weeks' Duration			4 Weeks' Duration					
	Triazolam 0.25 mg (n = 35) vs Flurazepam 15 mg (n = 58) and Placebo (n = 48)[a]			Triazolam 0.25 mg (n = 14) vs Flurazepam 15 mg (n = 13) and Placebo (n = 14)[b]			Triazolam 0.25-0.5 mg (n = 40) vs Flurazepam 15-30 mg (n = 40) and Placebo (n = 41)[c]		
Medical Event	TZ	FLU	PBO	TZ	FLU	PBO	TZ	FLU	PBO
Drowsiness/ sedation	19 (18.1)	17 (29.33)	3~ (6.3)	4 (25.6)	3 (23.1)	2 (14.3)	24 (60.0)	31 (77.5)	19 (46.33)
Dizziness	1 (1.0)	0	0	0	0	0	22 (55.0)	28 (70.0)	15 (43.9)
Headache	15 (14.3)	S (13.8)	4 (8.3)	1 (7.1)	1 (7.7)	0	5 (12.5)	3 (7.5)	4 (9.8)
Impaired coordination	2 (1.9)	1 (1.7)	0	1 (7.1)	1 (7.1)	0	5 (12.5)	7 (17.5)	4 (9.8)
Nervousness	3 (2.9)	0	2 (4.2)	1 (7.1)	0	0	12 (30.0)	8 (20.0)	6 (14.6)
Memory impairment	0	0	0	0	0	0	1 (2.5)	0	0
Confusion	1 (1.0)	1 (1.7)	0	0	0	0	0	1 (2.5)	1 (2.4)
Disorientation	0	0	0	0	0	0	2 (5.0)	0	
Paresthesia coordination	0	0	0	0	0	0	1 (2.5)	1 (2.5)	
Dysesthesia impairment	0	0	0	0	0	0	2 (5.0)	1 (2.5)	
Insomnia	1 (1.0)	0	0	0	0	0	5 (12.5)	3 (7.5)	1 (2.4)
Vasomotor disturbances	0	1 (1.7)	0	0	0	0	4 (10.0)	0	1 (2.4)
Dream abnormalities	0	0	0	0	0	0	1 (2.5)	1 (2.5)	2 (4.9)
Tremor	0	0	0	0	0	0	1 (2.5)	0	0
Fear	0	0	0	1 (7.1)	0	0	0	0	0
Intellectual impairment	0	0	0	0	0	0	1 (2.5)	0	0
Irritability	0	0	0	1 (7.1)	0	0	2 (5.0)	0	1 (2.4)
Shakiness	0	0	0	0	0	0	1 (2.5)	0	0
Excitement impairment	0	0	0	0	0	0	1 (2.5)	0	1 (2.4)
Mood changes	1 (1.0)	0	0	0	0	0	0	0	0

	1-2 Weeks' Duration			4 Weeks' Duration					
	Triazolam 0.25 mg (n = 35) vs Flurazepam 15 mg (n = 58) and Placebo (n = 48)[a]			Triazolam 0.25 mg (n = 14) vs Flurazepam 15 mg (n = 13) and Placebo (n = 14)[b]			Triazolam 0.25-0.5 mg (n = 40) vs Flurazepam 15-30 mg (n = 40) and Placebo (n = 41)[c]		
Medical Event	TZ	FLU	PBO	TZ	FLU	PBO	TZ	FLU	PBO
Depression	3 (2.9)	0	0	0	0	0	1 (2.5)	3 (7.5)	2 (4.9)
Concentration difficulty	0	0	0	0	0	0	1 (2.5)	2.(5.0)	0
Drug withdrawal symptoms	1 (1.0)	0	0	0	0	0	0	0	0
Drug habituation	0	0	0	1 (7.1)	0	0	0	0	0
Agitation	0	0	1 (2.1)	0	0	0	1 (2.5)	0	0
Sexual dysfunction	0	0	0	0	0	0	1 (2.5)	1 (2.5)	1 (2.4)
Apathy	0	0	0	0	0	0	2 (5.0)	1 (2.5)	1 (2.4)

NOTE: Abbreviations: n, number of subjects in the treatment group; TZ, triazolam; FLU, flurazepam; PBO, placebo.
[a] Includes Protocol 6401.
[b] Includes flexible-dose Protocols 6400 and 2401.
[c] Includes Protocols 6004, 6016, 6042, 6043, and 6044.
SOURCE: The Upjohn Company (1992).

Observation 2: Comparable Rates of CNS-Related Events

In studying the data in Tables 3-2 through 3-5 the committee concluded that for studies comparing Halcion, flurazepam, and placebo in non-geriatric adults, and geriatric subjects in studies of comparable length, the rates of CNS-related adverse events for the two drugs and placebo do not differ remarkably. There were, however, a very few instances in which the rate of CNS-related adverse events was at least threefold greater for Halcion relative to that for placebo. In comparing Halcion with flurazepam, the committee found a few comparisons in which the rate of adverse events for flurazepam is lower by twofold and a few instances in which the rate is lower by as much as threefold. For example, a significant difference in memory impairment was noted for the 0.5-mg Halcion dose.

As seen in the last two columns of Table 3-3, the occurrence of memory impairment in 9.2 percent of subjects treated with Halcion (0.5 or 0.6 mg) stands out in comparison with a rate of memory impairment of only 1 percent among subjects treated with flurazepam (30 mg). It is important to note that the data in these two columns are from studies in which relatively high doses (higher than the current Halcion labeling recommends as an initial or starting dose) of the two drags (0.5 or 0.6 mg of Halcion or 30 mg of flurazepam) were used, and in which there was a long duration of treatment (12 to 13 weeks). These differences were not observed at 4 to 6 Weeks of treatment.

Observation 3: Increased Sensitivity in Geriatric Subjects

Consistent differences can be seen for geriatric subjects, suggesting an increased risk of adverse CNS-related events with the highest Halcion dose and the longer duration of treatment compared with the risk with the lowest dose and shorter durations (Tables 3-4 and 3-5), and the same is true for flurazepam. Comparing the results for adults (younger and middle-aged adults) in Tables 3-2 and 3-3, there is little evidence of increases in the rate of any of the more than two dozen types of CNS-related adverse events listed for those receiving Halcion, and the same is true for flurazepam. However, the rates (in Tables 3-2 to 3-5) come from different studies and it is difficult to evaluate the significance of the comparisons in terms of possible dose and duration effects. No statistical analyses were presented as an aid in differentiating among the many possible comparisons to focus on those possibly occurring on a more than random basis.

Summary

Based on a visual inspection of the tabular data, the committee concludes that the currently recommended doses of Halcion (0.125 and 0.25 mg) and the shortest durations of use (1 to 7 days) have a safety profile comparable to those of both placebo and the lowest dose of flurazepam (15 mg), including comparable rates of CNS-related adverse events. The data also suggest that geriatric subjects may be at an increased risk of adverse CNS-related events with the highest Halcion dose and the longest duration of treatment compared with the risk with the lowest dose and shorter durations.

IOM Analysis of Upjohn's Integrated Summary of Safety

To provide a broader view of the dose-response relation, particularly for the lower doses that are relevant to current labeling (i.e., 0.25 mg for non-geriatric subjects and 0.125 mg for

geriatric subjects), the committee performed an additional statistical analysis of the tabulated data provided in the Integrated Summary of Safety (see Tables 3-2 through 3-5). Became the data were summarized by pooling data from studies with similar populations, durations, and doses, protocol-specific data were unavailable. Nevertheless, the fixed effects of duration, dose, and age and their interactions on the incidence of various adverse events can be examined by using a fixed-effects probit regression model applied to the frequencies listed in Tables 3-2 through 3-5. For this analysis the committee selected the adverse events nervousness, memory impairment, impaired coordination, and confusion. (The category "all psychiatric" adverse events was created by FDA and was not available in these tables for analysis.) Analyses were performed separately for Halcion and flurazepam, and placebo was used as the zero dose in both analyses. The overall observed proportions of adverse events for each drag and dose are presented in Table 3-6, as are the expected proportions of adverse events for geriatric and non-geriatric subjects for each drug and dose. Results of the analysis are as follows.

Nervousness

In the committee's analysis, significant dose, duration, and age effects were found for both Halcion ($p < 0.00001$ for dose, $p < 0.00004$ for duration, and $p < 0.005$ for age) and flurazepam ($p < 0.0002$ for dose, $p < 0.0015$ for duration, and $p < 0.04$ for age), indicating increased incidence of nervousness with increased dose, duration, or age. For Halcion (see Table 3-6), observed incidence rates were 4 percent (placebo), 2 percent (0.125-mg dose), 7 percent (0.25-mg dose), and 10 percent (0.5-mg dose), with expected rates ranging from 1.7 to 9.7 percent for non-geriatric subjects and 5.9 to 14.3 percent for geriatric subjects. For flurazepam (see Table 3-6), the observed incidence rates were 3 percent (placebo), 0 percent (15-mg dose), and 7 percent (30-mg dose), with expected rates ranging from 1.2 to 6.5 percent for non-geriatric subjects and 3.7 to 12.3 percent for geriatric subjects. These results indicate similar incidences of nervousness for Halcion at 0.25 mg and flurazepam at 30 mg.

Memory Impairment

A significant duration effect was found for Halcion ($p < 0.018$), indicating an increased incidence of memory impairment with increased duration of use. No statistically significant dose-related effects were observed for either drug. For Halcion, the overall observed incidence rates were between 0 and 2 percent (the highest rate was observed at a dose of 0.125 mg) and were all less than 1 percent for flurazepam (see Table 3-6). These results indicate similar incidences of memory impairment for placebo and all active doses for both drugs.

Impaired Coordination

A significant dose effect was noted for Halcion ($p < 0.0002$), indicating an increased incidence of impaired coordination with increased dose. For Halcion, observed incidence rates were 2 percent (placebo), 0 percent (0.125-mg dose), 4 percent (0.25-mg dose), and 8 percent (0.5-mg dose), with expected rates ranging from 1.3 to 6.4 percent for non-geriatric subjects and 1.2 to 9.5 percent for geriatric subjects. For. flurazepam, the observed incidence rates were 2 percent (placebo), 3 percent (15-mg dose), and 6 percent (30-mg dose), with expected rates ranging from 1.4 to 5.0 percent for non-geriatric subjects and 3.6 to 12.7 percent for geriatric subjects. These results indicate a similar incidence of impaired coordination for Halcion between doses of 0.25 and 0.5 mg and flurazepam at a dose of 30 mg.

TABLE 3-6 Comparisons of Observed and Expected Incidence of Four Adverse Events in Subjects in Controlled Clinical Trials Receiving Low Doses of Halcion and Flurazepama

	Halcion				Flurazepam			
			Expected Incidence[b]				Expected Incidence	
Adverse Event	Dose (mg)	Observed Incidence	Adult	Geriatric	Dose (mg)	Observed Incidence	Adult	Geriatric
Nervousness	0	0.04	0.017	0.059	0	0.03	0.012	0.037
	0.125	0.02	0.028	0.075	15	0.00	0.029	0.070
	0.25	0.07	0.044	0.094	30	0.07	0.065	0.123
	0.5	0.10	0.097	0.143				
Memory impairment	0	0.00	0.000	0.001	0	0.00	0.000	0.000
	0.125	0.02	0.001	0.003	15	0.00	0.000	0.000
	0.25	0.00	0.001	0.007	30	0.00	0.000	0.000
	0.5	0.01	0.006	0.026				
Impaired coordination	0	0.02	0.013	0.012	0	0.02	0.014	0.036
	0. 125	0.00	0.020	0.022	15	0.03	0.028	0.071
	0.25	0.04	0.030	0.038	30	0.06	0.050	0.127
	0.5	0.08	0.064	0.095				
Confusion	0	0.00	0.003	0.006	0	0.00	0.002	0.017
	0.125	0.00	0.003	0.005	15	0.01	0.001	0.013
	0.25	0.01	0.003	0.004	30	0.00	0.001	0.010
	0.5	0.00	0.003	0.003				

[a] The data used in these analyses were extracted from tabular data from the Upjohn Company, 1992; pp. 30-40
[b] Duration of 2 weeks.
SOURCE: The Upjohn Company (1992).

Confusion

No significant effects of dose, duration, or age were found for either drug. The overall observed incidence rates for both drags were between 0 and 1 percent (see Table 3-6).

Summary

In summary (as shown in Table 3-6), the committee's analysis of the data presented in the ISS tables (Tables 3-1 to 3-5; which present data for a wider range of doses and durations than the FDA analysis of adverse event data, i.e., particularly the lower doses that represent the current labeling) does show evidence of dose-response relations for nervousness and impaired coordination that are similar for patients treated with Halcion and flurazepam. In general, the 0.25-mg dose of Halcion seems similar to the 30-mg dose of flurazepam in terms of the incidence rates for these two adverse events. However, no statistically significant dose-related increases in the rates of memory impairment or confusion were noted for these two drugs over those for placebo.

Analysis of Dropouts

To examine the significance of adverse event occurrences further, the committee reviewed and analyzed the data for subjects who withdrew (i.e., dropouts) from the 25 studies[2] that had been selected by FDA for analysis of adverse events in 1992. The committee examined and assessed the FDA analysis of these data and then reanalyzed the data by its own methods.

FDA Analysis

In 1992, FDA reexamined adverse event data for Halcion derived from clinical trials sponsored by Upjohn and conducted before and after approval of the drug. FDA reviewed data from 116 clinical trials, and from among those studies selected the 25 parallel-group studies of 1 week or more in duration for analysis. Upjohn created a new database containing data from these 25 studies, and the FDA validated the data by checking data listings with case reports.

In their analysis of the data from these 25 studies, FDA focused on adverse events that led to the withdrawal of subjects from the trials (i.e., dropouts). However, "no attempt was made to pool data across different studies because of variability of study designs (dose, duration, population) and also variability in results, even for studies of the same design" (Laughren and Lee, 1992, p. 14). Instead, FDA provided a tabular display of the adverse event incidence data for each study protocol separately and grouped the data from each study by non-geriatric and geriatric subjects and ordered them by duration and dose (Laughren and Lee, 1992; see Appendix A, Tables A-1 through A-13).

[2] This is the same set of 25 studies that is described previously in this chapter (see the section on Adverse Events).

In addition, FDA pooled data for dropouts across studies to conduct statistical comparisons of risk ratios between Halcion and placebo and Halcion and flurazepam for various subgroups: study population (e.g., geriatric versus non-geriatric), dose (low dose [Halcion, <0.25 mg; flurazepam, 15 mg] versus high dose [Halcion, >0.25 and <0.6 mg; flurazepam, 15 to 30 mg]), and duration (short [<14 days] versus long [>28 days]) (see Table 3-7).

For the category "all psychiatric" adverse events (which includes anxiety, confusion, depression, psychosis, impaired concentration, insomnia, irritability, mood change, psychiatric miscellaneous, and unusual dreams, FDA found risk ratios of approximately 2.5 to 1 for Halcion versus flurazepam and placebo in clinical trials of longer duration that study the higher doses of Halcion in non-geriatric populations (see Table 3-7). A notable exception was a risk ratio of approximately 7 to 1 for Halcion versus placebo in long-term studies (Halcion, 10.6 percent; flurazepam, 4.1 percent; and placebo, 1.5 percent).

For any adverse events leading to dropping out of a study (Table 3-8), the rate for the placebo group was 6.9 percent, that for the Halcion group was 12.4 percent, and that for the flurazepam group was 9.6 percent. Note, for example, that the low-dose Halcion group has a rate of adverse events approximating that for the placebo group (7.0 and 6.9 percent, respectively), whereas the higher-dose Halcion group has a rate of adverse events of 14.1 percent. The rates for the low- and high-dose flurazepam groups were 4.2 and 10.3 percent, respectively. For short- and long-term durations of treatment with Halcion, the overall dropout rates were 7.6 and 20.6 percent, respectively, compared with rates of 7.0 and 6.6 percent, respectively, for the placebo group; the rates for the flurazepam groups were 6.6 and 12.7 percent, respectively. The committee notes, however, that these simple post-hoe marginal risk comparisons are somewhat confounded by the study designs that were selected for reanalysis. For example, the comparison of low-dose and high-dose studies is confounded by age, in that almost all of the low-dose studies were with geriatric populations. This does not bias the relative risk estimates between Halcion and flurazepam or placebo, but it does leave in question the source of the difference (i.e., one cannot attribute the difference in risk to dose or age, since the low dose was given almost exclusively to the geriatric subjects in these 25 studies).

Table 3-9 shows that for the 17 different adverse event groups, the rates for the placebo group range from 0.0 to 3.9 percent (with. miscellaneous reasons being the highest), the rates for the flurazepam group range from 0.0 to 7.6 percent (with sedation/hypnosis being the highest), and the rates for the Halcion group range from 0.0 to 7.5 percent (with sedation/hypnosis being the highest). Note that for 6 of the 17 categories of adverse events there was a sufficiently large frequency of events for which statistical significance could be assessed, and the increased rate for Halcion was high enough compared with that for placebo to judge the difference to be statistically: significant (denoted in the table). The categories were impaired coordination, light-headedness, dizziness, anxiety, memory impairment; and sedation/hypnotic. The rates for flurazepam also tended to be higher than those for placebo but lower than those for Halcion, with a few exceptions. No subjects receiving placebo or flurazepam reported memory impairment, but 8 of the 1,168 subjects assigned to the Halcion group reported memory impairment.

TABLE 3-7 FDA Analysis of Dropouts for "All Psychiatric" in the 25 Studies for 1992 Advisory Committee Meeting

	No. of Subjects with Adverse Event/Total No. of Subjects (%)			Risk Ratios for Dropouts	
Subject Group	Triazolam	Flurazepam	Placebo	Triazolam/ Flurazepam	Triazolam/ Placebo
All subjects	63/1,168 (5.4)	15/607 (2.5)	16/566 (2.8)	2.2[a]	1.9[a]
Sorted by age:[b]					
Geriatric	11/215 (5.1)	4/104 (3.8)	6/152 (3.9)	1.3	1.3
Non-geriatric	52/953 (5.5)	11/503 (2.2)	10/414 (2.4)	2.5[a]	2.3[a]
Sorted by dose:[c]					
Low	9/272 (3.3)	0/71 (0.0)	16/566 (2.8)	–[d]	1.2
High	54/896 (6.0)	15/536 (2.8)	16/566 (2.8)	2.1[a]	2.1[a]
Sorted by duration:[e]					
Short term	17/735 (2.3)	3/316 (0.9)	14/430 (3.3)	2.4	0.7
Long term	46/433 (10.6)	12/291 (4.1)	2/136 (1.5)	2.6[a]	7.2[a]

[a] $p < 0.05$, one-sided p value, Fisher's exact test.
[b] For sorted by age, the age groups are defined by nominal study designation, i.e., geriatric or non-geriatric, and not by actual age.
[c] For sorted by dose, the all patients placebo group is used for comparison. Dose groups are defined by assigned dose, as follows: for triazolam, low is 0.125, 0.125 to 0.25, and 0.25 mg and high is 0.25 to 0.5, 0.5, and 0.6 mg; for flurazepam, low is 15 mg and high is 15 to 30 and 30 mg.
[d] Risk ratio cannot be calculated because of zero denominator.
[e] For sorted by duration, groups are defined by assigned duration, as follows, Short term is ≤14 days and long term is ≥28 days.
SOURCE: Laughren and Lee (1992).

TABLE 3-8 FDA Analysis of Dropouts in the 25 Studies for 1992 Advisory Committee Meeting

	No. of Subjects with Adverse Event/Total No. of Subjects (%)			Risk Ratios for Dropouts	
Subject Group	Triazolam	Flurazepam	Placebo	Triazolam/ Flurazepam	Triazolam/ Placebo
All subjects	145/1,168 (12.4)	58/607 (9.6)	39/566 (6.9)	1.3[a]	1.8[a]
Sorted by age:[b]					
Geriatric	23/215 (10.7)	14/104 (13.5)	10/152 (6.6)	0.8	1.6
Non-geriatric	122/953 (12.8)	44/503 (8.7)	29/414 (7.0)	1.5[a]	1.8[a]
Sorted by dose:[c]					
Low	19/272 (7.0)	3/71 (4.2)	39/566 (6.9)	1.7	1.0
High	126/896 (14.1)	55/536 (10.3)	39/566 (6.9)	1.4[a]	2.0[a]
Sorted by duration:[d]					
Short term	56/735 (7.6)	21/316 (6.6)	30/430 (7.0)	1.2	1.1
Long term	89/433 (20.6)	37/291 (12.7)	9/136 (6.6)	1.6[a]	3.1[a]

[a] $p < 0.05$, one-sided p value, Fisher's exact test.
[b] For sorted by age, the age groups are defined by nominal study designation i.e., (geriatric or non-geriatric), and not by actual age.
[c] For sorted by dose, the all patients placebo group is used for comparison. Dose groups are defined by assigned dose, as follows: for triazolam, low is 0.125, 0.125 to 0.25, and 0.25 mg and high is 0.25 to 0.5, 0.5, and 0.6 mg; for flurazepam, low is 15 mg and high is 15 to 30 and 30 mg.
[d] For sorted by duration, groups are defined by assigned duration, as follows: Short term is ≤14 days and long term is ≥28 days.
SOURCE: Laughren and Lee (1992).

TABLE 3-9 IOM Summary of FDA Analysis of Dropout Rates by Category of Events

	Dropout Rates (%)		
Event Category	Halcion (n = 1,168)	Flurazepam (n = 607)	Placebo (n = 566)
All dropouts	12.4	9.6[a]	6.9[a]
Drowsiness	5.0	6.3	2.7[a]
Impaired coordination	2.7	2.0	0.4[a]
Light-headed	1.6	0.8	0.2[a]
Dizziness	2.7	1.3[a]	0.9[a]
Medical miscellaneous	5.8	4.0	3.9[a]
Anxiety	5.8	1.5[a]	2.1[a]
Memory impairment	0.7	0.0[a]	0.0[a]
Depression	0.8	0.5	0.4
Irritability	0.3	0.2	0.4
Confusion	0.5	0.0	0.2
Fatigue	1.3	0.8	0.5
Sedation/hypnotic	7.5	7.6	3.2[a]
Impaired concentration	0.0	0.2	0.0
Hallucination	0.2	0.0	0.0
Dreams	0.3	0.0	0.0
Mood change	0.2	0.0	0.0
Insomnia	0.1	0.0	0.2

[a] Statistically significant when compared to Halcion by chi-square analysis or the Fisher exact test, $p < 0.05$.
SOURCE: Laughren and Lee (1992) Tables 6.5 to 6.25.

For the other five categories of adverse events whose rates of occurrence were statistically significant, the rate for the Halcion group ranged from 2 to 8 times the rate for the placebo group, with the latter being the 1.6 percent versus 0.2 percent rates for light-headedness. The ratios for the 11 nonstatistically significant categories followed a similar pattern, with ratios (rate for the Halcion group to rate for the placebo group) being in the two-

to threefold range for categories in which the rates of adverse events were above 0.3 percent for those receiving placebo.

IOM Analysis

To shed further light on these issues and to provide a more rigorous review of the adverse events in general (i.e., not only those leading to dropping out of the study), the data from Tables A-1 through A-13 were used by the committee to reconstruct the actual adverse event frequencies and are reported in Tables 3-10 through 3-12 for Halcion, flurazepam, and placebo, respectively.[3] Tables 3-10 through 3-12 describe the research design (age, duration, dose) of each of the 25 studies, the sample size (number of subjects), and the frequency of the adverse events anxiety, depression, memory impairment, and the "all psychiatric" summary measure. A visual inspection of Tables 3-10 through 3-12 reveals that the primary adverse event reported was anxiety, and the inclusion of anxiety in the all psychiatric summary measure largely accounts for its high incidence. Note the low incidence of memory impairment under all conditions.

Statistical Analysis

To provide a further evaluation of these data that is sensitive to FDA's earlier concerns regarding their variability and different experimental designs, the committee analyzed the data in Tables 3-10 to 3-12 using a random-effect probit model (see Gibbons et al. [1994] for a similar example). Analyses were restricted to the all psychiatric summary category because it examines the possibility of a "Halcion syndrome" and because the frequency of adverse events for this measure was large enough for a meaningful analysis.

Using the data in Tables 3-10 to 3-12, the committee compared data for Halcion versus flurazepam and Halcion versus placebo separately from those studies in which they were both tested. Because the majority of studies with non-geriatric subjects were performed with doses of Halcion of 0.5 and 0.6 mg and doses of flurazepam of 30 mg, this comparison was restricted to these doses (lower-dose comparisons are presented elsewhere in this chapter). Similarly, because studies with geriatric and non-geriatric subjects were conducted with different doses, separate analyses were performed for geriatric and non-geriatric subjects. Use of the random-effect probit model allowed the committee to compare Halcion versus placebo and Halcion versus flurazepam adjusted for study duration and variability among studies (i.e., study is a random effect in the design, and standard errors and hypothesis tests of the main effects of duration and drug; and the duration-by-drug interaction are adjusted for the heterogeneity of those effects across the 25 studies).

[3] In a few instances, the reconstructed frequencies in Table 3-10 through 3-12 were fractional and were therefore rounded to an integer value. The fractional frequencies may be due to rounding errors made in the incidence rates in Tables A-1 through A-13 or small discrepancies in sample sizes given in Tables A-14 and A-15. These small differences should not change the results of the analyses in any substantial way.

TABLE 3-10 Adverse Event Frequencies for Halcion-Treated Groups in 25 Parallel-Group Studies

	Design				Frequency of Adverse Events			
Protocol	Geriatric Subjects	Weeks	Dose (mg)	Sample Size	Anxiety	Depression	Memory Impairment	All Psychiatric
6401	No	1	0.25	35	1	0	0	2
2401	No	1	0.375	66	3	0	0	4
6400	No	1	0.375	53	4	0	0	6
6041	No	1	0.5	70	3	I	0	4
6042	No	1	0.6	62	3	0	1	5
6004	No	1	0.5	16	1	0	1	4
6043	No	2	0.5	138	11	3	0	15
6016	No	2	0.5	14	I	0	0	1
6044	No	2	0.5	112	8	3	0	11
6042	No	4	0.25	54	11	2	0	14
6045	No	4	0.5	31	5	0	0	9
6046	No	4	0.5	55	6	I	0	7
6047	No	6	0.5	59	9	0	I	9
6048	No	6	0.5	72	3	3	1	7
6023B	No	12	0.5	9	1	0	1	1
6023	No	12	0.6	33	3	I	5	7
6049	No	13	0.5	74	10	5	5	17
6417	Yes	I	0.125	46	1	0	0	1
6417A	Yes	I	0.175	18	0	0	0	0
6061	Yes	1	0.025	31	0	0	0	0
6062	Yes	I	0.25	36	0	0	0	0
6063	Yes	2	0.25	18	1	I	0	2
6064	Yes	2	0.25	20	2	2	0	3
6065	Yes	4	0.25	14	2	0	0	2
2601	Yes	4	0.375	32	10	3	1	15

NOTE: FDA used these studies in an integrated evaluation of safety (Laughren and Lee, 1992). See Appendix A, Tables A-1 through A-13, for more specific information concerning dropout rates.
SOURCE: Laughren and Lee (1992).

TABLE 3-11 Adverse Event Frequencies for the Flurazepam-Treated Groups in the 15 of the 25 Parallel-Group Studies That Used Flurazepam as a Comparator Drug

	Design				Frequency of Adverse Events			
Protocol	Geriatric Subjects	Weeks	Dose (mg)	Sample Size	Anxiety	Depression	Memory Impairment	All Psychiatric
6400	No	1	22.5	52	2	0	0	2
6042	No	1	30	59	0	0	1	2
6004	No	1	30	21	5	0	0	9
6016	No	2	30	16	0	0	0	0
6044	No	2	30	110	6	4	0	11
6042	No	4	30	27	6	0	0	8
6046	No	4	30	50	1	0	0	0
6048	No	6	30	71	4	3	0	0
6023B	No	12	30	6	0	0	0	1
6023	No	12	30	18	0	0	0	4
6049	No	13	30	73	6	5	0	11
6062	Yes	I	15	35	0	0	0	0
6064	Yes	2	15	23	0	0	0	1
6065	Yes	4	15	13	0	0	0	0
2601	Yes	4	22.5	33	6	2	0	11

NOTE: FDA used these studies in an integrated evaluation of safety (Laughren and Lee, 1992). See Appendix A, Tables A-1 through A-13, for more specific information concerning dropout rates.
SOURCE: Laughren and Lee (1992).

TABLE 3-12 Adverse Event Frequencies for Placebo-Control Groups in the 12 of the 25 Parallel-Group Studies That Included a Placebo Control

	Design			Frequency of Adverse Events			
Protocol	Geriatric Subjects	Weeks	Sample Size	Anxiety	Depression	Memory Impairment	All Psychiatric
6401	No	1	35	1	0	0	1
2401	No	1	77	1	0	0	3
6041	No	1	72	2	2	0	4
6043	No	2	135	7	1	0	14
6045	No	4	31	4	0	0	4
6047	No	6	64	2	0	0	5
6417	Yes	1	44	4	0	0	6
417A	Yes	1	19	3	0	0	3
6061	Yes	1	28	0	0	0	0
6063	Yes	2	20	2	0	0	8
6065	Yes	4	14	0	0	0	0
2601	Yes	4	27	4	2	0	7

NOTE: FDA used these studies in an integrated evaluation of safety (Laughren and Lee, 1992). See Appendix A, Tables A-1 through A-13, for more specific information concerning dropout rates.
SOURCE: Laughren and Lee (1992).

Results of the analyses for all psychiatric adverse events revealed the following.

Halcion (0.5 mg) Versus Placebo in Non-geriatric Subjects

There were no statistically significant effects of duration or dose. The overall incidence of the event in those studies that tested both Halcion and placebo was 9 percent in the placebo group and 12 percent in the group treated with Halcion.

Halcion (0.5 mg) Versus Flurazepam (30 mg) in Non-geriatric Subjects

There were no statistically significant effects of duration or dose. The overall incidence of the event in those studies that tested both Halcion and flurazepam was 10 percent in the group receiving flurazepam and 15 percent in the group receiving Halcion. Note that the difference in the incidence for the Halcion group is due to the fact that different studies compared Halcion versus placebo and Halcion versus flurazepam. As such, the overall incidence of psychiatric events among those receiving Halcion will vary on the basis of the specific comparison. Within these two-group comparisons, however, variability between studies is directly

incorporated into the statistical comparisons.

Halcion (0.25 mg) Versus Placebo in Geriatric Subjects

There were no statistically significant effects of duration or dose. The overall incidence of the event in those studies that tested both Halcion and placebo was 12 percent in the placebo group and 13 percent in the group treated with Halcion.

Halcion (0.25 mg) Versus Flurazepam (15 mg) in Geriatric Subjects

There were no statistically significant effects of dose; however, a significant main effect of duration was noted (i.e., an increased study duration was associated with an increased frequency of psychiatric adverse events). The overall incidence of the event in those studies that tested both Halcion and flurazepam was 12 percent in the group treated with flurazepam and 20 percent in the group treated with Halcion. Note that the higher incidences for both Halcion and flurazepam are due to the smaller number of available studies (i.e., four studies in which both Halcion and flurazepam were tested in geriatric subjects) and the high incidence observed in Protocol 2601 (see Tables 3-10 and 3-11). The restriction of this effect to a single study increases the committee's uncertainty in the between-group comparison and yields nonsignificant statistical test results. It is important to note, however, that of all studies, Protocol 2601 had the longest duration and used the highest doses in geriatric subjects, and the results of the study might be confirmed if data from more studies of this length and with this dose were available. The question of whether such studies are relevant, given the package insert suggesting a dose of only 0.125 mg for elderly subjects for 7-10 nights, remains an open issue of concern since it is likely that many patients exceed the recommended dose and duration.

Summary

In summary, the committee's reanalysis of FDA's recompiled database for adverse psychiatric events reveals no significant difference in the incidence of adverse events between subjects receiving Halcion and placebo, or between subjects receiving Halcion and flurazepam, in protocols with geriatric and non-geriatric subjects when duration, dose, and interstudy variability are accounted for. Similarly, there was no evidence of a specific syndrome or clustering of psychiatric adverse events at the 0.25- or 0.125-rag doses. Although the rates of psychiatric adverse events in general are somewhat higher than the rates associated with study dropout, the relative risks remain statistically nonsignificant when heterogeneity between studies is incorporated. Although FDA found that significant adverse psychiatric events were associated with increased dropout rates by Halcion-treated subjects, the severity of these symptoms may have been greater in the Halcion-treated subjects, leading to somewhat increased rates of dropout due to adverse events. Inspection of the tabulated data suggests that differences may exist at doses in excess of 0.5 mg in non-geriatric subjects and at doses in excess of 0.25 mg in geriatric subjects; however, the data available in the recompiled database are too sparse for a meaningful analysis at these levels. Note that the studies evaluated by FDA were predominantly conducted with doses of 0.5 mg with non-geriatric subjects and 0.25 mg with geriatric subjects, when the currently recommended doses are 0.25 and 0.125 mg, respectively.

DATA SETS FOR POSTMARKETING STUDIES

Even though thousands of patients and study subjects may be exposed to a new molecular entity during the development of a product, given the difficulties of evaluating risks of low-frequency toxicities in randomized controlled studies done primarily for the assessment of efficacy, questions related to the toxicity of an entity can be resolved only with larger studies targeted to resolving such specific questions. The questions arising from the data summarized above have to do with the apparent increased risk of a number of toxicities that are associated with Halcion, especially for older subjects and at higher doses and for longer durations of use. It is important to note that this is true of most drugs, and in fact, among the 25 studies that FDA analyzed the percentage of geriatric subjects receiving Halcion who withdrew from the studies (10.7 percent) was lower than the percentage of geriatric subjects receiving flurazepam who withdrew (13.5 percent; see Table 3-8). For this drug, the use of higher doses and longer durations is likely.

The committee examined data from several postmarketing studies that investigated these safety issues. The following is a discussion of one large questionnaire study (Protocol M/2100/0235), 2 polysomnographic studies (Protocols M/2100/0366 and M/2100/0373) and a nonrandomized, controlled study (the Evaluation of Medications for Insomnia in Canada [EMIC]).

Randomized Study: Protocol M/2100/0235

One of the studies (Protocol M/2100/0235) recently completed under the sponsorship of Upjohn was a study of approximately 8,000 subjects randomly assigned to receive either Halcion (at a starting dose of 0.125 mg for older subjects and a starting dose of 0.125 or 0.25 mg for other subjects, with an option of increasing the dose as needed, with physician consultation) or temazepam (Restoril) (at a lower dose of 15 mg and a higher dose of 30 rag, with the instructions for dose escalation being the same as those for Halcion). The doses were chosen so that the two medications had equivalent efficacies estimated on the basis of prior information. The study was designed so that it was masked (i.e., blinded) with respect to study assignment for the subjects, the medical team, and the evaluators of efficacy and toxicity. There were 4,104 subjects in the Halcion group and 4,101 subjects in the temazepam group treated by a total of 946 investigators.

The IOM committee reviewed the protocol for the study, a detailed report of the methods, tables summarizing the data, the statistical analyses and results, and the conclusions drawn by Upjohn.

Subjects were admitted to the study by a physician. Medical information and informed consent were obtained, and the subject was then registered by telephone with a central contractor for the study. The center randomly assigned each subject a numbered bottle containing unidentified capsules. The center scheduled each subject for a telephone interview that was conducted within a day of entry into the study. The interview was carded out before the subject took the first capsule. Two more interviews were conducted, at 2 and at 4 weeks after entry into the study. The three telephone interviews were conducted by centrally located,

trained interviewers, under a contract to a private firm, who used set protocols for eliciting and recording the information. No visits to the physician were scheduled after the first visit, although contact by telephone or a visit could be initiated, and systematic capture and use of any resulting information was part of the protocol.

With regard to adverse events, this study provides valuable data on rates of toxicity categorized by type or category. However, the study was not placebo controlled, so there is no way of knowing the background, drag-flee rates of toxicity that would have been experienced. The rates of toxicity for the comparator drag, temazepam, at the doses studied do provide valuable information concerning the possible increases in the rates of toxicity that might characterize Halcion as a drug with peculiar toxicities or increased levels of toxicity relative to those for temazepam.

In examining the data, the committee saw no evidence of either special toxicities peculiar to Halcion compared with those for temazepam and no increases in the rates of putative CNS-related adverse events thought to be of possible concern. Some results of interest are as follows:

1. Overall dropout rates were essentially the same for subjects receiving the two drugs (16.2 percent for the Halcion group and 14.6 percent for the temazepam group), with the difference largely being due to the personal decision of the subjects among those receiving Halcion. The small difference was statistically significant because Of the large samples involved.
2. Examination of the Upjohn report on the study leads the IOM committee to confirm the conclusion of the FDA reviewer: "In summary, it appears that the effects of the two hypnotics are similar in terms of the kinds of medical events reported. There has been some concern about psychiatric events. There was no difference between triazolam (Halcion) and temazepam (Restoril) in the incidence of depression, anxiety, hostility, memory problems and nervousness. Among the reasons for dropout, there were 'possible' hallucinations, amnesia, unspecified dysphoria, CNS stimulation and suicide attempts. The incidence of these events was small and did not differ between treatments" (Lee, 1996, p. 17). Among the more than 4,000 patients in each of the groups, the latter events numbered 12 for the Halcion group and 11 for the temazepam group. The FDA reviewer concludes that "there was essentially no difference between the efficacy and safety for adults treated With insomnia" (Lee, 1996, p. 17).

Randomized Polysomnographic Studies

Protocol M/2100/0366 was a placebo-controlled, double-blind, five-site study with a single drug (Halcion) given as a single bedtime dose of 0.0625, 0.125, or 0.25 mg. A total of 240 participants were evaluated by inducing transient insomnia in a sleep-laboratory setting. Twelve medically related events, none serious, were reported; they included drowsiness, grogginess, heaviness, nausea, stomach cramps, headaches, restlessness, and sweating. This study showed a significant linear dose-response effect for polysomnographic sleep latency to stage 2 and total sleep time. Medical events possibly related to the study medication were infrequent, and none was serious.

Protocol M/2100/0373 was a placebo-controlled, double-blind, two-site study with a single drug (Halcion) administered at bedtime at a dose of 0.0625, 0.125, 0.25, or 0.5 mg in a sleep-laboratory setting for two nights. The 102 participants ranged in age from 21 to 54 years. Eleven medical events were reported. The events were categorized as mild, moderate, and severe, with no severe events being reported. The events reported were headaches, gastrointestinal symptoms, light-headedness, depression, lethargy, and irregular heartbeats. Sleep latency to stage 2 decreased, and total sleep time increased with increased doses. The medical events were infrequent, and none was serious.

In conclusion, both of the postmarketing sleep-laboratory studies (Protocols M/2100/0366 and M/2100/0373) showed minimal adverse events within 30 minutes to hours following the use of Halcion at the doses used in subjects who had not previously been exposed to Halcion or any other hypnotic agent within the previous 30 days.

A Nonrandomized Controlled Study: EMIC

Another earlier (mid-1980s) postmarketing study sponsored by Upjohn was the unpublished study entitled Evaluation of Medications for Insomnia in Canada, referred to as the EMIC study. The report on the EMIC study from Upjohn to FDA is dated December 2, 1988 (Mariano and Gardner, 1988). The IOM committee reviewed the protocol description, the final report, and summary tables. The committee believes that the method used and the data from this study provide useful information concerning the toxicity and use of Halcion.

The study serves to capture subjects in routine practice as they are prescribed one of three medications: Halcion, flurazepam, or oxazepam. The study follows the subjects from the time that they bring their prescription to a pharmacy and are enrolled in the study. Information was collected from these volunteers at the pharmacy and then from a 3-day diary that each subject filled out and mailed in and from a telephone call 2 weeks later. Over a period of 2.5 years, 7,554 subjects were recruited into the study by 264 cooperating pharmacies.

Because the labeling of Halcion recommends caution in the use of higher doses of the drug and for an extended duration, it is interesting that 64 percent of the subjects reported that they were continuing users, and most continued to use it during the period of study as needed, from the time of entry to the telephone interview at the end of their 2-week terminal-phase interview. Of the 488 subjects (6.5 percent) who did discontinue use of the drug during the study, the majority were first-time users. The most frequent reason given for discontinuation was that it was no longer needed. Among those continuing to use the drug, half reported using it at least once daily during this 2-week period.

This study, although not a randomized and blind experiment, provides a useful snapshot of a group large enough to provide statistically stable rates of toxicities for each of the drugs studied among groups of people prescribed specific doses. However, results depend on variations in prescription practices and the characteristics of patients who come for prescriptions, their continuation habits, and how they use the drugs that they are given. Nonetheless, the rates of adverse events after use of the three drugs at different doses complement those in the randomized studies described above. Table 3-13 presents some of the main results of the EMIC study. The toxicity profiles and the overall rates of toxicity are

strikingly similar for those receiving various doses of each drug and for the three drugs. The rate of toxicity for a small group of patients receiving the lowest dose of Halcion is a bit higher than those for the other groups, although the profile of toxicities is not remarkable. A noteworthy event is the rates of "memory problems," in which 0.4 and 1.1 percent of the subjects receiving Halcion at 0.25 and 0.50 mg, respectively, reported this adverse event, whereas 0.2 to 0.3 percent of the subjects receiving flurazepam and oxazepam, respectively, reported this adverse event.

VAMP: A COHORT STUDY

VAMP (Value Added Medicinal Products) Research Ltd. conducted but did not publish a study of Halcion and adverse events in the United Kingdom based on data from 2,000 general practices and an estimated 4 million patients. The computerized database for this study is part of a large system of linked databases in the British National Health Service that gathers information from practicing physicians.[4] The physicians enter their patients into a cohort and provide data for each patient at the time of entry along with the information accumulated for each patient during the course of his or her continuing care by the physician. The information includes diagnoses and medical interventions such as prescriptions, hospitalizations, and other outcomes.

The IOM committee reviewed copies of a past presentation to a professional meeting, but little more was available in the way of the protocol for the study, protocols or procedures for enlisting collaborating physicians, procedures for entering patient data into the database, the quality of the data in the database, or the quantitative information and statistical analysis used for the Halcion study presentation. Some general information on the database and how it operates is available in the paper by Mann et al. (1992a), but details on procedures and quality were not provided. One useful note in that paper was that protocols and analyses conducted with the data in the database are all reviewed by the United Kingdom Medical Advisory Board.

Despite difficulty in obtaining further information on the quality of the database and the VAMP Halcion study itself, the IOM committee believes that this approach to studies of adverse events can be a most useful strategy for detecting toxicities that are rare, unexpected, or due to off-label use and is especially valuable for testing hypotheses generated by spontaneous reports. Of course, there are barriers that preclude satisfactory study through the usual means of experimental evaluation and even the kinds of studies described in preceding sections. On the basis of the data provided and the information, albeit incomplete, on methods and quality, the committee believes that the VAMP study data provide a body of additional data that may be valid and informative.

[4] The database is now called the General Practice Research Database (GPRD).

TABLE 3-13 People Reporting Neurological, Medical, Psychological, and Emotional Medical Events in EMIC

	No. (%) of Subjects						
	Halcion			Flurazepam		Oxazepam	
Event Category and Adverse Event	0.125 mg (*n* = 92)	<0.25 mg (*n* = 2,265)	0.5 mg (*n* = 2,375)	15 mg (*n*= 416)	30 mg (*n* = 999)	≤15 mg (*n* = 462)	30 mg (*n* = 327)
Neurologic system							
Drowsiness or sleeping	4 (4.3)	99 (4.4)	94 (4.0)	21 (5.0)	46 (4.6)	19 (4.1)	21 (6.4)
Tired	11 (12.0)	228 (10.1)	227(9.6)	54 (13.0)	119 (11.9)	42 (9.1)	36 (11.0)
Dizziness	1 (1.1)	42 (1.9)	43 (1.8)	5 (1.2)	16 (1.6)	8 (1.7)	6 (1.8)
Balance disorders		11 (0.5)	3 (0.1)	1 (0.2)	5 (0.5)	1 (0.2)	3 (0.9)
Weakness	2 (2.2)	32 (1.4)	41 (1.7)	11 (2.6)	31 (3.1)	10 (2.2)	8 (2.4)
Hangover		7 (0.3)	16 (0.7)	2 (0.5)	4 (0.4)	2 (0.4)	
Medication too strong ·		1 (0.0)	2 (0.1)	1 (0.2)	1 (0.1)		1 (0.3)
Migraine		3 (0.1)	4 (0.2)		3 (0.3)	1 (0.2)	
Headache	4 (4.3)	74 (3.3)	77 (3.2)	10 (2.4)	21 (2.1)	11 (2.4)	6 (1.8)
CVA		1 (0.0)	1 (0.0)	1 (0.2)			1 (0.3)
Paresthesia		5 (0.2)	9 (0.4)		2 (0.2)	1 (0.2)	
Syncope	1 (1.1)	4 (0.2)	6 (0.3)		1 (0.1)		1 (0.3)
Seizure disorder		1 (0.0)	1 (0.0)				
Sleep difficulty and insomnia	2 (2.2)	24 (1.1)	24 (1.0)	3 (0.7)	12 (1.2)	8 (1.7)	2 (0.6)
Dream disorder/nightmare	2 (2.2)	13 (0.6)	7 (0.3)	2 (0.5)	12 (1.2)	5 (1.1)	2 (0.6)
Sleep walking		1 (0.0)	3 (0.1)				

	No. (%) of Subjects						
	Halcion			Flurazepam		Oxazepam	
Event Category and Adverse Event	0.125 mg (n = 92)	<0.25 mg (n = 2,265)	0.5 mg (n = 2,375)	15 mg (n= 416)	30 mg (n = 999)	≤15 mg (n = 462)	30 mg (n = 327)
Speech disorders		2 (0.1)				1 (0.2)	
Tinnitus		2 (0.1)	3 (0.1)	1 (0.2)			
Shaky or tremors		6 (0.3)	14 (0.6)	1 (0.2)	5 (0.5)		
Other		5 (0.2)	7 (0.3)	2 (0.5)	3 (0.3)	1 (0.2)	1 (0.3)
Total neurologic system	20 (21.7)	406 (17.9)	419 (17.6)	79 (19.0)	196 (19.6)	80 (17.3)	67 (18.4)
Mental, psychological, and emotional							
Addiction		8 (0.4)	5 (0.2)	1 (0.2)		1 (0.2)	
Alcohol abuse		1 (0.0)	2 (0. 1)				
Phobia				2 (0.5)	1 (0.1)		
Hallucinations			1 (0.0)				
Memory problems		9 (0.4)	25 (1.1)	1 (0.2)	2 (0.2)	1 (0.2)	1 (0.3)
Confusion		13 (0.6)	23 (1.0)	1 (0.5)	9 (0.9)	3 (0.6)	1 (0.3)
Nervous stomach		1 (0.0)	2 (0.1)				
Nervousness	6 (6.5)	65 (2.9)	82 (3.5)	10 (2.4)	20 (2.0)	12 (2.6)	12 (3.7)
Depression	3 (3.3)	52 (2.3)	66 (2.8)	7 (1.7)	23 (2.3)	10 (2.2)	9 (2.8)
Manic depression					2 (0.2)		
Emotional lability	1 (1.1)	27 (1.2)	35 (1.5)	2 (0.5)	14 (1.4)	5 (1.1)	4 (1.2)
Communication disorder		1 (0.0)	1 (0.0)				
Nervousness improved			3 (0.1)		2 (0.2)		1 (0.3)
Drag tolerance		3 (0.1)	1 (0.0)				
Paranoia			2 (0.1)				

	No. (%) of Subjects						
	Halcion			Flurazepam		Oxazepam	
Event Category and Adverse Event	0.125 mg (n = 92)	<0.25 mg (n = 2,265)	0.5 mg (n = 2,375)	15 mg (n= 416)	30 mg (n = 999)	≤15 mg (n = 462)	30 mg (n = 327)
Could not concentrate		2 (0.1)	2 (0.1)	2 (0.5)	2 (0.2)	4 (0.9)	2 (0.6)
Other		1 (0.0)	2 (0.1)				
Total mental, psychological, and emotional	9 (9.8)	156 (6.9)	203 (8.5)	22 (5.3)	62 (6.2)	34 (7.4)	25 (7.6)
Total combined	24 (26.1)	478 (2.1)	522 (22.0)	88 (21.2)	221 (22.1)	96 (20.8)	78 (23.9)

NOTE: The table includes data for participants for whom the dosage of the study medication was available. The numbers and percents do not sum because respondents may report in more than one category.
SOURCE: Mariano and Gardner (1988).

The VAMP study of Halcion was done over a 2-year period ending on October 2, 1991. The data are based on patients who were prescribed Halcion (n = 3,727), temazepam (n = 26,714), nitrazepam (n = 4,532), or a combination of more than one benzodiazepine, plus a control group of 41,127 subjects. The control subjects were chosen to match the subjects receiving a study drug by age at the time of the index prescriptions, gender, medical practice, period of follow-up for the study subject, and consultation date within half a year of the index prescription for the matching study patient.

The VAMP study investigators searched the database for the following adverse events of a drug in the treatment groups and over comparable times in matching control subjects: suicide and attempted suicide, amnesia, depression, psychosis, aggression, bizarre behavior, and anxiety. The percentage of patients with any target event for each of the treatments groups were as follows: Halcion group, 16.3 percent; temazepam group, 18.8 percent; nitrazepam group, 13.1 percent; and control group, 3.5 percent (Mann et al., 1992b). The times of follow-up and the rates of adverse events for subgroups by dose, age, and duration of use before and after taking the index prescription were not given. Although rates were not given by subgroups according to these variables, the percentages of adverse events for the seven subcategories of targeted adverse events had the following breakdown for the overall rate of 16.3 percent for patients receiving Halcion: depression, 49.3 percent; anxiety, 27.4 percent; psychosis, 19.0 percent; suicide and attempted suicide, 3.1 percent; amnesia, 0.5 percent; aggression, 0.4 percent; and bizarre behavior, 0.3 percent. The profiles for the other two drugs were similar.

SPONTANEOUS REPORTING OF ADVERSE EVENTS: THE FDA SYSTEM

The socialized medicine system in the United Kingdom allows for the ongoing surveillance of the population of patients under care, their experiences with health interventions for prevention and treatment, and the outcomes associated with those interventions. Few health care delivery systems in the United States have computerized patient records linked to prescription drag use, and the systems in general do not afford similar opportunities for uniform data collection on a defined-cohort basis. However, FDA requires the manufacturer to report all adverse events possibly associated with a drug product. In addition, FDA receives reports directly from health care providers and patients. FDA enters these events into a database, reports regularly on the data assembled, and interprets these data with a view to estimating rates and relationships that might signal toxicity problems with marketed drugs. This system is called the Spontaneous Reporting System (SRS).[5] In interpreting the numbers of reported adverse events and trends and in comparing a drug with other, similar drugs used for similar indications, it is necessary to take into account the relative rates of use of the drugs, the sizes of the populations taking the drugs, and the occurrences of other factors that might be changing or differentially affecting the rates of adverse events reported over time. To this end, for example, FDA uses other databases in conjunction with the data collected in SRS.

Two of these are the commercial National Prescription. Audit and the commercial National Disease and Therapeutic Index. The first provides national estimates of prescription drug use based on information from pharmacies; the second estimates drug use on the basis of prescription information obtained from physicians in various types of practice and from various geographic areas. Either of these databases can be used to estimate proportions of patients exposed to drugs with similar prescription patterns and indications for use.

Statistical Evaluation of the SRS Data

In contrast to the controlled clinical trials, from which little evidence of an increased incidence of adverse events associated with Halcion use was noted, the frequency of adverse events recorded for Halcion in SRS was reported by Wysowski and Barash (1991) to be high relative to the frequency recorded for temazepam. They noted risk ratios as high as 56 to 1 for amnesia (see Table 3-14). The results of these analyses led to considerable debate and criticism within FDA. As a result, these data were reanalyzed by Yi Tsong of the Division of Biometrics at FDA. Tsong's analysis is the most statistically rigorous analysis of these data to date. Tsong made attempts to adjust statistically for (1) time of entry into the market, (2) secular trends in overall reporting rates, (3) publicity through the popular literature and media, (4) variability in rate ratios, and (5) differences in manufacturer reporting patterns. Despite these statistical adjustments the rate ratio for amnesia was 28 to 1 for the period from 1983 to 1991 and 23 to 1 for the period before 1988 (i.e., when major media coverage began). For example, before 1988, there were 174 spontaneous reports of amnesia by people taking Halcion (155 of these were reported by the manufacturer), whereas there were only 3 reports for temazepam (all were reported by the manufacturer). During this period, however, there were 32,933,000 prescriptions for Halcion and 19,122,000 for temazepam. Over the entire 9-year period that Halcion was marketed (i.e., before 1992), there were 356 spontaneous reports of amnesia by people taking Halcion (324 were reported by the manufacturer),. whereas there were only 6 reports for temazepam (all were reported by the manufacturer). These signal an increase in the numbers of adverse events that cannot be accounted for by any of the previously mentioned methodological caveats. Note, however, that during the same periods (i.e., before 1988 and before 1992) the adjusted rate ratios for seizures were 17 to 1 and 26 to l, respectively. It would seem unlikely that Halcion would be responsible for this type of adverse event at relative rates that parallel those for amnesia. Even spontaneous reports of mortality exhibited rate ratios of 3 to 1 in both time periods.

In summary, careful statistical analysis of the SRS data did not eliminate the high relative rate of adverse events for Halcion. Note, however, that the rate ratios were comparable for amnesia and seizures, which seems inconsistent with the pharmacology of Halcion. The memory impairment effects of Halcion were not observed in the randomized controlled clinical trial data compiled by either Upjohn or FDA. This may be due to (1) remaining artifacts in the SRS, (2) the difference between controlled studies in which dose and duration are monitored and the natural environment, in which much higher doses at much longer durations may be used, or (3) the huge difference in the number of at-risk individuals whose data are included in the SRS database relative to the much smaller number of at-risk individuals whose

[5] The current system for monitoring and reporting adverse events is called Med Watch, the FDA Medical Products Reporting Program.

data are available in the clinical research database. On the basis of the available data there is no clear answer to this question.

The adjusted ratios of adverse events reported in SRS are based on very low numbers of reported events and very large numbers of prescriptions. For example, about 40 adverse events per 30 million prescriptions were reported for temazepam and about 1,000 adverse events per 50 million prescriptions were reported for Halcion, resulting in adverse event rates of roughly 10 per 1 million prescriptions for temazepam and 200 per 1 million prescriptions for Halcion (see Table 3-14). Converting numbers of prescriptions to approximate numbers of patients is difficult. Estimating the probability that an actual adverse event will be reported to FDA is much more difficult, even if one considers only the most serious and disturbing events. These speculations lead to the very considerations that FDA tries to deal with in assessing the signal that an SRS analysis might be imparting.

TABLE 3-14 Aggregate Number of Domestic Spontaneous Reports, Reporting Rates, and Reporting Rate Ratios for Certain Adverse Behavioral Reactions to Halcion and Temazepam for First 7 Years of Marketing of Each Drug, as Reported in SRS

	Halcion		Temazepam		Reporting Rate Ratios	
Adverse Event	No. (%)	Reporting Rate	No. (%)	Reporting Rate	A	B
Confusion	322 (17.0)	6.1	16 (6.9)	0.5	12.2	5.7
Amnesia	293 (15.5)	5.6	3 (1.3)	0.1	56	27.8
Bizarre behavior	109 (5.8)	2.1	2 (0.9)	0.1	21	15.5
Agitation	113 (6.0)	2.1	10 (4.3)	0.3	7	3.2
Hallucinations	138 (7.3)	2.6	10 (4.3)	0.3	8.7	3.9

NOTE: Data are for 1981 through 1987 for temazepam and 1983 through 1989 for Halcion and are based on 1,895 total domestic spontaneous reports for Halcion and 231 for temazepam. Reporting rates are based on 52,695,000 prescriptions for Halcion and 30,047,000 prescriptions for temazepam. Rates are per million prescriptions. Ratios are reporting rate for Halcion divided by reporting rate for temazepam (A) and ratio calculated with a doubling of reports for temazepam (B).
SOURCE: Wysowski and Barash (1991).

The IOM committee is left with what seems to be strongly suggestive evidence from SRS data that, among users of Halcion, there is some group of patients who, by personal characteristics, prescriptive pattern, or medication use, do experience CNS-related adverse events not seen at the same rates as those seen in patients taking comparator drugs. The rates of these adverse events in the Halcion group or among the various groups taking other drugs must be so small as to escape detection statistically in any of the variety of controlled studies

mounted so far. The alternative to this explanation is that the ratios of adverse events from SRS data are subject to biases that have at this point escaped close analysis or eluded the key to an alternative explanation. It is also possible that the use of concomitant medications could be involved in causing or otherwise confounding the expression of adverse events.

LITERATURE REVIEW

The IOM committee reviewed published literature pertinent to the safety of Halcion and constructed tables that are intended to provide relevant information from each paper. The review is based on publications that were referred to in the FDA task force report (U.S. Food and Drug Administration, 1996) and the Public Citizen petition (1992). These papers have been supplemented with additional papers, citations for which are provided at the bottom of the relevant tables (see Appendix B, Tables B-1 through B-10). The tables and the following discussion are organized to address the following areas of interest: pharmacokinetic and pharmacodynamic issues regarding the comparability of triazolam to other benzodiazepines; amnestic effects of Halcion; possible anxiogenic or insomniac effects associated with Halcion administration or withdrawal; ataxic, disinhibition, and psychotogenic, confusion, or dissociative effects; and other potential adverse events. The committee does not include the Wysowski and Barash paper (1991) in this review because that analysis is discussed in the preceding section.

Pharmacokinetic and Pharmacodynamic Issues Regarding the Comparability of Triazolam to Other Benzodiazepines

The information considered in this section is summarized in Table B-1. The topics covered in this section are important for the consideration of whether Halcion is a compound that could be expected to have a uniquely risky pharmacodynamic profile. They are also important for future considerations of the question of whether adequate comparisons of triazolam to other benzodiazepines have been conducted.

Pharmacokinetic Issues

Four factors that substantially contribute to the behavioral effects of benzodiazepines are (1) their affinity for benzodiazepine receptors, (2) their lipophilicity, (3) their status as agonists or antagonists, and (4) their levels in plasma and the brain.

Affinity for Benzodiazepine Receptors

Triazolam has a high affinity for benzodiazepine receptors relative to the other benzodiazepines currently used clinically in the United States. In a binding study (Richelson et al., 1991) conducted with human cortical tissue, it has greater affinity than clonazepam (4 times), lorazepam (8 times), desalkylflurazepam (the active metabolite of flurazepam and quazepam; 16 times), diazepam

and alprazolam (`20 times), oxazepam (`70 times), and flurazepam and temazepam (>100 times) (see Table B-2). Generally, the affinity ratios fit the relative amounts administered clinically, although the dose of triazolam used in comparison studies is generally relatively greater than that suggested by the affinity ratios based on binding to cortical tissue. For example, consistent with the binding data, 0.5 mg of triazolam appears to be similar to 60 mg of temazepam in terms of sedation (Rush et al., 1993). At these doses, triazolam produces relatively less cognitive impairment than temazepam. However, this pattern is not always found when the ratio of the triazolam dose/temazepam dose is less favorable for triazolam.

One complicating factor is that there are several benzodiazepine receptor subtypes with different receptor affinities and affinities for different anatomical locations. The importance of this effect Was illustrated in a study by Sanger and Benavides (1993) (see Table B-3). Although the order of affinity of benzodiazepines in the rat cortex and cerebellum is relatively consistent, most benzodiazepines have markedly less affinity for spinal cord benzodiazepine receptors because a different subgroup of receptors is expressed there. In particular, triazolam appears to bind to benzodiazepine receptor subtypes with relatively equal potency. However, zolpidem shows greater potency for subtypes bearing the alpha-1 and gamma-2 receptor subunits (Faure-Halley et al., 1993; Graham et al., 1996; Ramsey-Williams and Carter, 1996). Because triazolam has binding affinity in the brain and spinal cord comparable to those of most benzodiazepines, it is relatively more potent in the spinal cord than most benzodiazepines. The significance of spinal cord benzodiazepine receptors relative to that of brain benzodiazepine receptors is not known.

Another important issue in considering the affinity of a drug for its receptors is the issue of active metabolites. Triazolam has two active metabolites, alpha-hydroxy-triazolam and 4-hydroxy-triazolam, both of which have significant affinities for benzodiazepine receptors (Sethy and Harris, 1982; Richelson et al., 1991). Both metabolites are extensively converted to the glucuronide in plasma and are present as the unbound form (the form that can enter the brain) in negligible amounts in plasma (Eberts et al., 1981; Mauri et al., 1993). Although there is no evidence that these metabolites contribute to the acute behavioral effects of triazolam, studies have not ruled out the accumulation of metabolites with long-term administration.

In vivo binding data for humans obtained from position emission spectroscopy or single photon emission computerized tomography (SPECT) studies would be helpful for advancing the discussion of differences in drug affinity between triazolam and other drugs in different regions of the brain. However, these studies have not yet been conducted.

Lipophilicity

The time course of the availability of benzodiazepines to brain benzodiazepine receptors is highly dependent on their lipophilicity, which allows them to cross the blood-brain barrier (Arendt et al., 1987; Miller et al., 1988) (see Table B-4). In this regard, triazolam is moderately liphophilic relative to other benzodiazepines. Midazolam and diazepam appear to be more lipophilic. The lipophilicity of triazolam is comparable to that of lorazepam and alprazolam.

Agonist Status

Triazolam is a full agonist of benzodiazepine receptors, as are most of the other benzodiazepines studied.

Levels in Plasma

Two issues are of particular importance with regard to the levels of benzodiazepines in plasma: time to peak concentration and plasma clearance.

Peak plasma triazolam levels are reached quite rapidly, but not distinctively so among benzodiazepines. Zolpidem may reach peak levels the quickest, with some studies suggesting that peak levels are reached in. approximately 0.5 hour (Monti et al., 1994). Peak plasma triazolam and flurazepam levels are reached in approximately 1.0 hour (Greenblatt et al., 1989). However, flurazepam is much less potent than its metabolite desalkylflurazepam, which achieves peak levels later. Plasma temazepam levels peak in 1.5 hours, achieving peak levels more slowly than the other drugs mentioned. The rapidity with which peak levels are achieved in plasma is important for the behavioral effects of a drug. It is well known, for example, that more rapid onset is associated with the increased euphoric effects of drugs of abuse, as exemplified by the reduced abuse potential of methadone compared with that of heroin, Similarly, the more rapidly that peak levels are achieved in blood, the more 'rapidly sleep may be induced.

Triazolam has a plasma half-life of 2 to 3 hours. This is comparable to that of zolpidem (Greenblatt et al., 1989; Monti et al., 1994). Together, they have the shortest half-lives of the routinely administered hypnotic agents. A short half-life reduces the risk of carryover sedation and cognitive impairment, whereas it increases the risk of adverse events due to withdrawal. It should be noted that the short plasma half-life of triazolam might allow for more time without significant receptor occupancy between doses. Although this has yet to be demonstrated by in vivo receptor methods, if true this quality might be associated with reduced physical dependence with long-term drug administration.

Several factors alter the plasma half-life of triazolam. Pharmacokinetic interactions with other medications is a major issue for many medications. Triazolam is metabolized by P-450 CYP 3A4, an hepatic enzyme. Several drugs and foods, including ketoconazole, diltiazem, serotoninergic antidepressants, and grapefruit juice, inhibit this enzyme and produce dose-related increases in the plasma half-life of triazolam (Hukkinen et al., 1995; yon Moltke et al., 1996; Kosuge et al., 1997). One study failed to show the interaction with fluoxetine (Wright et al., 1992). Other drugs, such as rifampin, induce P-450 CYP 3A4 and substantially reduce blood triazolam levels (Villikka et al., 1997). Drug interactions are of significant clinical importance for triazolam, and doses should be adjusted accordingly. Among FDA-approved medications, however, this issue is not unique to Halcion.

Other issues influence Plasma clearance. Plasma triazolam levels are doubled in elderly individuals, and therefore recommended doses are reduced for this group (Greenblatt et al., 1991). Cirrhosis does not appear to influence triazolam levels in blood (Robin et al., 1993).

Pharmacodynamic Interactions

Pharmacodynamic interactions are also important for benzodiazepines and have been shown to affect the response to triazolam as well. Metabolites of progesterone stimulate brain gamma-aminobutyric acid type A receptors. Consistent with this finding, progesterone appears to potentiate the effects of triazolam in postmenopausal women (McAuley et al., 1995). However, it is not yet clear that variability in progesterone and neurosteroid levels during the

menstrual cycle are associated with altered sensitivity to triazolam (Rukstalis and de Wit, 1995). Similarly, ethanol comparably potentiates the behavioral effects of both triazolam and zopiclone in humans (Kuitunen, 1994). Caffeine reduces many of the cognition-impairing effects of triazolam in a dose-dependent manner (Rush et al., 1994).

Unique Effects of Triazolobenzodiazepines on Locus Coeruleus Neurons

The Public Citizen petition highlights potential unique effects of triazolobenzodiazepines upon locus coeruleus activity. The suggestion arises from three principal sources: (1) the initial impression that alprazolam had unique efficacy against panic disorder; (2) data indicating that benzodiazepines inhibited locus coeruleus neuron firing; and (3) clinical data suggesting that benzodiazepines, particularly alprazolam, reduced yohimbine-induced panic in subjects with panic disorder.

Given recent findings, these arguments are not as compelling as they may have been in 1992. First, all benzodiazepine anxiolytic compounds (diazepam, lorazepam, clonazepam, and alprazolam) have been shown to be effective in the treatment of panic disorder when adjusting for differences in the potency of each compound. Thus, alprazolam is not unique in this regard (Krystal et al., 1996).

Second, the initial reports of benzodiazepine inhibition of locus coeruleus neuron activation indicated rather modest effects that emerged at rather high benzodiazepine doses (Grant et al., 1980; Beck and Fibiger, 1995). It is not clear that triazolobenzodiazepines are uniquely potent in this regard (Laurent et al., 1983; Nakane et al., 1994). In addition, there are questions about whether the effects of benzodiazepines on noradrenergie neuron activity are direct or indirect (Simson and Weiss, 1989).

Third, studies by Krystal and colleagues (1996) suggest that triazolobenzodiazepines do not potently block the methoxyhydroxyphenylglycol (MHPG) increases produced by yohimbine. This finding suggests that the benzodiazepine effect is upstream from the locus coeruleus and that the primary effects of benzodiazepine withdrawal would not be via locus coeruleus activation.

Summary

Triazolam is a potent, broad-spectrum benzodiazepine agonist with a relatively short plasma half-life. Basic animal and clinical studies do not suggest a profile for this medication that is inconsistent with the information presented to FDA at the time of the FDA review in 1992. Its pharmacokinetic and pharmacodynamic profiles are associated with benefits and risks that are particular to the intended use of this medication. The studies reviewed here, however, suggest that most differences between triazolam (Halcion) and other benzodiazepines can be eliminated by manipulating the parameters of drug administration. In humans, when this type of parity is achieved, the effects of triazolam may be indistinguishable from those of other benzodiazepines (Oliveto et al., 1994).

Consideration of Amnestic Effects of Halcion

The information discussed in this section is summarized in Table B-5. Several levels are considered: expected dose-related anterograde memory impairment, and unexpected amnestic events evident only in subjective reports. Concern that Halcion might uniquely produce the latter type of amnesia was raised (Krystal et al., 1995).

Performance of Memory Tasks After Single and Multiple Doses

All benzodiazepines have dose-related amnestic effects. These have been demonstrated by impairment in performance of a variety of the memory tasks listed in Table B-5. Several studies indicated that information that could not be recalled after a delay could not be recalled at testing 24 hours later (Greenblatt et al., 1989; Milgrom et al., 1994). Similarly, a nighttime dose of 0.5 mg of Halcion, but not 30 mg of temazepam, had residual amnestic effects in the morning (Bixler et al., 1991). Interpretation of the comparisons of amnestic effects across drugs is difficult because of differences between routinely used doses and doses that actually produce comparable sedative or amnestic effects. This was illustrated by Rush et al. (1993), who suggested that the sedative effects of 0.5 mg of Halcion per 70-kg person are equivalent to those of 60 mg of temazepam per 70-kg person, but that the amnestic effects of Halcion are less than those of temazepam at these doses. However, the sedative and amnestic effects of 0.5 mg of Halcion per 70-kg person are greater than those of 30 mg of temazepam per 70-kg person. The bottom line of these studies appears to be that Halcion produces dose-related impairment in performance of memory tasks. This impairment appears to be roughly comparable to that found after the administration of other benzodiazepines, when adjusting for their relative receptor affinities. When comparing benzodiazepines on the basis of typically prescribed doses, Halcion appears to have greater amnestic effects. This is presumably because typically prescribed doses overestimate the dose of Halcion for comparison purposes.

Repeated dosing may differentially affect the amnestic properties of short- and long-acting benzodiazepines. Roehrs et al. (1983) found that single doses of Halcion at 0.5 mg had greater anterograde amnestic effects than flurazepam at 30 mg. However, after 6 days of dosing, the memory impairments associated with flurazepam became progressively worse and equivalent to those of Halcion. The increasing amnestic effects of flurazepam may have been consistent with the accumulation of this drug in the blood with chronic administration. This change did not occur with Halcion, consistent with the absence of drag accumulation with chronic administration. As a result, the report of Roehrs et al. (1983) raises the possibility that long-term treatment with Halcion or other short-acting benzodiazepines might spare subjects the progressive memory impairment that might be associated with long-term treatment with a long-acting medication. Among the publications reviewed, that of Roehrs et al. (1983) was the. only study that directly compared the time course of amnestic effects from short- and long-acting benzodiazepines. This finding awaits replication.

Spontaneous Reports of Memory Impairment

Of the studies that directly evaluated subjective reports of memory disturbances, the report by Bixler et al. (1991) stands out for consideration. In that study, subjects received 0.5 mg of Halcion, 30 mg of temazepam, or placebo for a total of 5 nights. It is important to note that this 30-mg dose of temazepam is approximately half of the equivalent of the 0.5-mg dose for Halcion. Drug administration was divided into two sessions (initially, either 3 or 4 days of drug treatment, then 2 days of placebo, and then 1 to 2 days of active drug). Five of six subjects receiving Halcion reported daytime episodes of amnesia or subjective memory impairment, no subjects receiving temazepam reported any events, and one subject receiving placebo reported an amnestic event.

One other study documented spontaneous reports of memory impairment during chronic treatment with Halcion (Fleming et al., 1990). In that study, 4 of 24 of subjects treated with 7.5 mg of zopiclone and 3 of 24 patients treated with 0.25 mg of Halcion reported memory impairment. These reports are the basis of the concern raised by these investigators in their petition to FDA. The magnitude and frequency of amnestic effects in the study of Bixler et al. (1991) are of concern. However, the high frequency of these severe effects is not evident in the other studies reviewed. Furthermore, the comparison of the low, nontherapeutically equivalent dose of 30 mg of temazepam with 0.5 mg of Halcion may have biased the study of Bixler et al. (1991) against Halcion.

Halcion and State-Dependent Learning

One report suggests that Halcion facilitates the recall of dissociative experiences in a state-dependent learning model (Weingartner et al., 1995a). State-dependent learning is a term applied to the tendency for the retrieval of learned information to be impaired when the behavioral state while learning (e.g., while on a benzodiazepine) is different from the behavioral state when retrieval occurs (e.g., while off of a benzodiazepine). State-dependent learning effects are generally small. However, they may contribute to the apparent anterograde memory impairment. For example, information learned while traveling after ingesting Halcion might be more difficult to recall when one has not taken Halcion. This hypothesis has yet to be tested.

Summary

Halcion produces dose-related amnestic effects. Particularly when higher doses are taken at night, these effects may persist into the morning. Depending on one's selection of comparator doses of other drugs, Halcion is either more amnestic than, or as amnestic as other benzodiazepines with comparable levels of benzodiazepine receptor occupancy. The controlled clinical trials do not resolve the frequency of clinically significant amnestic episodes among patients treated with Halcion, particularly at 0.5-mg dose or higher.

Review of Data Regarding Possible Anxiogenic or Insomniac Effects Associated with Halcion Administration or Withdrawal

The information discussed in this section is summarized in Table B-6. This section reviews reports that suggest that the use of Halcion as a hypnotic agent is associated with (1) an increase in daytime anxiety or (2) withdrawal-related anxiety or sleep disturbance.

Halcion Effects on Daytime Anxiety

Studies provide conflicting data regarding the possibility that Halcion is acutely anxiolytic (Pinnock et al., 1985; Stopperich et al., 1993). Studies also provide conflicting data on the effects of repeated administration. Some studies suggest that Halcion use as a hypnotic agent reduces daytime anxiety (Mauri et al., 1993; Saletu et al., 1994). Others (Bliwise et al., 1988; Scharf, 1993; Monti et al., 1994) suggest that use of other benzodiazepines or related agents, but not Halcion, as hypnotic agents reduces daytime anxiety.

Of most concern are studies that report increased daytime anxiety. Kales et al. (1986) noted a significantly higher rate of "excitatory events" including nervousness, anxiety, and hyperarousal among six subjects administered 0.5 mg of Halcion compared with the rate of such events among subjects given 15 mg of quazepam (both drugs were given on a short-term basis). Adam and Oswald (1988) reported a 52 percent increase in daytime anxiety on a visual analog scale for subjects treated with 0.5 mg of Halcion but not for those treated with placebo or lormetazepam. These anxiogenic effects are difficult to interpret because the effects of treatment, but not the treatment-time interaction, are significant. The authors do not present the raw data, compare baseline anxiety values between their groups, or use baseline anxiety values as a covariate. As a result, it is possible that their finding reflects a baseline difference between groups. Limited information about baseline differences between their groups also makes it difficult to evaluate the finding that 7 of 40 subjects receiving Halcion, but not those receiving placebo or lormetazepam, had panic attacks during the study. Two other studies reported infrequent anxiety-related adverse events among subjects receiving Halcion, but there is no indication of a greater frequency of adverse events for Halcion than for comparator benzodiazepines (Roger et al., 1993; Monti et al., 1994).

Withdrawal-Related Anxiety or Insomnia Following Short- and Long-Term Halcion Use

Rebound Anxiety

Pinnock et al. (1985) did not find evidence of increased anxiety 6 hours postoperatively in subjects treated with Halcion preoperatively. However, several studies report increases in anxiety following the termination of Halcion administration with short- and long-term treatments (Lee and Lader, 1988). Some studies suggest that withdrawal-related anxiety is not greater for Halcion than for zopiclone (Fleming et al., 1990).

Rebound Insomnia

Several studies describe increased rates of insomnia following discontinuation of Halcion treatment, even after only a few nights of treatment (Kales et al., 1986; Mamelak et al., 1990; Mauri et al., 1993). In general, the duration of rebound insomnia is limited to the first three nights of discontinuation (Adam and Oswald, 1988; Mouret et al., 1990; Elie et al., 1990; Monti et al., 1994). Several of these studies suggest that the magnitude of impairment with Halcion is greater than that with comparator benzodiazepines (Monti et al., 1994). The level of sleep impairment following termination of Halcion treatment in insomniac subjects does not generally exceed the initial level of sleep impairment (McCluskey et al., 1991). Furthermore, the degree of rebound insomnia following the discontinuation of Halcion treatment. appears to be more closely associated with the magnitude of clinical benefit than the duration of drug exposure in insomniac subjects (Merlotti et al., 1991). These data suggest that a component of the rebound insomnia is a return to the pretreatment level of insomnia. However, other data support the rebound insomnia model. For example, tapering the cessation of Halcion treatment reduces the cessation-related decline in sleep quality (Roehrs et al., 1992).

An issue facing the comparison of short- and long-half-life benzodiazepines is the possibility that long-acting benzodiazepines may not produce comparable levels of acute rebound anxiety. The short-half-life agents produce a relatively short period of sleep disruption. In contrast, there may be a less severe, but more protracted, disruption of sleep associated with withdrawal from long-acting benzodiazepines (Kales et al, 1982; Gillin et al., 1989; Mitler et al., 1984).

Summary

The published literature has documented both anxiolytic and anxiogenic effects in relatively small populations of individuals administered Halcion, Halcion does not appear to be as effective as longer-acting benzodiazepines for reducing daytime anxiety, and it may be associated with substantial increases in anxiety. Clinically significant anxiety increases appear to be relatively infrequent. However, the frequency of these reactions cannot be adequately assessed from the data published in the literature. Similarly, there appears to be increased risk of sleep impairment after the discontinuation of Halcion administration. The frequency of severe or protracted impairment is rare, but it is also impossible to determine this frequency from the data available in the literature. Overall, the data published in the literature do not contradict FDA or IOM analyses discussed elsewere in this report.

Ataxia, Disinhibition, and Psychotogenic, Confusional, or Dissociative Effects of Halcion

On the basis of data published in the literature, there do not appear to be compelling data singling out Halcion use as a risk factor for falls (see Table B-7). There are insufficient data to base a reconsideration of FDA approval of Halcion on the basis of published data on behavioral dyscontrol following Halcion administration (see Table B-8). The data from published studies consisting of case reports of the emergence of paranoia, hallucinations, or

confusion indicate that these conditions are infrequent consequences of Halcion administration (Wehli et al., 1985; Kales et al., 1986; Adam and Oswald, 1988) (see Tables B-9 and B-10).

Consideration of Other Potential Adverse Effects

The information discussed in this section is summarized in Table B-10. This section reviews several issues. raised in the published literature.

Early Termination of Use

Two reports indicate higher rates of early terminations of use after Halcion use than after use of comparator drugs (Fleming et al., 1990; Roger et al., 1993). Another report failed to find evidence of excessive terminations after Halcion use relative to that after zolpidem use (Hajak et al., 1994). These data do not permit the development of conclusions regarding an increased incidence of termination of use associated with Halcion use compared with that of other benzodiazepines.

Adverse Effects Defined Generally

Two studies (Wehli et al., 1985; Fleming et al., 1990) reported increased rates of adverse events in general associated with Halcion use relative to the rates associated with the use of comparator drugs. However, the difference between Halcion and the comparator drugs in the study of Wehli et al. (1985) was limited to mild side effects. Other studies failed to find differences between Halcion and comparator drugs (Roger et al., 1993; Hajak et al., 1994; Jacobsen et al., 1994) or did not note any significant or unexpected adverse effects (Thorpy et al., 1992; Mauri et al., 1993).

Other Adverse Effects

A recent report suggests an advantage of short- versus long-half-life benzodiazepines regarding driving safety among elderly subjects (Hemmelgarn et al., 1997). That study reported a 50 percent increase in the number of injurious motor vehicle crashes among elderly drivers during the first 7 days of use of long-half-life benzodiazepines compared with the numbers among elderly drivers Using short-half-Fife benzodiazepines or a placebo. The risk remained increased after continuous long-half-life benzodiazepine use for up to 1 year.

Summaries and Meta-Analyses

In the time since the introduction of Halcion, a growing number of studies have reviewed the safety and efficacy of Halcion. These reviews have supported both its relative safety and efficacy (Greenblatt et al., 1984; Jonas et al., 1992; Klett, 1992; Rothschild, 1992; Mendelson and Jain, 1995; Lobo and Greene, 1997) or concluded that serious questions regarding the safety and efficacy of Halcion remain (Kales et al., 1996). These reports echo two concerns about the published literature: (1) essentially all studies evaluate only a single dose of Halcion or its comparator drug, which makes it difficult to equate Halcion doses with the doses of other medications on the basis of equal potency, and (2) most trials with a single dose of Halcion have used doses that are relatively larger (in terms of anticipated receptor occupancy) than that of the drug with which it is compared. The net. result is that many trials appear to be biased in favor of associating adverse effects with Halcion (Lobo and Greene, 1997). Overall, the reviews do not convincingly support the existence of an unexpected clinical profile for Halcion.

Closing Comments

The bulk of the published reports related to Halcion's safety were not designed to evaluate the relative frequency of rare, but serious, side effects. A small number of these studies suggest that Halcion use is associated with frequent and serious side effects. The frequency or severity of these side effects is not replicated broadly. in the published studies. However, the presence of these serious side effects warrants the review of other data that might provide a better understanding of these effects, which are of concern. The published studies, however, do not provide convincing evidence that there is associated with Halcion a unique or serious health risk relative to those associated with other benzodiazepines or benzodiazepine-like hypnotic agents. There is the possibility that, relative to other benzodiazepines, individuals receiving Halcion tend to remain on higher doses for longer than the recommended duration (Martinez-Cano et al., 1996). Use patterns may interact with the pharmacologic properties to give rise to increased rates of adverse effects. Even if this is true, however, this conclusion cannot be evaluated on the basis of the published literature. Kales and colleagues (1996) raised the concern that the available data from both controlled trials and SRS might be inadequate to evaluate the effects of Halcion on autobiographical memory (amnestic events). To the committee's knowledge, this phenomenon has not received direct attention in a published study and could be evaluated in a controlled trial. However, the subsequent modification to the labeling of Halcion reflects an integration of reports of serious, but infrequent, adverse effects of this drag into clinical practice.

CONCLUSIONS AND RECOMMENDATIONS

It is important to note that the conclusions and recommendations are based on a review of the available public information. Various types of data were reviewed and evaluated: (1)

randomized, controlled (dose and duration) clinical trials, (2) spontaneous reports of adverse events, (3) survey data, and (4) the published literature. The committee did not review original, raw data or case reports but, rather, the data that were summarized in the New Drug Application and other sources. The committee's analyses were based on these summary data.

Clinical Trials and Surveillance

The committee is confident in the quality and adequacy of the data from clinical trials (pre- and postmarketing). supporting the safety of using Halcion within the current labeling guidelines. The committee recognizes, however, that the lack of significant adverse events reported from clinical trials appear to conflict with the numbers and types of adverse events (e.g., anterograde amnesia, confusion) that have appeared in the SRS of FDA and in some case reports in the literature. Many factors contribute to this apparent conflict (which is not uncommon among drugs), including the nature and design of clinical trials and external events that can affect the reporting of adverse events.

It is important to note that the statistical power to detect rare events is necessarily limited in controlled clinical trials because such trials include a small number of subjects compared with the number of patients using the drug in the postmarketing period, and subjects admitted to the trials must conform to carefully defined inclusion and exclusion criteria, narrowing the likely range of adverse events; rare events are unlikely to be detected in sample populations of a few hundred subjects. In addition, the treatment regimens in these trials are designed to avoid untoward or adverse events that might be expected to occur with higher doses or with dose dependent or duration-dependent use.

With respect to surveillance and reports of adverse events, the committee notes that apparent inconsistencies in the data from clinical trials and spontaneous reports are likely to occur for the reasons stated above, and concludes the following:

- The popularity and consequent widespread use of Halcion produced large at-risk populations from which spontaneous reports of adverse events emerged.
- Many people take Halcion (and other hypnotic drugs) for more than a year and at dosages above those recommended in the labeling.
- In general, the types and frequencies of reported adverse events are subject to many external influences, including media attention, marketing, litigation, differential reporting rates, ability to connect drug use to a health event, and other factors, all of which affect the accuracy of interpreting the results.

***Recommendation. 5: Improve Surveillance, Analysis, and Integration of Findings*. The committee recommends that FDA develop improved methods for integrating the findings of clinical trials and postmarketing surveillance, and for resolving discrepancies in the interpretation of data from spontaneous reports, clinical case reports, and controlled clinical trials. This would include the reestablishment of a biostatistics and epidemiology advisory committee (in addition to having biostatistics and epidemiology expertise on the other advisory committees) that**

would be charged with the rapid and thorough assessment of the potential health risks suggested by reports of adverse events, identification and resolution of conflicts that may arise in the review of clinical trial and surveillance data, and the provision of expert advice on the maintenance and operation of effective postmarketing surveillance systems.

4

Additional Comments on Broader Implications

During the course of this study, the Institute of Medicine (IOM) committee was led by the data and other information to consider some important, broader implications of its findings. The committee's concluding remarks therefore address, first, the need for more research to improve the fundamental understanding of sleep and the related condition of insomnia; and secondly, the need to improve both the integration of the various types of postmarketing information and the attention that is paid to the information that is collected.

Insomnia is often an acute, short-term disorder, but for many it is a chronic condition that requires longer-term attention. It is also a disorder that is poorly understood from a diagnostic perspective, and the available tools for the management of insomnia are fairly limited. Furthermore, little is known about the interaction of hypnotic drags with other drugs and substances in people of differing ages, gender, and diagnoses. Furthermore, large numbers of people take hypnotic drugs for longer periods of time and at higher doses than those that are recommended, despite limited knowledge of potential benefits or adverse events. A better understanding of the basic science of sleep and insomnia would facilitate the development of improved therapeutic agents as well as the clinical management of insomnia. The committee believes, therefore, that additional research is needed in this area, in conjunction with the development of improved guidelines for the evaluation of hypnotic agents (see Chapter 2).

The second broad implication arose from information that was collected in an attempt to reconcile the apparent discrepancy between the clinical trial data and the reports of adverse events related to the use of Halcion (triazolam). It seemed that at least some of the adverse events that were being reported through the Spontaneous Reporting System (SRS) of the U.S. Food and Drug Administration (FDA) were similar to those that had been reported in some of the early clinical trials with higher doses of Halcion and with longer durations of use. This, combined with survey data that indicates that many people use hypnotic agents for very long periods of time (a Canadian survey [the Evaluation of Medications for Insomnia in Canada (EMIC)] reported average use of 1.7 years) led the committee to consider the possibility that

the adverse events that were being reported for Halcion might be due, at least in part, to the use of Halcion for much longer periods of time and at higher doses than those currently recommended in the labeling.[1]

The committee believes that this type of use may be a problem common to all hypnotic medications and that it is complicated by incomplete understanding of insomnia and its clinical management. Although prescription of hypnotic drugs at higher doses and for longer durations than those recommended in the product labeling may provide benefit to some patients, the magnitude of Halcion use at higher doses and for longer durations than those that are recommended, also suggests that alternatives (e.g., other medications or diagnoses) are not fully explored, to the potential detriment of patients.

Spontaneous reporting of adverse events provides a "signal" to FDA of the possibility of serious unintended threats to the health of the patient. The pharmacoepidemiolgist, among others, then has the task of deciding which signals should be followed up and which can be ignored. The severity of the events, the size of the at-risk population (and the potential for larger numbers of adverse events), and information concerning use at higher doses or for longer durations than those that are recommended are all important factors in the decision to pursue the spontaneous report(s) further. Further investigations, if they are conducted, could include the following:

- Verification of possible adverse drug reactions (ADRs);
- Collection of estimates of drug use in a population;
- Search for more ADRs attributable to the suspect drug;
- Examination of in toxicology animal regarding the suspect drug;
- Examination and reanalyses of the data from clinical trials;
- Launching ad hoc case-control or cohort studies exploring the association of the drug and the suspected adverse event;
- Querying various drug surveillance systems under contract to FDA and regulatory bodies in other countries;
- Querying the drag company that markets the suspect drug; and
- Research studies with other designs, including rechallenge and withdrawing the drug (experiment in prevention).

Postmarketing surveillance requires the collection and assessment of at least two very different types of information: data from controlled trials, and data from spontaneous reports of adverse events. These two types of data vary significantly in their quality, and, thus, their interpretation as a body Can be quite complicated. This was true for Halcion, because some of the clinically significant adverse events (e.g., memory impairment, nervousness) were detected not in the clinical trials but only in the spontaneous reports. In such circumstances and in those instances in which adverse events are difficult to detect—but are clinically

[1] The FDA task force also observed that "marketing data suggest that Halcion is sometimes prescribed by physicians for longer periods of time and at higher doses than is recommended in the labeling" (FDA, 1996, p. iii).

significant in terms of the health and well-being of the patient—the need for objective, critical assessments, better methods for detecting behavioral or psychological adverse events, and integrated evaluations of the entire body of information is critical.

Recommendation 6: Improve Postmarketing Data Collection and Analysis. **The committee recommends that additional effort be dedicated to the postmarketing surveillance and monitoring of hypnotic agents and other drug products, and that this include objective and critical evaluations of integrated data sets of adverse events, actual patient use, and clinical trials. This effort should include special emphasis on developing improved methods for (1) collecting and integrating evaluation of patient use data and clinically significant adverse events, including behavioral or psychological events, and (2) responding effectively when signals appear in the spontaneous reports that correlate with data indicating patient use at higher doses and for longer durations than those that are recommended**.

Recommendation 7: Educate Health Care Providers. **The committee recommends that FDA establish an independent task force with the charge of reviewing and developing mechanisms for improving prescribing practices and patient use of hypnotic medications. This task force should pay special attention to issues raised by the actual use of these agents and to the issues of appropriate differential diagnosis when addressing the problem of insomnia in patients. It would be useful to provide physicians with efficacy and adverse effects dose-response curves for durations comparable to those being used in practice, even if they are greater than those recommended in the labeling**.

In addition, the committee recommends that professional societies of primary care and other health care providers increase their members' attention to the need for caution in prescribing hypnotic drugs at higher doses and for longer durations than those that are recommended. Efforts in this area should include increased attention to this issue in medical education and in residency programs, including the addition of questions about the use of hypnotic drugs on medical specialty examinations.

FDA should identify ways to disseminate information on the diagnosis and management of insomnia more effectively to medical students and in training programs for primary care physicians.

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FDA Safety Tables

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TABLE A-1 Non-Geriatric Studies: Anxiety

TABLE 5.4
NON-GERIATRIC STUDIES: ANXIETY

		DOSE (MG)			% WITH ANXIETY		
STUDY	WEEKS	TRZ	FLZ	N	TRZ	FLZ	PBO
6401	1	.25	—	70	2.9	—	2.9
2401	1	.25-.5	—	145	4.4	—	1.3
6400	1	.25-.5	15-30	105	7.5	3.8	—
6041	1	.5	—	143	4.3	—	2.7
6042	1	.5	30	127	4.7	0.0	—
6004	1	.6	30	37	6.3	23.8	—
6043	2	.5	—	277	8.0	—	5.0
6016	2	.5	30	30	7.1	0.0	—
6044	2	.5	30	232	6.9	5.2	—
6402	4	.25	30	81	20.4	22.2	—
6045	4	.5	—	62	16.1	—	12.9
6046	4	.5	30	103	10.9	2.0	—
6047	6	.5	—	125	15.0	—	3.1
6048	6	.5	30	145	4.1	5.6	—
6023B	12	.5	30	18	8.3	0.0	—
6023	12	.6	30	51	9.1	0.0	—
6049	13	.5	30	139	13.5	8.2	—

TABLE A-2 Non-Geriatric Studies: Confusion

TABLE 5.5
NON-GERIATRIC STUDIES: CONFUSION

		DOSE (MG)			% WITH CONFUSION		
STUDY	WEEKS	TRZ	FLZ	N	TRZ	FLZ	PBO
6401	1	.25	—	70	0.0	-	0.0
2401	1	.25-.5	—	145	0.0	—	0.0
6400	1	.25-.5	15-30	105	0.0	0.0	—
6041	1	.5	—	143	0.0	—	0.0
6042	1	.5	30	127	1.6	0.0	—
6004	1	.6	30	37	12.5	0.0	—
6043	2	.5	—	277	0.0	—	0.7
6016	2	.5	30	30	0.0	0.0	—
6044	2	.5	30	232	0.0	0.0	—
6402	4	.25	30	81	0.0	0.0	—
6045	4	.5	—	6'2	6.5	—	0.0
6046	4	.5	30	10.3	0.0	0.0	—
6047	6	.5	—	125	0.0	—	0.0
6048	6	.5	30	145	0.0	0.0	—
6023B	12	.5	30	18	0.0	0.0	—
6023	12	.6	30	51	3.0	5.6	—
6049	13	.5	30	139	2.7	0.0	—

TABLE A-3 Non-Geriatric Studies: Depression

TABLE 5.6
NON-GERIATRIC STUDIES: DEPRESSION

		DOSE (MG)			% WITH DEPRESSION		
STUDY	WEEKS	TRZ	FLZ	N	TRZ	FLZ	PBO
6401	1	.25	—	70	0.0	—	0.0
2401	1	.25-.5	—	145	0.0	—	0.0
66400	1	.25-.5	15-30	105	0.0	0.0	—
6041	1	.5	—	143	1.4	—	2.7
6042	1	.5	3.0	127	0.0	0.0	—
6004	1	.6	30	37	0.0	0.0	—
6043	2	.5	—	277	2.2	—	0.7
6016	2	.5	30	30	0.0	0.0	—
6044	2	.5	30	232	2.6	3.4	—
6402	4	.25	30	81	3.7	0.0	—
6045	4	.5	—	62	0.0	—	0.0
6046	4	.5	30	103	1.8	0.0	—
6047	6	.5	—	125	0.0	—	0.0
6048	6	.5	30	145	4.1	4.2	—
60238	12	.5	30	18	0.0	0.0	—
6023	12	6	30	51	3.0	0.0	—
6049	13	.5	30	139	6.8	6.8	—

TABLE A-4 Non-Geriatric Studies: Irritability

TABLE 5.7
NON-GERIATRIC STUDIES: IRRITABILITY

		DOSE (MG)			% WITH IRRITABILITY		
STUDY	WEEKS	TRZ	FLZ	N	TRZ	FLZ	PBO
6401	1	.25	—	70	0.0	—	0.0
2401	1	.25-.5	—	145	1.5	—	3.9
6400	1	.25-.5	15-30	105	0.0	0.0	—
6041	1	.5	—	143	0.0	—	0.0
6042	1	.5	30	127	3.1	1.6	—
6004	1	.6	30	37	0.0	0.0	—
6043	2	.5	—	277	0.0	—	2.2
6016	2	.5	30	30	0.0	0.0	—
6044	2	.5	30	232	0.0	1.7	—
6402	4	.25	30	81	0.0	3.7	—
6045	4	.5	—	62	0.0	—	0.0
6046	4	.5	30	103	1.8	0.0	—
6047	6	.5	—	125	0.0	—	0.0
6048	6	.5	30	145	0.0	0.0	—
6023B	12	.5	30	18	0.0	0.0	—
6023	12	.6	30	51	0.0	0.0	—
6049	13	.5	30	139	1.4	0.0	—

TABLE A-5 Non-Geriatric Studies: Memory Impairment

TABLE 5.8
NON-GERIATRIC STUDIES:
MEMORY IMPAIRMENT

		DOSE (MG)			% WITH MEMORY IMPAIRMENT		
STUDY	WEEKS	TRZ	FLZ	N	TRZ	FLZ	PBO
6401	1	.25	—	70	0.0	—	0.0
2401	1	.25-.5	—	145	0.0	—	0.0
6400	1	.25-.5	15-30	105	0.0	0.0	—
6041	1	.5	—	143	0.0	—	0.0
6042	1	.5	30	127	1.6	1.6	—
6004	1	.6	30	37	6.3	0.0	—
6043	2	.5	—	277	0.0	—	0.0
6016	2	.5	30	30	0.0	0.0	—
6044	2	.5	30	232	0.0	0.0	—
6402	4	.25	30	81	0.0	0.0	—
6045	4	.5	—	62	0.0	—	0.0
6046	4	.5	30	103	0.0	0.0	—
6047	6	.5	—	125	1.7	—	0.0
6048	6	.5	30	145	1.4	0.0	—
6023B	12	.5	30	18	8.3	0.0	—
6023	12	.6	30	51	15.2	0.0	—
6049	13	.5	30	139	6.8	0.0	—

TABLE A-6 Non-Geriatric Studies: All Psychiatric

TABLE 5.9
NON-GERIATRIC STUDIES: 'ALL PSYCHIATRIC'

		DOSE (MG)			% WITH 'ALL PSYCHIATRIC'		
STUDY	WEEKS	TRZ	FLZ	N	TRZ	FLZ	PBO
6401	1	.25	—	70	5.7	—	2.9
2041	1	.25-.5	—	145	5.9	—	3.9
6400	1	.25-.5	15-30	105	11.3	3.8	—
6041	1	.5	—	143	5.7	—	5.5
6042	1	.5	30	127	7.8	3.2	—
6004	1	.6	30	37	25.0	42.9	—
6043	2	.5	—	277	10.9	—	10.1
6016	2	.5	30	30	7.1	0.0	—
6044	2	.5	30	232	9.5	9.5	—
6402	4	.25	30	81	25.9	29.6	—
6045	4	.5	—	62	29.0	—	12.9
6046	4	.5	30	103	12.7	0.0	—
6047	6	.5	—	125	15.0	—	7.7
6048	6	.5	30	145	9.5	0.0	—
6023B	1.2	.5	30	18	8.3	16.7	—
6023	12	.6	30	51	21.2	22.2	—
6049	13	.5	30	139	23.0	15.1	—

TABLE A-7 Non-Geriatric Studies: Sedative/Hypnotic

TABLE 5.10
NON-GERIATRIC STUDIES:
'SEDATIVE/HYPNOTIC'

		DOSE (MG)			% WITH 'SEDATIVE HYPNOTIC'		
STUDY	WEEKS	TRZ	FLZ	N	TRZ	FLZ	PBO
6401	1	.25	—	70	17.1	—	11.4
2401	1	.25-.5	—	145	75.0	—	84.4
6400	1	.25-.5	15-30	105	20.8	21.2	—
6041	1	.5	—	143	24.3	—	12.3
6042	1	..5	30	127	21.9	17.5	—
6004	1	.6	30	37	50.0	47.6	—
6043	2	.5	—	277	35.5	—	19.4
6016	2	.5	30	30	14.3	25.0	—
6044	2	.5	30	232	37.1	44.0	—
6402	4	.25	30	81	33.3	59.3	—
6045	4	.5	—	62	54.8	—	12.9
6046	4	.5	30	103	43.6	36.0	—
6047	6	.5	—	125	36.7	—	13.8
6048	6	.5	30	145	25.7	31.0	—
6023B	12	.5	30	18	41.7	50.0	—
6023	12	.6	30	51	33.3	77.8	—
6049	13	.5	30	139	37.8	42.5	—

TABLE A-8 Geriatric Studies: Anxiety

TABLE 5.11
GERIATRIC STUDIES: ANXIETY

		DOSE (MG)			% WITH ANXIETY		
STUDY	WEEKS	TRZ	FLZ	N	TRZ	FLZ	PBO
6417	1	.125	—	90	2.2	—	9.1
6417A	1	.125-.25	—	37	0.0	—	15.8
6061	1	.25	—	59	0.0	—	0.0
6062	1	.25	15	71	0.0	0.0	—
6063	2	.25	—	38	5.6	—	10.0
6064	2	.25	15	43	10.0	0.0	—
6065	4	.25	15	41	14.3	0.0	0.0
2601	4	.25-.5	15-30	121	30.0	17.5	14.6

TABLE A-9 Geriatric Studies: Confusion

TABLE 5.12
GERIATRIC STUDIES: CONFUSION

		DOSE (MG)			% WITH CONFUSION		
STUDY	WEEKS	TRZ	FLZ	N	TRZ	FLZ	PBO
6417	1	.125	—	90	0.0	—	2.3
6417A	1	.125-.25	—	37	0.0	—	0.0
6061	1	.25	—	59	0.0	—	0.0
6062	1	.25	15	71	0.0	0.0	—
6063	2	.25	—	38	5.6	—	0.0
6064	2	.25	15	43	0.0	4.3	—
6065	4	.25	15	41	0.0	0.0	0.0
2601	4	.25-.5	15-30	121	5.0	2.5	2.4

TABLE A-10 Geriatric Studies: Depression

TABLE 5.13
GERIATRIC STUDIES: DEPRESSION

		DOSE (MG)			% WITH DEPRESSION		
STUDY	WEEKS	TRZ	FLZ	N	TRZ	FLZ	PBO
6417	1	.125	—	90	0.0	—	0.0
6417A	1	.125-.25	—	37	0.0	—	0.0
6061	1	.25	—	59	0.0	—	0.0
6062	1	.25	15	71	0.0	0.0	—
6063	2	.25	—	38	5.6	—	0.0
6064	2	.25	15	43	10.0	0.0	—
6065	4	.25	15	41	0.0	0.0	0.0
2601	4	.25-.5	15-30	121	7.5	5.0	7.3

TABLE A-11 Geriatric Studies: Irritability

TABLE 5.14
GERIATRIC STUDIES: IRRITABILITY

		DOSE (MG)			% WITH IRRITABILITY		
STUDY	WEEKS	TRZ	FLZ	N	TRZ	FLZ	PBO
6417	1	.125	—	90	0.0	—	0.0
6417A	1	.125-.25	—	37	0.0	—	0.0
6061	1	.25	—	59	0.0	—	0.0
6062	1	.25	15	71	0.0	0.0	—
6063	2	.25	—	38	0.0	—	0.0
6064	2	.25	15	43	0.0	0.0	—
6065	4	.25	1.5	41	7.1	0.0	0.0
2601	4	.25-.5	15-30	121	5.0	0.0	2.4

TABLE A-12 Geriatric Studies: Memory Impairment

TABLE 5.15
GERIATRIC STUDIES:
MEMORY IMPAIRMENT

		DOSE (MG)			% WITH MEMORY IMPAIRMENT		
STUDY	WEEKS	TRZ	FLZ	N	TRZ	FLZ	PBO
6417	1	.125	—	90	0.0	—	0.0
6417A	1	.125-.25	—	37	0.0	—	0.0
6061	1	.25	—	59	0.0	—	0.0
6062	1	.25	15	71	0.0	0.0	—
6063	2	.25	—	38	0.0	—	0.0
6064	2	.25	15	43	0.0	0.0	—
6065	4	.25	15	41	0.0	0.0	0.0
2601	4	.25-.5	15-30	121	2.5	0.0	0.0

TABLE A-13 Geriatric Studies: All Psychiatric

TABLE 5.16
GERIATRIC STUDIES: 'ALL PSYCHIATRIC'

		DOSE (MG)			% WITH 'ALL PSYCHIATRIC'		
STUDY	WEEKS	TRZ	FLZ	N	TRZ	FLZ	PBO
6417	1	.125	—	90	2.2	—	13.6
6417A	1	.1250.25	—	37	0.0	—	15.8
6061	1	.25	—	59	0.0	—	0.0
6062	1	.25	15	71	0.0	0.0	—
6063	2	.25	—	38	11.1	—	10.1
6064	2	25	15	43	15.0	4.3	—
6065	4	.25	15	41	14.3	0.0	0.0
2601	4	.25-.5	15-30	121	47.5	32.5	26.8

TABLE A-14 Non-Geriatric Studies

TABLE 2.2:
NON-GERIATRIC STUDIES

		DOSE (MG)		GROUPS/SAMPLE SIZE		
STUDY	WEEKS	TRZ	FLZ	TRZ	FLZ	PBO
6401	1	.25	—	35	—	35
2401	1	.25-.5	—	66	—	77
6400	1	.25-.5	15-30	53	52	—
6041	1	.5	—	70	—	72
6042	1	.5	30	62	59	—
6004	1	.6	30	16	21	—
6043	2	.5	—	138	—	135
6016	2	.5	30	14	16	—
6044	2	.5	30	112	110	—
6402	4	.25	30	54	27	—
6045	4	.5	—	31	—	31
6046	4	.5	30	55	50	—
6047	6	.5	—	59	—	64
6048	6	.5	30	72	71	—
6023B	12	.5	30	9	6	—
6023	12	.6	30	33	18	—
6049	13	.5	30	74	73	—

TABLE A-15 Geriatric Studies

TABLE 2.3:
GERIATRIC STUDIES

		DOSE (MG)		GROUPS/SAMPLE SIZE		
STUDY	WEEKS	TRZ	FLZ	TRZ	FLZ	PBO
6417	1	.125	—	46	—	44
6417A	1	.125-.25	—	18	—	19
6061	1	.25	—	31	—	28
6062	1	.25	15	36	35	—
6063	2	.25	—	18	—	20
6064	2	.25	15	20	23	—
6065	4	.25	15	14	13	14
2601	4	.25-.5	15-30	32	33	27

B

Summary Tables of Literature Reviewed for Safety of Halcion

TABLE B-1 Evaluation of Comparability, Pharmacokinetics, and Pharmacodynamic Interactions of Halcion

Source	Type	Population	Number of Subjects	Drug and Dose	Duration	Outcome/Comments
Greenblatt et al. (1989)	Placebo-control	Healthy	16	Placebo	Single dose	Time to peak: flurazepam, 1-1.2 h[a]; temazepam, 1.5 h; Halcion, 0.95 h. Time to elimination: flurazepam, >24 h[b]; temazepam, 8.7 h; Halcion, 2.0 h.
12	flurazepam 15 mg					
13	Temazepam 15 mg					
12	Halcion 0.25 mg					
Mouret et al. (1990)	?	?	?	Zopliclone	Single dose	Time to peak: 75 min; time to elimination: 5-6.5 h
Mauri et al. (1993)	?	?	?	Quazepam Desalkylflurazepam Oxoquazepam OH-Triazolam	Single dose, Very low concn.	Time to elimination: quazepam, 30-40 h; Desalkylflurazepam Oxoquazepam, 40-70 h; OH-Triazolam, 30-40 h.
Monti et al. (1994)	?	?	?	Zolpidem	Single dose	Time to peak: 0.33-0.67 h. Time to elimination: 2-3 h
Adam and Oswald (1988)	?	?	?	Lormetazepam	Single dose	Time to elimination: 10-20 h. Humpel et al. (1980)
Eberts et al. (1981)	NA	Bedtime	6	71.1 mCi of Halcion Free alpha-OH triazolam Free 4-OH triazolam	Single dose	Time to peak: Halcion, 1.3 h; Alpha-OH triazolam gluconate, 1.3 h; 4-HTT-gluconate, 2.5 h; others, levels low for kinetics. Time to elimination: Halcion, 2.3 h; Alpha-OH triazolam gluconate, 3.9 h; 4-HTT-gluconate, 3.8 h.
				Alpha-OH triazolam gluconate 4-HTT-gluconate		Free alpha-OH triazolam 69% of urine ^{14}C (free + conjugated); Free 4-OH triazolam 11% of urine ^{14}C (free + conjugated)

Source	Type	Population	Number of Subjects	Drug and Dose	Duration	Outcome/Comments
Greenblatt et al. (1991)	Placebo Halcion at 0.125 and 0.25 mg	Elderly	26 young, 21 elderly		Single dose	Halcion levels doubled in elderly controls, with greater cognitive/behavioral effects.
Oliveto et al. (1991)	Placebo, diazepam	Bedtime	7	Halcion 0.25 mg Halcion 0.1-0.56 mg/70 kg Diazepam 10-32 mg/70 kg Hydromorphone 1-6 mg/70 kg	Single dose	Halcion and diazepam are indistinguishable
Rukstalis and de Wit (1995)	Placebo	Female	6	Halcion 0.25 mg	Three doses over 1 month	No significant change in behavior over menstrual cycle.
Rush et al. (1994)	Placebo, dose	Male	9	Halcion 0 mg, 0.375 mg/70 kg, 0.75 mg/70 kg in combination with caffeine 0 mg, 250 mg/70 kg	Balanced design	Caffeine reduced Halcion sedation and cognitive effects, but not sense of Halcion strength.
Villikka et al. (1997)	NA	Bedtime	10	500 mg/70 kg Halcion 0.5 mg	One dose after 5 days of rifampin	Rifampin induces CYP 3A4. It reduced peak Halcion levels to 12.4% of levels in subjects receiving placebo, proportionately reducing behavioral effects.
Kosuge et al. (1997)		Bedtime	7	Halcion 0.25 mg	One dose after 3 days of diltiazem 180 mg	AUC of concentration by time doubled; elimination half-life increased from 4.1 to 7.6 h; intensity of behavioral effects increased.
von Moltke et al. (1996)	NA	In vitro		Liver microsome preparation		SSRIs (norfluoxetine most potent, fluoxetine least potent) and ketoconazole inhibit Halcion metabolism via cytochrome P-450 CYP 3A4 system.

Source	Type	Population	Number of Subjects	Drug and Dose	Duration	Outcome/Comments
Hukkinen et al. (1995)		Bedtime	10	Halcion 0.25 mg with 250 ml of grapefruit juice		Mean AUC of plasma Halcion concentration increased 1.5 times and peak plasma Halcion concentration increased 1.3 times; peak Halcion level delayed from 1.6 to 2.5 h; potentiation of drowsiness was noted.
Robin et al. (1993)	Placebo	Bedtime, cirrhosis	6 6	Halcion	Single dose	No potentiation of PK or behavioral effects.
Wright et al. (1992)	Placebo	Bedtime	24	Halcion 0.25 mg	Repeated before and after, 8 days of treatment with fluoxetine at 60 mg/day	No potentiation of PK or behavioral effects.
McAuley et al. (1995)	Placebo	Post menopause	16	Halcion 0.5 mg administered intravenously with oral progesterone at 300 mg, (eight groups each)		Potentiation of DSST, CPT, hand-eye parallel coordination; impairments produced by Halcion. Intravenous treatment terminated before maximum Halcion dose was admin. due to SE more frequent after progesterone (7/8 vs. 5/8 group).
Kroboth et al. (1993)		Bedtime		Halcion	Intravenous infusion	Evidence of acute tolerance (review based on abstract only).

NOTE: NA, not available; AUC, area under the concentration-time curve; PK, pharmacokinetic; DSST, Digit Symbol Substitution Test; CPT, current perception threshold; and SE, side effects.

[a] Flurazepam and hyroxyethylflurazepam.

[b] Desalkylflurazepam.

TABLE B-2 Results of In Vitro Binding Studies: Displacement of Flunitrazepam in the Human Cortex

Drug	K_d (37§C) nM[a]	$t_{1/2}$-off (min)[b]	Ratio to K_d Halcion[c]
Halcion	0.5 ± 0.01	5.3	1
Alpha-hydroxytriazolam	2.2 ± 0.06		4
Clonazepam	2.2 ± 0.2	3.4	4
Lorazepam	3.8 ± 0.2		8
Midazolam	4.9 ± 0.07		10
Diazepam	9.8 ± 0.7		20
Desmethyldiazepam	48 ± 2		96
Alprazolam	10.6 ± 0.4	3.4	21
Oxazepam	39 ± 3		78
Flurazepam	51 ± 2	4.6	102
Desalkylflurazepam	8.2 ± 0.3		16
Quazepam	58 ± 4		116
Desalkylflurazepam	8.2 ± 0.3		16
Temazepam	66 ± 1		132
Chlordiazepoxide	694 ± 8		$>10^3$

[a] Ratio of K_d of drug to K_d of Halcion
[b] $t_{1/2}$-off, dissociation half-life.
[c] K_d dissociation constant.
SOURCE: Richelson et al. (1991).

TABLE B-3 Displacement of [3H]Flumazenil in Rats as Determined by In Vivo Autoradiography

	Cortex		Spinal Cord		Cerebellum	
Drug	IC_{50} (mg/kg)	Ratio	IC_{50} (mg/kg)	Ratio	IC_{50} (mg/kg)	Ratio
Halcion	0.7 ± 0.1	1	0.1 ± 0.8	1	0.5 ± 0.08	1.0
Clonazepam	0.3 ± 0.07	0.04	0.3 ± 0.08	3	0.3 ± 0.07	0.6
Lorazepam	0.8 ± 0.3	1.1	1.0 ± 0.3	10	0.4 ± 0.09	0.8
Alprazolam	3.9 ± 1.2	5.6	1.9 ± 0.4	19	3.4 ± 0.9	6.8
Zopiclone	6.6 ± 1.1	9.4	5.7 ± 0.5	57	4.7 ± 0.7	9.4
Zolpidem	7.0 ± 1.6	10.0	13.4 ± 2.8	134	6.8 ± 1.0	13.6
Diazepam	10.9 ± 0.5.	15.6	7.4 ± 0.6	74	10.6 ± 0.5	21.2

NOTE: IC_{50} is the 50% inhibitory concentration. Ratio indicates ratio of IC_{50} of drug to IC_{50} of Halcion.
SOURCE: Sanger and Benavides (1993).

TABLE B-4 Relative Lipophilicity of Benzodiazepines

Source and Drug	HPLC Retention Index[a]	Concentration in Whole Brain/ Unbound Concentration in Serum	Inhibitory Constant K_i
Arendt et al. (1987)			
Halcion	0.6	19.5	0.4[b]
Diazeparn	1.0	26.05	9.57[b]
Desmethyldiazepam	0.8	22.18	5.58[b]
Alprazolam	0.5	2.62	4.4[b]
Lorazepam	0.5	16.0	1.6[b]
Midazolam	1.5	33.91	0.4[b]
Miller et al. (1988)			
Flurazepam	56.8[c]	8.2	12.7[b]
Desalkylflurazepam	29.1[c]	7.0	0.85[b]
Sethy and Harris (1982) (flunitrazepam displacement, "brain" pellet)			
Halcion			0.76[d]
Alpha-hydroxytriazolam			0.92[d]
4-Hydroxytriazolm			0.32[d]

[a] Relative to diazepam. HPLC, high-pressure liquid chromatography.
[b] Units of K_i (inhibitory constant) are $IC_{50}/1 + S/K_d$ where IC_{50} is the 50% inhibitory concentration and S is the flunitrazepam concentration.
[c] In minutes.
[d] In nanomolar.

TABLE B-5 IOM Summary of Studies Investigating Possible Unique Amnestic Effects of Halcion

Source	Type	Population	Number of Subjects	Drug and Dose	Duration	Outcome/Comments
Roth et al. (1980)	Placebo/BZ	Bedtime	11	Placebo Flurazepam 30 mg Halcion 0.5 mg Lorazepam 4 mg	2 nights/week over 4 weeks	Lorazepam equivalent to Halcion impairing, immediate and delayed (tested following morning) recall (both amnestic) vs. placebo and flurazepam. Flurazepam impairs vs. placebo to typical dose, but appropriate for the comparison. More rapid return to sleep may be a factor contributing to interference with memory consolidation with Halcion (difference in minutes).
Spinweber and Johnson (1982)	Placebo	Male, insomniac	10 10	Halcion 0.5 mg Placebo	6 treatment nights 2 withdrawal	Reaction time, digit symbol, Williams Word Memory and Card Song Sorting Deficits Evident Immediate to 5 h after drug administration. Paired associate task administered prior to Halcion did not show a.m. memory impairment.
Roehrs et al. (1983)	Placebo/flurazepam secobarbital	Male, Bedtime	12	Halcion 0.25 and 0.5 mg Placebo Flurazepam 30 mg Secobarbital 200 mg Lorazepam 4 mg	6 days of administration for each agent, 1 day of withdrawal	Halcion memory impairment was dose-dependent. Acute: lorazepam = Halcion, 25 = flurazepam < Halcion. 0.5 = Secobarbital. Over 6 days no change with Halcion or secobarbital. Effect from flurazepam worsened (accumulation?) to equal that of Halcion at 5 mg. Tolerance to lorazepam appeared to develop.
Scharf et al. (1988)	Three studies	Bedtime Insomniac Insomniac	22 22 30	Halcion 0.5 mg/placebo Halcion 0.5 mg/placebo Temazepam 30 mg	Single dose	Halcion, but not temazepam, showed evidence of anterograde memory impairment.
Greenblatt et al. (1989)	Placebo/active	Bedtime	16 12 13 11	Placebo Flurazepam 15 mg Temazepam 15 mg Halcion 0.25 mg	Single dose	List learning at 24 h: Halcion < flurazepam = temazepam ≤ placebo. Possible bias against Halcion from a State Department learning perspective.
Penetar et al. (1989)	Placebo	Bedtime, Aerial Deployment	33 35	Halcion 0.5 mg Placebo	Single dose	Logical memory WMS impairment at 8 h by Halcion vs. placebo. Stimuli presented while receiving drug.
Griffiths et al. (1986)	Placebo/active	Bedtime (within subject)	10	Zopiclone 7.5 mg Flurazepam 15 mg Lormetazepam 1 mg Halcion 0.25 mg Placebo	Single dose	Stroop, memory span, logical reasoning, mood, and saccadic eye movement all were similarly drug sensitive.

Baughman et al. (1989)	Placebo/diazepam	Surgery, Premedical	12 12 12 12	Placebo Halcion 0.125 mg Halcion 0.25 mg Halcion 0.5 mg	Single dose	Percent picture recall by dose: Halcion, 95, 82 and 63%; Diazepam, 100, 100 and 82%. Only Halcion 0.5 mg decreased recall significantly.
Fleming et al. (1990)	Zopiclone	Insomniacs	24 24	Zopiclone 7.5 mg Halcion 0.25 mg	21 days	4/24 subjects receiving zopiclone vs. 3/24 subjects receiving Halcion reported memory difficulties.
Balter and Uhlenhuth (1991)	Survey	Insomniac		Untreated (U) Halcion (H) Flurazepam (F) Temazepam (T)		U: 44% subjective report of memory impairment. H: 12% subjective report of memory impairment. F: 12% subjective report of memory impairment. T: 14% subjective report of memory impairment.
Bixler et al. (1991)	Placebo/temazepam	Insomniac	6 6 6	Halcion 0.5 mg Temazepam 30 mg Placebo	5 nights on medication per subject by placebo, then 1–2 nights, then placebo	Five of six subjects in Halcion group report inability to recall (3/4 followed episodes of (amnesia). No report of inability to recall or memory impairment in other group. Frequency increased over 5 nights. Better performance in immediate recall (vs. placebo) and delayed word recall (vs. placebo and temazepam) in Halcion group following drug withdrawal in morning test after p.m. drug. Worse delayed task recall in a.m. during drug administration for Halcion (temazepam not significant) vs. placebo group.
Hedenbro et al. (1991)	Placebo	Endoscopy	177 182	Placebo Halcion 0.125 mg	Single dose	No clear amnestic effects regarding surgery events.
Rush et al. (1993)	Placebo/temazepam	Bedtime	6	Halcion 0.125, 0.25, and 0.5 mg/70 kg; Placebo Temazepam 15 and 30 mg/70 kg	Single dose	Halcion more amnestic, intoxicating sedating than temazepam.
	Placebo/temazepam	Bedtime	6	Halcion, Placebo, 0.5 mg/70 kg Temazepam, placebo, 60 mg/70 kg	Single dose	Halcion equally sedating, subjective drunkeness, less cognitive impairment than temazepam.
McMarten et al. (1995)	ABA	Alzheimer's disease	7	Halcion 0.125 mg	8 days	No effect on delayed matching to sample. Not a clearly efficacious hypnotic.

Source	Type	Population	Number of Subjects	Drug and Dose	Duration	Outcome/Comments
Milgrom et al. (1994)	Placebo/dose	Anxious dental patients	31	Halcion 0.375 mg Halcion 0.50 mg	Single dose	Drug reduced anxiety and observed movement, 75% strong preference for drug, 25% prefer drug, 0% neutral or negative. Impairment in implicit and explicit memory on drawings and word association task both when testing occurred during drug administration and when testing occurred after drug was eliminated (24 h).
Weingartner et al. (1995c)	Placebo	Bedtime alcoholics	9 8	Halcion 0.375 mg	Single dose	Halcion increased recall of past dissociative experiences in both groups as assessed by Dissociative Experiences Scale.
Weingartner et al. (1995a)	Placebo/dose	Bedtime	15	Halcion 0, 0.25, 0.375, and 0.5 mg	4 days	Halcion effects on subjective and objective measures of sedation differed. Authors hypothesize an effect of drug on reflective processes.
Weingartner et al. (1995b)	Placebo/dose	Bedtime	9 15	Halcion 0, 4.5, and 61 μg/kg, and 0, 0.25, 0.375, and 0.5 mg	Repeated measures	Enhancement of learning of information presented before Halcion administration suggested to be reduction in interference from stimuli presented while receiving drug.
Wesensten et al. (1996)	Placebo/zolpidem	Bedtime		Halcion 0.125, 0.25, and 0.5 mg Zolpidem, 5, 10, and 15 mg Placebo	Single dose	Equal impairment produced by halcion and Zolpidem on Walter Reed Performance Assessment Performance Battery.
Hindmarch et al. (1993)						In relation to its sedative effects, the amnestic effects of Halcion are proportionate.
Berlin et al. (1993)				Zolpidem 10 mg Halcion 0.25 mg		Comparable amnestic effects.
Kuribara and Asahi (1997)	Several BZs	Mice		Diazepam 10 mg/kg Alprazolam 1–10 mg/kg Halcion 1 and 3 mg/kg	Single dose	No evidence of increased amnestic potency relative to sedative potency.

NOTE: BZ, benzodiazepine; WMS, working memory system.

TABLE B-6 IOM Summary of Studies Investigating Possible Unique Anxiogenic Effects During Administration of Halcion, and Anxiogenic or Insomnia-Promoting Effects with Withdrawal

Source	Type	Population	Number of Subjects	Drug and Dose	Duration	Outcome/Comments
Greenblatt et al. (1989)	Placebo, active drug	Bedtime	16 12 13 11	Placebo Flurazepam 15 mg Temazepam 15 mg Halcion 0.25 mg	Single dose	Halcion only hypnotic to initially slow thinking speed. Similar increase above baseline for all but flurazepam at 24 h. Increased thinking speed could be related.
Pinnock et al. (1985)	Placebo, diazepam	Medical	28 30 29	Placebo Diazepam 10 mg Halcion 0.25 mg	Single dose presurgery	VAS anxiety diazepam, but not Halcion acutely anxiolytic; no difference 6 h postawakening.
Kales et al. (1986)	Placebo, quazepam; sleep laboratory	Insomnia	6 6	Placebo, Halcion 0.25 mg Placebo, Quazepam 15 mg	2 days then 14 days; 3-day withdrawal	Carryover sedation with quazepam. (SWS suppression) rebound insomnia with halcion. Rate of "excitatory" effects reported to be 0.5 for Halcion vs. 0.14 for quazepam. Withdrawal-related anxiety/panic for Halcion ("excitatory effects": anxiety, hyperarousal, inability to concentrate, paranoid ideation, nightmares). Not clear that quazepam group was followed long enough to adequately rule out rebound (loss of quazepam).
Hegelbach-Feller et al. (1988)	Placebo, midazepam; crossover	Insomnia	30	Placebo Halcion 0.5 mg Midazepam 15 mg	11 days	More rebound decline in sleep quantity and restlessness during night with Halcion.
Lee and Lader (1988)	Placebo, quazepam; crossover	Bedtime	12	Placebo Quazepam 15 mg	14 days	Mild rebound anxiety more clear with quazepam. Withdrawal-related onset of metallic taste with Halcion.
Fleming et al. (1990)	Zopiclone	Insomniacs	24 24	Zopiclone 7.5 mg Halcion 0.25 mg	21 days	In first week of withdrawal subjective agitation equivalent: 3 zopiclone, 2 Halcion.
Mouret et al. (1990)	Zopiclone	Elderly insomniacs	10	Halcion 0.25 mg Zopiclone 7.5 mg	15 days	Withdrawal insomnia during treatment with zopiclone but not Halcion; 3 days for Halcion vs. 2 days for zopiclone. Did not see "extremely marked" withdrawal as described by Kales et al. (1976, 1983).
Elie et al. (1990)	Zopiclone	Elderly insomniacs	44	Halcion 0.125 mg Halcion 0.25 mg Zopiclone 5 mg Zopiclone 7.5 mg	3 weeks	After withdrawal from Halcion, increased sleep latency and decreased sleep soundness and quality for 3 days. No significant change with zopiclone.

Source	Type	Population	Number of Subjects	Drug and Dose	Duration	Outcome/Comments
Mamelak et al. (1990)	Placebo, dose	Bedtime	10 10 10	Placebo Halcion 0.25 mg Halcion 0.5 mg	1 dose	Halcion at 0.5 mg was most effective, but rebound reduction in subjective sleep soundness and quality of sleep relative to those for baseline and other groups. First withdrawal night, 0.5 mg increased REM index and reduced stage 3/4 sleep relative to those at baseline.
McClusky et al. (1991)	Behavior therapy	Insomniac	15 15	Behavior therapy Halcion 0.5 mg	4 weeks, then 5-week follow-up	Over the 4 weeks of treatment, Halcion is as good or better than behavior therapy. At follow-up, behavior therapy is superior for sleep onset latency (both groups better than baseline), restedness (Halcion back to baseline), difficulty falling asleep (Halcion at baseline).
Stopperich et al. (1993)	Placebo	Preoperative dental patients	11 11	Placebo Halcion 0.25 mg	1 dose	Reduced anxiety.
Scharf (1993)	Placebo, quazepam	Insomniac	26 19 20	Placebo Halcion 0.5 mg Quazepam 15 mg	9 days nightly; 14 every other night	Both equally effective. Quazepam, but not Halcion, reduced daytime anxiety. Rebound reduction in sleep satisfaction with Halcion in night schedule.
Roger et al. (1993)	Zolpidem	Elderly insomniac inpatients	70 74 77	Zolpidem 5 mg Zolpidem 10 mg Halcion 0.25 mg	3 weeks	One patient receiving Halcion withdrew because of nightmares, agitation, and sense of "imminent death." Nightmares: 2 patients receiving zolpidem at 5 mg, 2 patients receiving Halcion, and 3 patients receiving zolpidem at 10 mg. Agitation: 1 patient receiving zolpidem at 5 mg, 3 patients receving zolpidem at 10 mg, and 2 patients receiving Halcion.
Mauri et al. (1993)	Quazepam	Insomniac outpatients	32 33	Quazepam 15 mg Halcion 0.5 mg	8 weeks	After discontinuation, Halcion group only showed increased awakening duration, reduction in total sleep time, reduction in sleep quality (vs. active treatments, not vs. pretreatment). (Ham A) anxiety reduction at week 1 with quazepam and week 2 with Halcion. No significant rebound.

Monti et al. (1994)	Placebo, zolpidem	Insomniac outpatients	8 8 8	Zolpidem 10 mg Halcion 0.5 mg Placebo	27 nights	Subjective change of unclear statistical significance. Daytime Ham A reduction with zolpidem (relative to that at baseline) only. During withdrawal, Halcion worse than placebo (night 1) and zolpidem (nights 1, 2) for total sleep and wake time (EEG). One adverse event for nervousness with zolpidem and Halcion during treatment; one adverse event for anxiety with Halcion during withdrawal. Worsening in nervous, discomfort VAS with Halcion and improvement with zolpidem of unclear statistical significance.
Bliwise et al. (1988)	Placebo	Insomnia	7 7	Halcion 0.5 mg Placebo	3 nights baseline, 9 nights placebo, 35 nights drug/placebo	No increase in morning or evening anxiety measured by POMS. Power of anxiogenic effect estimated to be 0.26.
Adam and Oswald (1988)	Placebo	Insomnia	40 40 40	Halcion 0.5 mg Lormetazepam 2 mg Placebo	15 nights placebo, 25 nights medication, 5 nights placebo	VAS anxiety: 52% increase with Halcion; –25% with placebo, 0.2% with lormetazepam (treatment: $p = 0.004$; no treatment-by-block interaction). Raw anxiety data not shown. Presence of treatment effect, but absence of treatment by-block interaction suggests baseline group differences. In Halcion group, 38% reported bad dreams on the first withdrawal night. Seven subjects on halcion, but no others reported panic attacks. Derealization with Halcion reported.
Kales et al. (1991)	Placebo, temazepam	Insomniac	6 6 6	Halcion 0.5 mg Temazepam 30 mg Placebo	Baseline nights 2–4, drug nights 5–7, withdrawal 2 nights, drugs 2 nights, withdrawal 1 night	Halcion associated with rebound decrease in total sleep time (50–60%) with each episode of administration. Temazepam decreased total sleep time with second episode (39%). Halcion, but not temazepam increased percent REM.
Merlotti et al. (1991)	Duration	Healthy subjects	11	Halcion 0.5 mg	1, 6, or 12 nights of Halcion with 1 week between	Except for percent stage 1 and REM latency, no evidence of tolerance. Rebound insomnia (reduction in sleep efficiency time asleep/time in bed x100). Not associated with duration. Rebound evident in subjects with lower efficiency at baseline and great drug benefit.

Source	Type	Population	Number of Subjects	Drug and Dose	Duration	Outcome/Comments
Roehrs et al. (1992)	Taper rate	Insomniac with normal sleep;	7	Halcion 0.5 mg	Abrupt vs. taper	Taper substantially reduces rebound insomnia.
		insomniac without normal sleep.	7			
		Bedtime	7			
Hajak et al. (1994)	FNZ/Placebo	See other adverse reations				
Saletu et al. (1994)	Quazepam	Insomniac	45	Halcion 0.25–0.5 mg Quazepam 15–30 mg	Placebo 1 week, drug 4 weeks, placebo 2 weeks	Anxiety improved with both drugs. Rebound insomnia in Halcion group only, and only on first night.

NOTE: VAS, Visual Analog Scale; SWS, slow wave sleep; EEG = electroencephelogram; POMS = Profile of Mood States.

TABLE B-7 IOM Summary of Studies Investigating Possible Unique Ataxic or Dyscoordination Effects of Halcion

Source	Type	Population	Number of Subjects	Drug and Dose	Duration	Outcome/Comments
Open Label						
Gales and Menard (1995)	Matched group	Hospitalized elderly ± falls	100 with fails	Mixed	17 mo	Benzodiazepines received by more falling patients (40% vs. 20%; odds ratio, 2.7). Falls more common in patients with three or more psychoactive medication.
			100 without falls			
Cooper (1994)	Case-control	Elderly	44	No drug or receiving psychotropic drugs	6 mo	Number of subjects was too small to draw inferences about specific drugs.
			38			
Double-Blind						
Fleming et al.	Zopiclone	Insomniacs	24	Zopiclone 7.5 mg	21 days	In first week of withdrawal, psychomotor behavior worse in Halcion group on the basis of subjective report.
	Halcion 0.25 mg		24			
Chaudoir et al.	Zopiclone	Insomniacs	19	Zopiclone 7.5 mg	2 weeks	Improved alertness in a.m. and improved sense of balance and coordination.
	Halcion 0.25 mg		19			
Robin et al. (1996)	Placebo	Elderly Young	9	Halcion 0.375 mg	Single dose	Increased body sway with Halcion in elderly subjects. No greater magnitude of change in the elderly. Rather, elderly start with greater baseline body sway. More loss of balance ("fall") in elderly subjects receiving Halcion, also predicted by baseline body sway.
	Placebo		9			

SOURCES: Cooper (1994) and Robin et al. (1996).

TABLE B-8 IOM Summary of Studies Investigating Possible Unique Disinhibiting Effects of Halcion

Source	Type	Population	Number of Subjects	Drug and Dose	Duration	Outcome and Comments
Monti et al. (1994)	Placebo, zolpidem	Insomniac outpatient	8	Zolpidem 10 mg	27 nights	One episode of aggressiveness only for a subject receiving Halcion
8	Halcion 0.5 mg					
8	Placebo					
Adam and Oswald (1988)	Placebo	Insomnia	40	Halcion 0.5 mg	15 nights of placebo, 25 nights medication, 5 nights placebo	One subject irritable, bragging, sarcastic
40	Lormetazepam 2 mg					
40	Placebo					

TABLE B-9 IOM Summary of Studies Investigating Possible Unique Psychotigenic, Confusion, or Dissociation-Generating Effects of Halcion

Source	Type	Population	Number of Subjects	Drug and Dose	Duration	Outcome/Comments
Greenblatt et al. (1989)	Placebo, flurazepam, temazepam	Bedtime	16 12 13 11	Placebo Flurazepam 15 mg Temazepam 15 mg Halcion 0.25 mg	Single dose	"Spacey." Halcion ≥ temazepam > flurazepam = placebo. Halcion effects were at 6 h. Highly correlated with sedation.
Pinnock et al. (1985)	Placebo, diazepam	Medical	28 30 29	Placebo Diazepam 10 mg Halcion 0.25 mg	Single dose	Letter search. No significant difference at 6 h.
Elie et al. (1990)	Zopiclone	Elderly insomniacs	44	Halcion 0.125 mg Halcion 0.25 mg Zopiclone 5 mg Zopiclone 7.5 mg	3 weeks	Nightmares in 5 patients not associated with treatment.
Bonnet and Arand	Placebo, dose	Elderly insomniac (within subject)	12	Placebo Halcion 0.125 mg Halcion 0.25 mg	4-day episodes	Subjects receiving Halcion at 0.25 mg were initially worse on a.m. addition and vigilance. Better than placebocebo after 4 days.
Roger et al. (1993)	Zolpidem	Elderly insomniac inpatients	70 74 77	Zolpidem 5 mg Zolpidem 10 mg Halcion 0.25 mg	3 weeks	
Wehli et al. (1985)	Placebo, midazolam	Trainee pilots	8 8 8	Placebo Midazolam 15 mg Halcion 0.5 mg	Single dose, tested 7 h later	More pilot errors with Halcion relative to placebo and midazolam (flight simulator).
Adam and Oswald (1988)	Placebo	Insomnia	40 40 40	Halcion 0.5 mg Lormetazepam 2 mg Placebo	15 nights of placebo, 25 nights of medication, 5 nights placebo	Three patients developed paranoid psychoses with visual hallucinations.

TABLE B-10 IOM Summary of Studies Investigating Other Possible Adverse Events Related to Halcion

Source	Type	Population	Number of Subjects	Drug and Dose	Duration	Outcome/Comments
Fleming et al. (1990)	Zopiclone	Insomniacs	24 24	Zopiclone 7.5 mg Halcion 0.25 mg	21 days	Early termination: 10/24 (42%) Halcion, 2/24 (8%) zopiclone, chi-square = 5.4, $p < 0.02$. Subjects receiving zopiclone had taste changes. Moderate to severe adverse effects: 18% zopiclone, 42% Halcion ($p < 0.05$). Combined dropouts from lack of efficacy and side effects.
Thorpy et al. (1991)	Single blind	Narcoleptics	10	Halcion 0.25 mg		No unexpected side effects.
Roehrs et al. (1992)	Taper rate	Insomniacs with normal sleep; Insomniacs without normal sleep; Bedtime	7 7 7	Halcion 0.5 mg		Bedtime did not use prn to restore sleep during withdrawal. Insomniacs did use prn, Halcion, and placebo, although not differently.
Roger et al. (1993)	Zolpidem	Elderly insomniac inpatient	70 74 77	Zolpidem 5 mg Zolpidem 10 mg Halcion 0.25 mg	3 weeks	Rate of AE (CNS AEs): 16% (10%) zolpidem 5 mg, 11% (11%) zolpidem 10 mg, 21% (16%) Halcion. One patient withdrew for tremor and malaise. Total withdrawal: 1 zolpidem 5 mg, 1 zolpidem 10 mg, 5 Halcion (1 inefficacy, 2 for AEs, and 2 for "other reasons").
Mauri et al. (1993)	Quazepam	Insomniac outpatients	32 33	Quazepam 15 mg Halcion 0.5 mg	8 weeks	No unexpected effects.
Jacobsen et al. (1994)	Placebo	Surgery for breast cancer	49 51	Halcion 0.125 mg increased to 0.25 mg prn. Placebo to 2 caps prn.	3 nights	Halcion effective, less likely increased to 0.25 mg (2 caps) then placebo (7/49 vs. 15/51). Halcion prescription associated with less opiate (acetaminophen + oxycodone) use. No adverse reaction significantly more frequent in Halcion group.

Hajak et al. (1994)	Flunitrazepam Zopiclone Placebo	Insomnia outpatient	307 612 290 298	Halcion 0.25 mg Zopiclone 7.5 mg Flunitrazepam 1 mg Placebo	28 nights	Premature termination: 12.6% zopiclone (15 AEs; 5 metal taste), 12.4% Halcion (2 AEs), 10.3% flunitrazepam (6 AEs), 12.8% placebo (3 AEs). Twelve to 14% of each group on other CNS dropped out prior to study. "Total response," zopiclone one better than total placebo and flunitrazepam. Halcion not better than placebo and all better than baseline. Response was not defined. "Total response" during withdrawal, zopiclone better than Halcion and placebo. No other differences. No clear rebound. Daytime well-being, zopiclone reported as only drug significantly better than placebo, statistic not reported. Of 9 checklist items: no significant differences in spontaneously reported items, metallic taste associated with zopiclone (6.7% zopiclone, 2.0% Halcion, 0.3% flunitrazepam, 0.7% placebo).
Wehli et al. (1985)		SwissAir pilots	36 34 32	Placebo Midazolam 15 mg Halcion 0.5 mg	1 night tested 7 h after dose	Side effects: no difference for moderate or severe. Mild: halcion > midazolam = placebo (vertigo, mild confusion, drowsiness, fatigue). Total side effects: 72% Halcion, 21% midazolam, 19% placebo.
Adam and Oswald (1988)	Placebo, active drug	Insomnia	40 40 40	Halcion 0.5 mg Lormetazepam 2 mg Placebo	15 nights of placebo, 25 nights medication, 5 nights of placebo	Global ratings: very bad, 16 in Halcion group, 4 in lormetazepam group, 0 in placebo group; bad, 6 in halcion group, 2 in lormetazepam group, 4 in placebo group; neutral, 2 in Halcion group, 6 in lormetazepam group, 25 in placebo group; good, 13 in Halcion group, 14 in lormetazepam group, 9 in placebo group; very good, 3 in Halcion group, 14 in lormetazepam group, 2 in placebo group. Hypothesize accumulation of metabolite for toxic reactions. Only known metabolite is OH-triazolam. Distress-related ratings increased after 10 days of treatment.
Kamien et al. (1995)	Placebo	Bedtime	50	Halcion 0.32 mg/70 kg	Drug discrimination training plus test.	Thirty-one subjects able to discriminate placebo from Halcion; 19 unable to do this due to high placebo response.

Source	Type	Population	Number of Subjects	Drug and Dose	Duration	Outcome/Comments
Kitunen (1994)	Multiple	Bedtime	12	Zopiclone 7.5 mg Halcion 0.25 mg Placebo Alcohol 0.8 g/kg Zopiclone + alcohol Halcion + alcohol		Alcohol comparably potentiates motor incoordination, vestibular impairment; subjective inebriation with zopiclone and Halcion.
Derry et al. (1995)	Placebo	Bedtime, obese subjects	12 12	Halcion 0.5 mg Halcion 0.5 mg	Two doses separated by 1 week.	Small increase in half-life in obese subjects (31.6 vs. 3.83 h). Increases in sedative and amnestic effects with second Halcion exposure.
Kroboth et al. (1995)	Placebo	Bedtime, Study 1: obese subjects	12	Halcion 0.5 mg	Two doses separated by 6 days.	In all three studies, there were incremental increases in observed sedation and impairment in performance on a continuous performance test of attention suggestive of potentiated effects (learning?) with repeated dosing.
		Study 2: bedtime	11	Halcion 0.2, 0.25 mg	Three doses of 0.25 mg followed by a test dose of 0.2 mg all separated by 6 days.	
		Study 3: Bedtime	?	Halcion 0, 0.5, 4 mg	Balanced crossover of placebo and 0.5 and 0.4 mg twice on test days all separated by 6 days.	
Mendelson et al. (1996)						Review of AEs, highest rate with lorazepam most mild. Halcion not distinctive.
Mendelson et al. (1996)						Same review of AEs. Halcion was the only BZ not associated with increased falls.
Faure et al. (1996)	Flunitrazepam, placebo			Flunitrazepam 0.5, 2 mg Halcion 0.25, 0.5 mg	Single dose	Flunitrazepam causes greater euphoria.
Martinez-Cano et al. (1996)						Halcion more commonly used than several other BZs by individuals dependent on doses at high end of clinical spectrum.

NOTE: CNS, central nervous system; AE, adverse event; SE, side effect; BZ, benzodiazepine.

C

Glossary

Adverse event	Any untoward medical occurrence in a patient or a subject is a clinical investigation administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. (See Serious event)
Adverse drug reaction	In the preapproval clinical experience with a new medicinal product or its new usages, particularly bemuse the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose. The phrase related to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, that is, the relationship cannot be ruled out.
Benefit/risk ratio	The ratio of benefit to risk in the use of a drug; a means of expressing a judgment concerning the role of the drug in the practice of medicine, based on efficacy and safety data along with consideration of misuse potential, severity and prognosis of the disease, etc. The concept may be applied to a single drug or in comparisons between two or more drugs used for the same indication.
Bioavailability	The rate and extent of absorption of a drug from a dosage form as determined by its concentration-time curve in the systemic circulation or by its excretion in urine.

Compliance	Faithful adherence by the patient to the prescriber's instructions.
Dosage form	The form of the completed pharmaceutical product, for example, a tablet, capsule, elixir, suppository.
Drug	Any substance in a pharmaceutical product that is used to modify or explore physiological systems or pathological states for the benefit of the recipient.
Drug formulation	The composition of a dosage form, including the characteristics of its raw materials and the operations required to process it.
Drug utilization	The marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social, and economic consequences.
Efficacy	The ability of a drug to produce the purported effect as determined by scientific methods.
Exclusion Criterion	A standard or rule for judging the shutting out or disconnection from the main part.
Pharmaceutical product	A dosage form containing one or more drugs, along with other substances included during the manufacturing process.
Serious event	Any adverse event that is fatal, life-threatening, permanently or significantly disabling, requires or prolongs hospitalization, congenital anomaly, or requires intervention to prevent permanent impairment or damage.
Therapeutic equivalence	Pharmaceutical products that, when administered to the same individuals in the same regimen, will provide essential the same efficacy and toxicity.
Tolerance	The pharmacological term indicating a waning effect with the continuing use of the same dose of a drug. The ability to endure or be less responsive to a stimulus, especially over a period of continued exposure.

D

Acronyms

ANOVA	analysis of variance
CDER	Center for Drug Evaluation and Research (FDA)
CNS	central nervous system
CPMP	Committee on Proprietary Medicinal Products (European Union)
CSM	Committee on the Safety of Medicines (United Kingdom)
EEG	electroencephalogram
EMIC	Evaluation of Medications for Insomnia in Canada
FDA	U.S. Food and Drug Administration
IOM	Institute of Medicine
ISS	Integrated Summary of Safety
MCA	Medicines Control Agency (United Kingdom)
MHPG	methoxyhydroxyphenylglycol
NDA	New Drug Application
NDTI	National Disease and Therapeutic Index
NPA	National Prescription Audit
PAAC	Psychopharmacologic Agents Advisory Committee
PDAC	Psychopharmacologic Drugs Advisory Committee
PLMS	periodic limb movements of sleep
REM	rapid eye movement
SPECT	single photon emission computerized tomography
SRS	Spontaneous Reporting System
VAMP	Value Added Medicinal Products Research

E

Resources Reviewed by the Committee

Title	Contents	Source
General background		
FDA Task Force Report		FDA
Public Citizen Petition	The Public Citizen Petition to Remove Halcion from the Market	Public Citizen
Upjohn Response to Petition	Upjohn's Response to the Public Citizen Petition	FDA
IOM Study on Sleep	Basic Sleep Research, 1990	IOM
IOM Study on Sleeping Pills	Sleeping Pills, Insomnia, and Medical Practice, 1979	IOM
Miscellaneous information provided by Upjohn	Sales data, patent data, and information on generic compounds	Upjohn
Miscellaneous information provided by FDA	Summary basis of approval, labeling information, information on generic compounds, and guidelines for the clinical evaluation of hypnotic drugs	FDA
Published literature		
IOM search	Articles concerning Halcion	IOM
Literature on Halcion		FDA

Title	Contents	Source
Upjohn literature search	Literature search identifying later studies	Upjohn
Literature provided by Public Citizen	All cited references, including Kales (1996), A Reassessment of Triazolam and Conflicting Scientific Expertise in British and American Medicines Control	Public Citizen
International data		
Canadian product monograph for Halcion		Canada
Evaluations of Medications for Insomnia in Canada (EMIC)		Upjohn
Medicines Control Agency letter	Letter from the Licensing Authority to Upjohn, 1992	Public Citizen
Report of the Committee on Proprietary Medicinal Products		Upjohn
Report of the Committee on the Safety of Medicines		Public Citizen
UK Panel Report	Report of the Panel of Persons Appointed	United Kingdom
VAMP Information	Information on the General Practice Research Database (previously known as the Value Added Medical Practice [VAMP] Database)	Upjohn
Premarketing clinical trial data (from the New Drug Application)		
Preapproval reviews		FDA
Premarketing clinical trials		FDA
Report of the database remake		FDA

Title	Contents	Source
Upjohn summaries of non-pivotal clinical trials		FDA
Efficacy protocols	Protocols for 20 studies with lower dosages reviewed for efficacy	Upjohn
Information from FDA Psychopharmacologic Drugs Advisory Committee meetings		
Transcript of the PDAC meetings: 1977, 1989, 1992		FDA
FDA mailing to 1989 and 1992 PDACS	FDA mailing to 1989 PDAC	Upjohn
Brochures with summary information prepared by Upjohn for the PDAC meetings, 1989 and 1992	Upjohn brochure prepared for the PDAC 1989	Upjohn
Integrated Summaries of Safety and Efficacy		
Integrated safety study	Integrated studies' of safety	Upjohn
Integrated efficacy study	Integrated studies of effectiveness	Upjohn
Integrated dropout listings	Integrated summary of safety dropout listings	Upjohn
Statistical reviews		FDA
Epidemiological reviews		FDA
Pharmocokinetic and pharmacodynamic data		Upjohn
Postmarketing surveillance data		
Annual Adverse Event Reports		FDA
Postmarketing protocols: 1994-1996	Protocols, M/2100/0235, M/2100/0366, and M/2100/0373	FDA
Upjohn Annual Reports to FDA, 1990-1997		FDA

Title	Contents	Source
Spontaneous report data		
FDA memoranda	FDA memoranda provided by Diane Wysowski	FDA
SRS data	Data on the FDA Spontaneous Reporting System	FDA
Use, sales, and prescription data		
IMS statistics	IMS statistics regarding reasons for prescriptions, high dose usage, and chronic usage	Upjohn
Use statistics	Use statistics from IMS and health maintenance organization data regarding reasons for prescriptions, high dose usage, and chronic usage	FDA
Sales information	Number of packages sold in the United States, 1982-1997	Upjohn

F

Consent to Disclosure

For the purposes of this study, Pharmacia and Upjohn, Inc., agreed to disclose all pertinent information to the IOM Committee. A copy of their consent agreement follows.

CONSENT TO DISCLOSURE

On behalf of Pharmacia & Upjohn Company, I hereby consent to disclosure of the following documents by the United States Food and Drug Administration (FDA) to the Institute of Medicine at the National Academy of Science (IOM) for the purpose of performing an independent review of the data. I understand that the documents as disclosed to IOM may contain trade secrets and confidential commercial or financial information within the meaning of 18 U.S.C. 1905, 21 U.S.C. 331(j) and 5 U.S.C. 552(b)(4) and agree to hold FDA harmless for any injury caused by FDA's disclosing the documents to IOM. IOM is authorized to include any portion of any document so disclosed, as well as any description or summary of any document so disclosed, in a report to be made available to the public by IOM at the conclusion of the independent review.

Documents to be disclosed:

NDA Clinical Trial Data

1. FDA's medical reviews of the NDA
2. Complete study reports (Upjohn) for the three pivotal premarketing studies (6024, 6045, 6041)
3. Complete study reports (Upjohn) for the three major postmarketing studies (0366, 0373, 0235)
4. Case report forms/line listings for the clinical trials (i.e., new data)

1992 Re-Analysis

5. FDA Report on the Database remake and re-analysis of 1992

Annual Reports

6. The last 10 annual reports for the NDA

1996 Task Force Report

7. The task force report (including Dr. Williams' regulatory history of the NDA)

Statistics & Epidemiology

8. All reports on Halcion from FDA Office of Epidemiology & Biostatistics

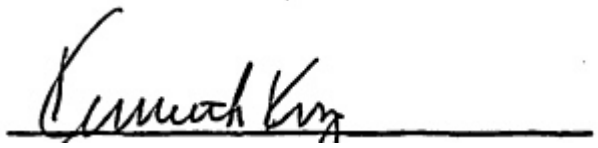
Medical Literature

9. The medical literature cited in the task force report

Other

10. Transcripts and minutes of the three advisory committee meetings on the drug
11. FDA's Biopharmaceutic reviews of the NDA

We understand that physicians' and patients' names will not be disclosed to the public.



Kenneth F. King, Ph.D.
Vice President, Regulatory Affairs
Pharmacia & Upjohn Company

Date

G

Committee and Staff Biographies

COMMITTEE

WILLIAM E. BUNNEY, JR., is Distinguished Professor and Della Martin Chair of Psychiatry in the Department of Psychiatry, College of Medicine, University of California, Irvine. He received his M.D. from the University of Pennsylvania Medical School and took his residency at Yale School of Medicine. His previous positions have included Chief, Biological Psychiatry Branch, National Institute of Mental Health (NIMH), and Director, Division of Narcotic Addiction and Drug Abuse, NIMH. He has been past President of the American College of Neuropsychopharmacology and the Collegium Internationale Neuropsychopharmacologicum (CINP). Dr. Bunney is a member of the Institute of Medicine (IOM) of the National Academy of Sciences. He served for a number of years as the Cochair of an IOM division previously named the Division of Biobehavioral Sciences and Mental Disorders. He has been a past member of the Scientific Advisory Council of NIMH and currently. is on the Scientific Advisory Boards for National Alliance for Research on Schizophrenia and Depression (NARSAD) and the NDMA Associations. Dr. Bunney serves on 13 editorial boards and has published more than 340 scientific articles.

DANIEL L. AZARNOFF is President of D.L. Azarnoff Associates. He brings to the group more than 20 years of academic experience in research and clinical medicine, plus 8 years as Past President of Research and Development for the Searle Pharmaceutical Company and 10 years as a consultant in drug development. Before joining Searle he was Distinguished Professor of Medicine and Pharmacology and Director of the Clinical Pharmacology Toxicology Center at the University of Kansas Medical Center, a job he held for 16 years. He has published more than 175 articles in scientific and medical journals, Dr. Azarnoff is a member of the Institute of Medicine and a fellow of the American Association of Pharmaceutical Scientists, New York Academy of Sciences, American

Association for the Advancement of Science, and the American College of Physicians. He

maintains a teaching appointment at the University of Kansas School of Medicine. Dr. Azarnoff is on the editorial board of several journals and has been on committees within the U.S. Food and Drug Administration, World Health Organization, American Medical Association, National Academy of Sciences, Institute of Medicine, and National Institutes of Health, advising them on drags and drag development.

BYRON WM. BROWN, JR., is Professor and Head of the Division of Biostatistics in the Department of Health Research and Policy, School of Medicine, Stanford University. He received a Ph.D. degree in 1959 in biostatistics from the University of Minnesota, where he served on the faculty from 1959 to 1968. Leaving the position there as Division Chief in Biometry to join the faculty at Stanford University, he has served as Division Head of Biostatistics since 1968 and served as Chairman of the Department of Health Research and Policy from 1988 to 1996. His special interests are in the design and analysis of clinical trials, in biological assay statistical methodology, and in the role and methodology of statistics in health enhancement and health policy. He has served on the Veterans Administration Cooperative Studies Evaluation Committee and the Clinical Cancer Investigations Review Committee and as a consultant to the Federal Trade Commission, the U.S. Food and Drug Administration, the INCAP, numerous clinical trial advisory boards and review committees, and government and private industry. He is Past President of the Society for Controlled Clinical Trials and the Western Region of the Biometrics Society and a Fellow of the American Statistical Association and the American Heart Association. He is an elected member of the Institute of Medicine and the International Institute of Statistics.

ROBERT CANCRO obtained his M.D. degree in 1955 from State University of New York, Downstate Medical Center, and his Doctor of Medical Science degree in 1962 from the same institution. His more recent academic activities have involved serving as Professor and Chair of the Department of Psychiatry at the New York University Medical Center since 1976. He is Director of the Nathan Kline Institute for Psychiatric Research, which is a New York State-funded research institute. His major professional interest has been at the brain-behavior interface in psychoses and in particular the schizophrenic disorders. This interest has led to a deep involvement with psychoactive medications, including their use and misuse.

ROBERT D. GIBBONS received his Ph.D. from the University of Chicago in 1981. He is currently a Professor of Biostatistics at the University of Illinois at Chicago. In 1985 he received a Young Scientist Award from the Office of Naval Research, which funded his statistical research in the areas of the analysis of multivariate binary data and the analysis of longitudinal data. Dr. Gibbons has also received additional grant support from the National Institutes of Health and the John D. and Catherine T. MacArthur Foundation. He currently has a Research Scientist Award from the National Institutes of Health that provides full-time. support for statistical research. Applications of Dr. Gibbons work are widespread in the general areas of mental health and environmental sciences. Dr. Gibbons has authored more than 100 peer-reviewed scientific papers and two books. He is currently working on a new book entitled *Statistical Methods for Detection and Quantification of Environmental Contamination*, which will be published by John Wiley & Sons.

JOHN CHRISTIAN GILLIN received a B.A. degree (magna cure laude) from Harvard College and a M.D. degree from Case-Western Reserve School of Medicine, performed his psychiatric residency at Stanford University, and participated in the Intramural Program of the National Institute of Mental Health. Dr. Gillin is currently Professor of Psychiatry at the University of California, San Diego (UCSD), and is Director of the UCSD Mental Health Clinical Research Center. He is past Director of the Fellowship Program in Psychopharmacology and Psychobiology, (UCSD) Department of Psychiatry, the past President of the Sleep Research Society and Society for Light Therapy and Biological Rhythms, and Chair of the Mental Health Panel, United States Pharmacopeia (1994-present. He is a Board Certified Diplomate of the American Board of Neurology and Psychiatry and he currently serves on the Board of Directors of the American Sleep Disorders Association. Dr. Gillin was a member of the Institute of Medicine's Steering Committee, Study on the Appropriate Use of Hypnotic Agents; the National Academy of Sciences Health Systems Panel of the Strategic Technologies for the Army (STAR); the National Institutes of Health (NIH)-NIMH National Consensus Development Conference on Drugs and Insomnia: The Use of Medications to Promote Sleep; the Surgeon General's Initiative on Insomnia and Sleep Disorders (Project Sleep) and the Advisory Board of the National Center for Sleep Disorders Research, NIH. Dr. Gillin is on numerous editorial boards of prestigious medical journals.

SANDRAL HULLETT is Executive Director of West Alabama Health Services, a community health center located in rural west Alabama. She has a bachelor's degree from Alabama A&M University in Normal, Alabama, a medical degree from the Medical College of Pennsylvania, Philadelphia, and a master's degree in public health from the University of Alabama at Birmingham. Since completing a residency in family practice and fulfilling a National Health Services Corp. obligation, Dr. Hullett developed an interest in rural health care, including health care planning and delivery to the underserved, underinsured, and poor in rural areas. Dr. Hullett is a member of the Board of Trustees of the University of Alabama System and has been appointed a member of the Practicing Physicians Advisory Council of the U.S. Department of Health and Human Services. Dr. Hullett is a member of the Institute of Medicine and the Alabama Health Care Reform Task Force.

KEITH F. KILLAM, Professor Emeritus, is the Founding Chair of the Department of Pharmacology and Toxicology at the University of California, Davis, and has previously served as President of the American Society of Pharmacology and Experimental Therapeutics, President of the American College of Neuropsychopharmacology, President of the College on Problems of Drug Dependence, an adviser on President John F. Kennedy's Scientific Board, and a member of numerous Study Sections of the National Institutes of Health (NIH). Two of his NIH-funded active programs are (1) the study of the interaction of drug abuse and AIDS and (2) the study of opioid receptors on immune cells. Both grants involve important areas of research whose continued progress are in the interest of the public.

JOHN H. KRYSTAL is Associate Professor of Psychiatry at Yale University and Director of the Division of Cognitive and Clinical Neuroscience at the Abraham Ribicoff Research Facilities, Connecticut Mental Health Center. His research has covered aspects of the

neurobiology and psychopharmacology of psychiatric and substance abuse disorders, with a particular focus on alcoholism and schizophrenia. He graduated from the University of Chicago and completed medical school and psychiatry residency training at Yale University. Since joining the faculty of the Yale Department of Psychiatry in 1988, his work has highlighted the human psychopharmacology of drugs acting at glutamate receptors. This work has employed drugs acting at NMDA receptors and the strychnine-insensitive glycine site as probes of altered receptor sensitivity in pathological conditions. It has evaluated ketamine in a model psychosis, including the study of the capacity of drugs to block the effects of ketamine in humans. His ketamine research, in turn, stimulated an interest in the role of amino acid neurotransmission in the function of the frontal cortex. To this end, he recently initiated studies employing functional magnetic resonance imaging, magnetic resonance spectroscopy, and SPECT neuroreceptor imaging to better characterize cortical pathology associated with psychiatric and substance abuse disorders.

DAVID J. KUPFER, Thomas Detre Professor and Chair of the Department of Psychiatry and · Professor of Neuroscience at the University of Pittsburgh School of Medicine. He received his bachelor's (magna cure laude) and M.D. degrees from Yale University. Following completion of an internship, Dr. Kupfer continued his postgraduate clinical and research training at the Yale New Haven Hospital and at the National Institute of Mental Health (NIMH). In 1969 he was appointed an Assistant Professor of Psychiatry at Yale University School of Medicine. Dr. Kupfer joined the faculty at the University of Pittsburgh in 1973 as an Associate Professor of Psychiatry and Director of Research and Research Training at Western Psychiatric Institute and Clinic. He was promoted to Professor of Psychiatry in 1975 and became Chair of the department in 1983. In 1994 he was named the Thomas Detre Chair in Psychiatry. For more than 20 years Dr. Kupfer's research has focused primarily on the conceptualization, diagnosis, and treatment of mood disorders. He has written more than 600 articles, books, and book chapters that examine the use of medication in recurrent depression, the causes of depression, and the relationship between biological rhythm, sleep and depression. In recognition of his contributions to the field, Dr. Kupfer has been the recipient of numerous awards and honors. He was elected to the Institute of Medicine of the National Academy of Sciences in 1990.

PAUL D. STOLLEY is Professor and Chair of the Department of Epidemiology and Preventive Medicine at the University of Maryland at Baltimore School of Medicine. Dr. Stolley is an epidemiologist and internist who trained at the Epidemic Intelligence Service of the Centers for Disease Control and Prevention and the Johns Hopkins School of Hygiene and Public Health, where he has also joined the faculty in the Department of Epidemiology. He then founded and led the Clinical Epidemiology Unit at the University of Pennsylvania, where he served as the Herbert Rorer Professor of Medicine. Dr. Stolley has had a long interest and experience in the investigation of obscure illnesses and epidemics: asthma mortality in Europe, hexachlorophene poisoning in France, and Legionnaires' disease and the eosinophilia-myalgia syndrome in the United States. He is a member of the Institute of Medicine of the National Academy of Sciences and is past President of the American Epidemiological Society, the American College of Epidemiology, and the Society of Epidemiology Research. Dr. Stolley's research interests include epidemiology, public health, stroke, minority health, uterine fibroid

growth, and violence. His current research includes studies on repeat victims of violence, women's health issues, and the epidemiology of adverse drug reactions.

IOM STAFF

ANDREW M. POPE is Senior Staff Officer and Study Director in the Institute of Medicine's Division of Health Sciences Policy. With expertise in physiology, toxicology, and epidemiology, his primary interests focus on the environmental and occupational influences on human health. As a Research Fellow in the Division of Pharmacology and Toxicology at the U.S. Food and Drug Administration, Dr. Pope's research focused on the biochemical, neuroendocrine, and reproductive effects of various environmental substances on food-producing animals. During his tenure at the National Academy of Sciences and since 1989 at the Institute of Medicine, Dr. Pope has directed and edited numerous reports on environmental and occupational issues; topics include injury control, disability prevention, biologic markers, neurotoxicology, indoor allergens, and the inclusion of environmental health content in medical and nursing school curricula.

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