Antihistamines and Driving-Related Behavior

A Review of the Evidence for Impairment

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16. Abstract

A review of the scientific literature concerning the effects of antihistamines on driving-related skills was conducted. After reviewing all pertinent publications from 1998 and earlier, a total of 130 publications were found to meet criteria for inclusion in the data summaries. A data base was created with study results being indexed, and summarized, by specific drug, dose, dosing schedule (i.e., single versus repeated) and H1-antagonist generation as well as by behavioral area or subjective measure. For each H1-antagonist generation, five drugs were evaluated: chlorpheniramine, clemastine, diphenhydramine, hydroxyzine and tripolidine for the 1st-generation, and astemizole, cetirizine, fexofenadine, loratadine and terfenadine for the 2nd-generation. It was concluded that:

1. There is some slight, but ambiguous, evidence from epidemiological studies of a connection between antihistamine use and traffic collision rates. However, these studies were done primarily when use of only 1st-generation (but not 2nd- generation) antihistamines was prevalent; thus, more study is needed.
2. There is overwhelming evidence from the experimental literature that the 1st-generation antihistamines produce objective signs of skills performance impairment as well as subjective symptoms of sedation.
3. While 2nd-generation antihistamines represent a major triumph for the pharmaceutical industry in reducing potential side effects, there still remains some evidence that all antihistamines, even the 2nd- generation drugs, may cause sedation and objective skills impairment at least in some cases and for some individuals.
4. Within both the 1st- and 2nd-generation antihistamine groupings, there is considerable variation in objective evidence of impairment and in subjective effects such as sedation. Thus, there clearly are drugs that are to be preferred for use to avoid side effects such as sedation and driving-related performance impairment.
5. Methodologically, it is apparent that among the many diverse techniques for investigating driving-related impairment, some methods and behavioral domains are more sensitive to the effects of antihistamines. Future studies of antihistamines, therefore, must utilize the most methodologically-sound techniques so as to permit a better comparison between different drugs.

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ANTIHISTAMINES AND DRIVING-RELATED BEHAVIOR: A REVIEW OF THE EVIDENCE FOR IMPAIRMENT BY FIRST- VERSUS SECOND-GENERATION H_1-ANTAGONISTS

Herbert Moskowitz, Ph.D. and Candace Jeavons Wilkinson, Ph.D.

1. INTRODUCTION

1.1 Statement of The Problem

The single largest contributing factor in fatal motor vehicle crashes in the United States is alcohol-induced impairment (AMA Council on Scientific Affairs, 1986). While this has been the case for many years, there also has been an increasing awareness of the traffic safety risks due to the behavioral toxicity of drugs other than alcohol. These include not only illicit drugs, such as cocaine and marijuana, but also medicinal drugs available by prescription or over the counter. In particular, the widespread use of antihistamines (i.e., histamine H_1-receptor antagonists, or H_1-antagonists for short) presents a particular focus for concern since the 1^{st}-generation H_1-antagonists are well recognized for often causing sedation and central nervous system (CNS) dysfunction which can jeopardize safe driving. Moreover, these drugs also have additive effects with alcohol and other CNS depressants. An awareness of such safety risks actually was known more than 50 years ago with the initial introduction of clinically-useful H_1-antagonists. For example, in the same year that it received marketing approval by the Food and Drug Administration (FDA), 1946, diphenhydramine (Benadryl) was implicated as a contributing cause of a workplace accident involving impaired driving of a platform cargo truck (Slater & Francis, 1946). And more recently, a study of the association of 3,394 work-related injuries and prior usage of medication (as determined from actual pharmacy records) found a statistically significantly increased risk of injury (odds ratio = 1.5) among users of sedating antihistamines (Gilmore et al., 1996).

Currently, there are more than 60 antihistamines available for oral administration (Maibach, 1988) and many of these are freely available without prescription (i.e., over-the-counter). Commonly, antihistamines are the primary active ingredients in the myriad of cold and flu preparations. Antihistamines also are used individually as 1^{st}-line treatment for the prevalent allergic conditions of rhinitis and chronic urticaria. Other treatment indications for these H_1-antagonists include motion sickness, vertigo associated with Meniere's disease, vascular headaches, and tremors of Parkinsonism. These drugs also are used for their antipruritic (i.e., for itching), antiemetic (i.e., for nausea), antitussive (i.e., for cough), anxiolytic (i.e., for anxiety) and sedative effects (i.e., for insomnia). Such widespread use underscores the increasing scope of the potential safety risks associated with their use by the driving population.

Notably, most states have enacted laws which prohibit driving under the influence of any drug that impairs driving (U.S. DOT, 1996); this, of course, would include sedating antihistamines that disrupt alertness, perception and performance. At the federal level, recent reports have focused on safety standards relating to the use of antihistamines both by workers in the transportation industry as well as by the driving public (cf. Office of the Assistant Secretary for Transportation Policy, Office of Environment, Energy and Safety, 1998). In brief, there have been increasing

traffic safety concerns about the possible detrimental effects of medicinal drugs including the widely used antihistamines. But what evidence is there? The answer requires an examination of the problem from several perspectives. As suggested in an early review of alcohol, drugs and traffic safety (Smiley & Brookhuis, 1987; p. 83), "epidemiological studies, laboratory tests of driving-related skills, simulator studies and on-road studies each provide a vital part of the evidence establishing the role of any given substance to traffic safety." The current review will focus on each of these perspectives, but will only provide a brief summary below of the epidemiological data and its limitations.

1.2 Limitations of Epidemiological Data

The scientific literature regarding impairment of driving-related skills performance by antihistamines consists primarily of experimental studies. These are studies where subjects or patients are administered known doses of antihistamines and then their performance is compared with that under placebo treatment or under comparable antihistamines. The emphasis on experimental studies in this report is due to the paucity of epidemiological studies and the difficulties in interpreting their results.

One of the earliest epidemiological studies of drugs and traffic safety was performed by Skegg, et al. (1979). The authors reviewed the prescription history for more than 43,000 patients over a two-year period. During that period, 57 people in the sample were injured or killed while driving either an automobile, motorcycle or bicycle. For these victims, the drugs prescribed in the preceding three months were compared with those in 1,425 control patients who were selected from the overall sample population as having the same gender, age and prescribing physician. Three of the crash-involved drivers, or 5.3% of the crash group, had been prescribed an antihistamine. Forty-three control drivers, or 3.0% of the control group, had received an antihistamine prescription. The relative risk is 1.8, but obviously this is not significant since it is based on only three injured drivers. It should be noted that in this study, tranquilizers and sedatives as a class showed a statistically significant, relative risk of 5.2.

Ray, et al. (1992) performed a similar study examining the relationship between psychoactive drugs and the risk of a motor vehicle injury crash in elderly drivers in a medicaid program. The advantage of using elderly drivers, over age 65, is that objective data were obtained from the Tennessee medicaid program regarding prescription drug use. Only drivers involved in an injury crash were included in the study, because it was believed that collisions involving only property damage are substantially under-reported and therefore would be less reliable. More than 16,000 people were in the study group which reported 495 injury crashes in a four-year period. Considerable information was available, both from the medical records and the drivers license records. The study employed a multiple regression analysis which controlled for many of these factors. The relative risk of involvement in an injury crash was 1.2 for current antihistamine use. The 95% confidence interval ranged from a relative risk of 0.6 to 2.4. Again there appears to be only a trend (i.e., statistically insignificant effect) to suggest that the use of antihistamines actually results in an increased crash rate. As noted, this study examined an elderly population. Whether or not an interaction exists between the effects of antihistamine use and age, however, has not been determined.

In a 1992 study by Terhune, et al., blood samples were collected from 1,882 fatally injured drivers from seven states during fourteen months in1990 and 1991. The prevalence of antihistamines in body fluid samples from these drivers was 0.6%. In order to determine the significance of the presence of antihistamines, since no comparable control group was available, the authors used a culpability/responsibility analysis which relied on expert raters

utilizing police reports of the crash to assign responsibility. Only six drivers had antihistamine present and the responsibility rate was not explicitly stated by the authors, except to indicate that it was not significant.

A 1993 study by Crouch, et al., of 168 fatally injured truck drivers failed to uncover any drivers with an antihistamine present. In contrast, in a study by Warren, et al. (1981) of 768 fatally injured drivers from Ontario, Canada in 1978 to 1979, nine drivers were found to be using antihistamines. A culpability rate analysis indicated a 1.5 culpability rate.

It should be noted that there is considerable difficulty inherent in the attempts to use culpability analysis to compensate for the difficulty of obtaining adequate control groups. Shinar, et al. (1983) compared traffic crash reports by the police with those generated by a university-based investigational team, for example, and found that the police reports frequently omitted important information especially with regard to human factors. In addition, Waller (1982) criticized epidemiological studies of drug effects in driving which relied on culpability/ responsibility analysis because they failed to control for important determinants of driving crash rates such as time and place of collision and characteristics of the drivers. Waller compared studies using culpability analysis with studies utilizing the data of the Grand Rapids alcohol study (Borkenstein, et al., 1964). The Grand Rapids study provided information regarding covariates from both the crash-involved and control groups. This enabled researchers examining the Grand Rapids findings to extract the specific effect of alcohol on crash probability from the influence of variables such as age, gender, drinking practices, etc., which all contribute to an overall crash probability.

It would appear that epidemiological studies involving known populations with verifiable drug use are more likely to produce secure information than epidemiological studies that begin with drivers injured or killed on the road. These latter types of epidemiological studies have no comparable control groups even were we to rush to the scene of crashes, such as was done in the Grand Rapids study. While the Grand Rapids study was able to obtain breath alcohol samples from both crash and control drivers, efforts to obtain blood or urine samples from drivers have been notably unsuccessful. Moreover, even if we had blood samples from both groups, crash and control drivers, interpreting the behavioral implications of plasma drug levels is extremely difficult, as others have already elucidated in detail (e.g., Chesher, 1985).

We typically know the most about drugs detected in fatally injured drivers. However, we also know from studies on alcohol that the probability of being involved in a fatal crash is highly dependent on the blood alcohol concentration (BAC). It is not merely the probability of being involved in a crash that increases with BAC level; but given that you are involved in a crash, there is an additional interacting factor that the probability of death increases with BAC. There is nothing about the studies on antihistamines, however, that would suggest that the magnitude of behavioral effects are comparable with those associated with moderate to higher BAC levels. Thus, the lower magnitude of impairment by the antihistamines would be unlikely to show up in studies of fatal crashes unless the numbers were huge.

We conclude that the epidemiological evidence obtained from studies where 1st-generation antihistamines were commonly used suggests a trend toward some impairment, but not of great magnitude compared with the increased risks associated with alcohol. In summary, given the limitations of epidemiological studies, we believe that experimental studies provide the fundamental method for investigating the direct relationship between a given medication dose and driving efficiency in actual practice. That is, our evaluation of the effects of antihistamines on driving must rest primarily on experimental laboratory studies where we have known dose levels, placebo controls and established experimental response measures. As a background for evaluating such experimental studies of the effects of antihistamines on driving-related performance, a brief description of the clinical pharmacology of the H_1-antagonists is presented next.

1.3 Clinical Pharmacology & Issue of Drug Choice

Although the exact mechanisms of action for the histamine H_1-receptor antagonists remain unknown, the role of histamine as a neurotransmitter is now firmly established. Histaminergic pathways are widespread in the CNS and appear to be related to mechanisms that support alertness and vigilance during the wakeful state and the balance between wakefulness and slow-wave activity during sleep (Nicholson et al. 1985). Histamine, an endogenous substance first recognized in 1927, has strong vasodepressant and smooth muscle stimulant actions (Garrison, 1990). Considerable research since then has elucidated histamine's roles in mediating the immediate allergic response [via H_1-receptors], regulating gastric acid secretion [via H_2-receptors] and possibly functioning as a neurotransmitter [via H_3-receptors] (White, 1990). The focus of the current review is limited to the H_1-receptor antagonists.

The H_1-antagonists bind to peripheral and central H_1-receptors and thereby block or, more accurately, compete with histamine's effects. That is, the effectiveness of the H_1-antagonist medications is related to the relative concentrations of histamine and its antagonist at the receptor site: an adequately high and frequent enough dosage of the drug is required in order to maintain sufficient concentrations to compete with histamine. An effective dose, however, often is associated with deleterious side effects which include, at least for the classical or 1st-generation drugs, sedation and anticholinergic effects such as dry mouth, nose or throat. The sedative side effects of the 1st-generation H_1-antagonists are due to their affinity for central H_1-receptors and their liposolubility which enables them to cross the blood-brain barrier. The anticholinergic and other adverse side effects arise from the 1st-generation H_1-antagonists' affinity for muscarinic anticholinergic, "-adrenergic, and serotonin receptors.

Newer, 2nd-generation H_1-antagonists have been developed in the past decade. Their availability provides allergy patients the choice of new drugs which have little or no side effects such as the sedation and psychomotor impairment often found with the 1st-generation drugs. The 2nd-generation drugs penetrate poorly into the CNS and so are *relatively* non-sedating, in contrast to the 1st-generation drugs which readily penetrate the blood-brain barrier. Also, the newer drugs have little or no affinity for muscarinic cholinergic, "-adrenergic, and serotonin receptors. This is in contrast to the 1st-generation drugs which do possess such activity. These factors may contribute to the relative lack of adverse CNS or peripheral effects by the 2nd-generation drugs (Simons, 1994). Of note, in the 2nd-generation drugs, there appears to some difference in potential side effects associated with the piperidine class (e.g., astemizole, fexofenadine, loratadine, and terfenadine) versus the piperazine class (e.g., cetirizine).

In sum, the pharmacodynamics and side effects profiles of the 2nd-generation H_1-antagonists suggest that these newer drugs offer a safety advantage particularly for patients who drive, pilot

aircraft or operate machinery and must avoid the sedation and impaired performance which are commonly found with the 1st-generation drugs. Prior reviews of the experimental studies which have examined the effects of H_1-antagonists on performance measures from laboratory tests, driving simulators and on-road driving generally have concluded that the 2nd-generation drugs do pose little or no risk to safe driving. The major prior reviews of those findings are summarized below.

1.4 Prior Reviews of H_1-antagonists

Starmer (1985) provided the earliest review of the evidence concerning antihistamines and traffic safety. He concluded that experimental studies found sedation, impaired performance skills and additive effects with alcohol and other CNS-depressant drugs to be prominent within the heterogenous group of 1st-generation H_1-antagonists. He noted, however, that these drugs were seldom identified as causative factors in traffic crashes, possibly due to inadequate reporting. Finally, the several newer, or 2nd-generation H_1-antagonists available for study at that time all appeared to have little CNS effect and so presented less risk of impaired driving.

More recent reviews have included those by Rombaut & Hindmarch (1994), Hindmarch (1995), and Adelsberg (1997). The most comprehensive evaluation, however, is provided by Simons (1994) who reviewed the comparative safety of the 1st- and 2nd-generation H_1-antagonists in terms of CNS function as well as for cardiovascular adverse effects (specifically seen with some of the newer drugs). Simons, as other reviewers, concluded that the 2nd-generation H_1-antagonists are *relatively* devoid of sedation and CNS impairment, and so they clearly do provide a better "benefit-risk ratio" than do the 1st-generation drugs. Nonetheless, most reviewers also noted that the findings for cetirizine, a 2nd-generation drug, were rather mixed, with some reports of sedation and performance impairment on laboratory tasks as well as on actual driving. The prior reviews also emphasized the difficulty in evaluating the safety profiles of a given drug since the doses, tasks and measures across the studies varied widely.

1.5 Focus of Current Review

Over five years have passed since the most comprehensive review of antihistamines' effects was published (Simons, 1994). Thus, the present review was undertaken to provide a current status of the experimental evidence for impairment of driving-related skills by 1st- versus 2nd-generation H_1-antagonists. Importantly, many more studies of the 2nd-generation drugs have been published during this time. Hopefully, these newer studies have employed refined methods and more sensitive measures to detect drug-induced sedation and impairment. Also of note, Simons' (1994) review included approximately 50 controlled studies which compared drugs from the two generations in a single design. However, there are many more studies of the H_1-antagonists if one also considers experiments which only examined drugs from one generation or the other. For example, the 1st-generation H_1-antagonists often are included as a positive control drug in studies of various drugs other than the antihistamines. Also, some study designs test only a single drug, from the 1st- or 2nd-generation, against a placebo control.

The purpose of the current review is to summarize and evaluate the results of experimental studies measuring the effects of 1st- and/or 2nd -generation H_1-antagonists on behavioral and cognitive performance skills relevant for driving. Measures of subjective sedation also are evaluated but only if they were part of a study primarily investigating behavioral or cognitive effects. That is, this review did not include clinical trials which were limited only to reported

adverse effects or subjective ratings. Alcohol's effects on driving-related performance have been studied extensively and can be used as benchmark to evaluate the traffic safety profile of medicinal drugs. Thus, for consistency and comparison, the current review organized the performance measures generally within the same behavioral categories as employed in the first author's prior reviews on alcohol's driving-related effects (Moskowitz & Robinson, 1988; Moskowitz and Fiorentino, 2000). Finally, studies investigating acute and chronic doses were considered for this review, whereas studies of drug-alcohol (and drug-drug) interactions were not included since such studies were more limited in number.

2. METHOD

Computer-assisted searches of bibliographical data bases were conducted to identify scientific publications for the initial review. Specifically, MEDLINE and related search engines were used to identify well-designed human studies investigating the behavioral, cognitive and sedative effects of antihistamines. Search terms included: antihistamines, H1-antagonists, psychomotor performance, driving, performance impairment, and cognitive effects. Publications through the end of 1998 were included; no particular date limit was set regarding earlier publications, although it should be noted that MEDLINE typically does not include publications prior to 1966. This primary computer-assisted search was supplemented by review of the references cited in the retrieved publications as well as consideration of reports of pertinent studies known to the authors. Therefore, in addition to published journal articles, some abstracts, proceedings, and reports of conference presentations also were included. Although an extensive literature search was conducted, the results cannot be viewed as exhaustive.

The titles (or abstracts) of the identified references were evaluated for initial inclusion according to the following criteria: the article (or detailed abstract) was available in English, the study tested healthy human subjects (or allergy patients), measures included driving-related performance tasks, antihistamines were administered in an experimental setting, a placebo control treatment was included, and statistical tests compared the treatment(s) to placebo. All publications appearing to meet these initial criteria were indexed as the master reference set and copies of the articles were sought for intensive review. This master set included 386 references selected from more than 500 titles/abstracts reviewed in the initial focused search. Of the 386 references identified, 256 were excluded from the intensive review and analysis for the following reasons, as shown in Table 1 below:

EX#	TABLE 1. REASONS FOR STUDY EXCLUSION:	no.	%
1	NOT in English; OR English summary lacks sufficient detail to review	14	5.5
2	NOT adult subjects; OR not healthy volunteers or allergy patients; Excluded other clinical patients (e.g., abstinent alcoholics, depressed patients)	10	3.9
3	NO driving-related tasks used in the experiment; (but coded subjective sedation only from studies which tested at least one behavioral/cognitive measure)	42	16.4
4	NO key drugs included (per top 5 for each H1-antagonist generation; see lists)	67	26.2
5	Inadequate methodology (need at least Placebo; best if +Control also included) OR statistical tests only used baseline change, not comparison with Placebo	10	3.9
6	NOT an experiment; e.g., Review paper with no new experiments reported; or Review of pharmacology or clinical effects, epidemiology, or case report, etc.	80	31.2
7	Prior published data; (Note: included earliest publication unless later paper provided a more detailed report of the findings)	17	6.6
8	Unable to obtain copy of article for detailed review	13	5.1
9	Copy obtained, but article had insufficient detail to allow review of criteria	3	1.2
	TOTAL:	**256**	**100%**

The remaining 130 publications which met all inclusion criteria were then subjected to intensive review and the findings were coded and entered into the data base for summary and analysis. The complete citations for this final set of 130 publications appear as REFERENCE LIST B at the end of this report. Originally, 132 articles were deemed appropriate for the intensive review and so they are indexed in the data base (and in all appended Tables and listings) as Reference

Numbers 1-132 in alphabetical order by first author. Subsequently, four of these articles were excluded from the review set (Ref# 10, 52, 72, and 118) and two additional publications (published in late 1998) were identified and added to the data base. However, to avoid major recoding and reorganization of the data base, the two added articles simply were indexed as Reference #133 (Comer et al., 1998) and #134 (Scavone et al., 1998). As such, they appear at the end of the data base and reference list, rather than in alphabetical order.

A complete listing of the individual studies, with impairment findings grouped according to the behavioral skill categories (discussed in detail below), is presented in Appendix A. In addition, for each task category, an overall summary table of "Skills performance impairment as a function of antihistamine (Drug/Dose), task category and dosing (Acute/Repeated)" was generated to present the counts of YES and NO for significant impairment. An example of such a "YES/NO Counts" table is presented in Appendix B. The tables in Appendix A and B also summarize the findings by drug generation as a class.

Details of the data base coding system can be found in an example of one of the individual Study Summary Sheets which were generated for all 130 articles (see Appendix C for an example). In brief, each article was reviewed and the information for the Citation, Method, and Results of each reported study was entered in the data base. Of note, seven publications reported more than one experiment; in these cases, the data base includes the single Citation, but separate Methods and Results sections for each of the studies which are indexed by the single Reference number plus a letter; (e.g., Reference #18 reports two separate studies: these are indexed as Reference #18A and #18B). The 130 publications reflect a total of 138 separate studies; these are included in the data base for this review.

The results from each study were coded, at the level of drug dose and task measure, for evidence of significant impairment, i.e., YES or NO. With few exceptions, "significant" means that the study reported a statistical test of the given drug's dose versus placebo at $p < 0.05$.

Nearly 40 different antihistamines were represented in the master data set of publications which were identified in the initial, focused literature search. In many cases, only a few studies (and sometimes only one study) examined a given drug, and many of the drugs are (were) only available in Europe. Consequently, in order to ensure an adequate sample of studies for this review, and to be relevant to the medications available to the U.S. population of drivers, we decided to focus only on the five most widely prescribed and/or studied drugs from each generation. These 10 drugs are described in detail in Table 2, as shown on the next page.

A table which lists all of the studies in this review, presented with the YES/NO codes across all 10 drugs, is presented in Appendix D. This listing provides a concise overview of the specific drugs examined in a given study. Of note, the majority of studies focused on only one of the 10 drugs. Only 12 studies involved a comparison of two different 2nd-generation drugs, and only a single study (Simons, 1996) examined a group of 2nd-generation drugs in comparison to placebo and to a 1st-generation antihistamine as the positive control (e.g, diphenhydramine).

TABLE 2. THE TEN DRUGS SELECTED FOR REVIEW

First-generation H1-receptor antagonists						
Code	**generic name:**	**Trade name:**	**Drug CLASS**	**Indicated DOSE**	**Tmax**	**Steady State**
D1	**chlorpheniramine**	Chlor-Trimeton	Alkylamines	4 mg tid, qid	2-6 hr	T1/2: 20-24hr
D2	**clemastine**	Tavist	Ethanolamines sss	1.34 bid - 2.68 tid	2-4 hr	
D3	**diphenhydramine**	Benadryl	Ethanolamines	25-50 mg tid,qid	2-4 hr	T1/2: 8 hr
D4	**hydroxyzine**	Atarax	Piperazines	25 mg tid, qid	2-3 hr	T1/2: 29 hr
D5	**tripolidine**	Actidil	Alkylamines	2.5 mg tid, qid or 10 mg SR	~ 2 hr	T1/2: ~2 hr
Note: There are six generally recognized chemical classes of antihistamines: Alkylamines, Ethanolamines, Ethylenediamines, Phenothiazines, Piperazines, and Piperidines.					SR = sustained release T1/2 = Half-life	
Second-generation H1-receptor antagonists:						
Code	**generic name:**	**Trade name:**	**Drug CLASS**	**Indicated DOSE**	**Tmax**	**Steady State**
N1	**astemizole**	Hismanal	Piperidines	10 mg qd	1 hr	6-9 days
N2	**cetirizine**	Zyrtec	Piperazines	10 mg qd, bid	1 hr	T1/2: 7-11 hr
N3	**fexofenadine**	Allegra	Piperidines	60 mg bid	1-2 hr	T1/2: 13-16 hr
N4	**loratadine**	Claritin	Piperidines	10 mg qd	1-1.5 hr	5 days
N5	**terfenadine**	Seldane	Piperidines	60 mg bid	2.5 hr	2-3 days
Note: loratadine was derived from azatadine; cetirizine is the carboxylated metabolite of hydroxyzine; fexofenadine is the hydrochloride salt of terfenadine's active metabolite.						

Each drug was indexed in the data base and in all generated figures and listings by a drug code number: D1-D5 and N1-N5, respectively, reflect the five drugs in the 1st-, and 2nd-, generations. Only one study of fexofenadine's effects on driving-related behavior has been published to date (i.e., through the end of 1998 in this review). Its inclusion in this review, however, is warranted by its current status as one of the most widely prescribed antihistamines and the fact that its chemical structure is identical to terfenadine's active metabolite, except that fexofenadine is the hydrochloride salt. Terfenadine was taken off the market in early 1998 after increased reports of cardiovascular adverse effects. Nonetheless, as the parent drug to fexofenadine, the many studies of terfenadine are included in this review for their continued relevance for understanding the drug mechanism and impairment effects of the 2nd generation drugs. In addition, astemizole recently was removed from the market due to safety concerns.

In addition to the drug coding, the results for each study were entered in the data base according to the planned analysis of the **ten behavioral skill categories,** as shown in Table 3 below. In addition, as noted earlier, **subjective measures of sedation** were analyzed if the study also had tested at least one behavioral or cognitive measure.

Table 3. NUMBER OF STUDIES AND TEST FINDINGS FOR EACH SKILL CATEGORY AND SUBJECTIVE SEDATION: ACUTE (A) AND REPEATED (R) DOSING

SC #	SKILL CATEGORY	Examples of Measures Tested (with specific sub codes shown)	Number of STUDIES		Number of Findings	
			A	R	A	R
1	**DRIVING & PILOTING**	1R: on road, 1C: closed course, 1S: simulator	17	14	55	28
2	**PSYCHOMOTOR**	2B: body sway, balance, hand steadiness, 2D: dexterity, 2T: finger tapping; 2: all others	35	9	70	17
3	**PERCEPTION**	time perception, visual search tasks	14	7	26	13
4	**VISUAL FUNCTIONS**	4: visual functions, 4C: critical flicker fusion	34	10	83	16
5	**COGNITIVE TASKS**	5D: digit symbol substitution test, 5M: memory tasks, 5T: trail-making, 5: all other cognitive tasks	63	20	201	61
6	**DIVIDED ATTENTION**	typically visual search performed with tracking task	28	8	52	14
7	**VIGILANCE**	sustained attention; lengthy monotonous tasks	25	12	46	24
8	**TRACKING**	8Cr: critical or adaptive tracking, 8: pursuit, compensatory, or unspecified tracking tasks	39	10	80	23
9	**REACTION TIME**	9S: simple RT, 9C: complex RT	50	20	98	44
10	**PHYSIOLOGICAL**	10: EEG, ERP, 10M: Multiple Sleep Latency Test	23	14	56	33
99	**Subjective Sedation**	Visual analogue scales, Stanford Sleepiness Scale	85	29	171	50
(from n = 135 studies of Acute and/or Repeated Doses)		**TOTALS:**	113	47	938	323

Note: **A = ACUTE Doses; R = REPEATED Doses**; (excluded 3 studies with only Residual effects). Many studies tested more than one skill category, measure, drug, and dose level and schedule.

*It should be noted that the terms **"test" or "finding"** are used interchangeably in this report to describe the **unit of data analysis** for this comprehensive review of 138 studies.* A given study, for example, may have evaluated several drugs and doses, both acute and repeated dosing schedules, and included multiple behavioral measures and subjective measures. The resultant total number of specific "tests" or "findings" from that single study, therefore, would be the product of multiplying all the levels for each factor studied. Thus, as shown in the table above, there is a total of 1,261 test findings; obviously this number is much greater than the total number of studies included in the review. Also, the number of findings for repeated dosing was rather limited (n=323) compared to the greater number for acute dosing (n=938).

The decision for classifying the many performance measures into 10 behavioral categories is admittedly somewhat arbitrary. Prior reviewers also have noted the difficulties inherent in this process of assigning a given task to a specific category (e.g., Adelsberg, 1997; Rombaut & Hindmarch, 1994), but most concur with the general areas of actual driving, simulated driving, various psychomotor skills, sensorimotor tasks, cognitive effects, and subjective measures of sedation. In order to evaluate more precisely the drug effects on the wide variety of measures, we also included sub codes in an effort to restrict the variability of findings within a given area. Specific task names and the individual response measures can be found in the detailed tables which list the impairment results by study (see Appendix A).

3. RESULTS

There is considerable complexity in the task of evaluating 10 drugs for evidence of subjective sedation and objective impairment of a variety of performance measures grouped into 10 specific behavioral categories. Moreover, each drug has been studied across multiple dose levels as well as for acute versus chronic dosing schedules. Therefore, the results of this review are organized into the following major sections below: Overall impairment, Impairment by individual drugs, and Impairment by behavioral categories and subjective sedation.

3.1. Overall Impairment

3.1.1. Impairment Findings by Study for each Drug (Figure 1 and Appendix D)

Of the 135 studies which examined acute or repeated dosing (or both) of any of the 10 key drugs, 120 tested 1st generation drugs and 87 tested 2nd generation drugs. (Since many studies evaluated several drugs, often from both generations, the numbers overlap. Also, the three studies which only evaluated residual effects are excluded from the data summaries.) As can be seen in Figure 1, the most frequently studied drugs for the 1st and 2nd generations, respectively, were diphenhydramine (49 of 120 studies, or 41%) and terfenadine (37 of 87 studies, or 43%). As noted earlier, only a single study of fexofenadine had been published as of the 12/98 cutoff date (i.e. for the published articles of the studies) for this review. Thus, those findings must be viewed cautiously until additional studies are reported to determine if those findings generalize or not to other samples of subjects and measures.

First, we considered the category of studies, (as distinguished from the number of behavioral task *measures* of which typically there are several per study), which tested *either acute or chronic doses* and found *any evidence* of statistically significant impairment (relative to a placebo control treatment) of *either objective or subjective measures*. We found that 88% (106 of 120) of the studies of the 1st generation drugs found impairment as compared to 22% (19 of 87) of the studies of the 2nd generation drugs. And as expected, for each of the five drugs within each generation, more studies found impairment than not for the 1st generation drugs, whereas the majority of the studies of the 2nd generation drugs found no significant impairment. Nonetheless, there is considerable variability for the findings of significant impairment within each drug generation. Specifically, the significant findings range from 69% (11 of 16 studies of clemastine) to 95% (18 of 19 studies of chlorpheniramine) for the 1st generation drugs, and from 9% (1 of 11 studies of astemizole) to 35% (7 of 20 studies of cetirizine) for the 2nd generation drugs. This excludes, of course, the single study of fexofenadine which did find some evidence of impairment. Given this wide variability, a more focused analysis is needed.

3.1.2. Impairment Findings as a function of Objective/Subjective Measures, Drug Generation, and Dosing Schedule (Acute versus Repeated) (Figure 2)

Since the overall impairment findings by study obviously reflect considerable variation in terms of objective versus subjective measures as well as acute versus repeated dosing, the next step was to summarize the findings as a function of these key factors. Moreover, instead of

evaluating impairment at the study level, all subsequent analyses focused on the findings for the individual and specific *"behavioral task measures*" which, as described earlier, present a finer level of analysis for this comparative review of 1st versus 2nd generation antihistamines. That is, for a given study, the individual test findings reflect the outcome of the statistical significance test for impairment for a given drug, at a given dose and dosing schedule, and for a specific measure within one of the 10 behavioral categories or for subjective sedation.

Considering first the *acute dose findings* (Figure 2), the 1st generation drugs as a group were found more often than not to be impairing in both objective and subjective measures. The 2nd generation drugs, in contrast, showed substantially fewer findings of impairment for either objective or subjective measures.

Relative to the acute effects, the *repeated dose findings* for both drug generations generally show less impairment, at least for the objective measures, as might be expected given that tolerance may develop with chronic dosing. For the subjective measures, however, the 1st generation drugs still have more findings of significant sedation than not even after repeated dosing. In contrast, none of the findings for the 2nd generation drugs indicate any significant sedation after repeated doses. Again, there is wide variability in these studies and so no firm conclusions can be drawn from this review. For example, the repeated dose studies range from investigations of two doses in a single day to multiple doses over several weeks. An additional limitation, as noted earlier, is the fact that far fewer studies (and test findings) are available in this review for the effects of repeated dosing. *Therefore, no figure is included here for the limited number of repeated dose findings and the remainder of the results section will focus only on the acute dose findings.*

3.2. Impairment by Individual Drugs as a function of Acute Dose Level

As noted earlier, details of the impairment findings as a function of drug generation, individual drugs, as well as specific dose can be found in Appendix B (e.g., number of NO versus YES impairment findings as well as %YES; presented for each category as well as for summaries).

3.2.1 Dose Response Curves for Objective Measures (Figure 3A)

Looking at the overall findings for all objective measures grouped together, the acute dose findings for each drug separately show the clearest dose response effects for all of the 1st generation drugs except perhaps chlorpheniramine. And, while the 2nd generation drugs typically show few findings of any significant impairment, a dose-response still is apparent. That is, when impairment was reported, usually a higher dose was being tested.

3.2.2 Objective Measures by Individual Drugs and by Generation (Figure 3B)

For the 2nd-generation drugs, all 45 findings for astemizole, with doses ranging from 10 to 40 mg, showed no significant impairment. In contrast, cetirizine was reported to cause significant impairment of objective measures in 18% of the cases (14 of 80 findings), whereas the other 2nd generation drugs had fewer reports of impairment (4 of 53 findings or 8% for loratadine, and 5 of 126 findings or 4% for terfenadine). As expected, the 1st generation drugs more often showed significant impairment: 61% (70 of 114 findings) for tripolidine and 53% (112 of 211 findings) for diphenhydramine, the two drugs used most frequently as positive control treatments in many of the studies.

3.2.3 Dose Response Curves for Subjective Measures (Figure 4A, Table 4 in Appendix A)

The subjective measures reveal even stronger dose response curves, particularly for the typically sedating 1st generation drugs. For example, significant sedation was reported increasingly more often when higher doses of diphenhydramine were tested: 57% for 25 mg, 71% for 50 mg, 85% for 75 or 100 mg, and 100% for >100mg. In contrast, the 2nd generation drugs were strikingly devoid of any significant findings of subjective sedation, that is, with the exception of cetirizine. Specifically, at all doses tested, cetirizine was reported to show some evidence of significant sedation: 33% (1 of 3 findings) for 5 mg, 14% (2 of14 findings) for the indicated dose of 10 mg, and 17% (1 of 6 findings) for the highest dose tested, 20 mg.

3.2.4 Subjective Measures of Sedation by Individual Drugs and by Generation (Figure 4B)

Looking at the subjective measures of sedation by drug generation, the older H_1-antagonists had significant findings for 67% of the cases (62 of 92 findings) in contrast to only 5% (4 of 79 findings) for the newer drugs. As noted, cetirizine was the only 2nd-generation drug showing significant sedation (17%, 4 of 23 of the findings), whereas each of the five 1st-generation drugs produced significant sedation in over 50% of the times tested. Specifically, significant impairment was reported in 55% (6 of 11) of the test findings for clemastine, 64% (18 of 28 findings) for tripolidine, 67% (8 of 12 findings) for chlorpheniramine, 72% (26 of 36 findings) for diphenhydramine, and 80% (4 of 5 findings) for hydroxyzine.

3.3. Acute Dose Impairment by Behavioral Categories

This next section presents the impairment results of the reviewed studies as a function of the 10 behavioral categories of driving-related performance measures. As noted earlier, only the acute dose findings are presented since there were relatively few repeated dose studies.

3.3.**1. DRIVING AND PILOTING** (Figure 5, Table 5 in Appendix A)

There were 55 testing findings produced by the 17 studies which examined the effects of at least one of the key drugs on driving behaviors. Note that this category includes measures of actual driving on the road, or in a closed course, as well as a variety of measures from many different types of driving simulators and some piloting tasks. With such a wide range of different tasks and measures, it is not surprising that some of the tasks are not sensitive and so, for the 1st generation drugs as a class, only 48% (11 of 23) of the findings showed significant impairment. This compares to significant impairment reported in 13% (4 of 32) of the findings for the 2nd generation drugs.

Notably, when considering only the specific subset of *on-road driving* measures, the number of significant findings of impairment by the 1st generation drugs is much more pronounced, with 89% (8 of 9 findings) showing significant on-road driving impairment, versus only 10% (2 of 20 findings) for the 2nd generation drugs. Also, looking at the findings for the individual drugs, it is clear that all of the 1st generation drugs studied consistently show the on-road driving impairment. In contrast, the only 2nd generation drugs showing significant impairment of on-road driving skills were cetirizine (1 of 2 findings) and terfenadine (1 of 11 findings). The findings for these two drugs mirror those for the complete group of driving measures. That is, significant impairment of any type of driving-related behavior was found in 29% (2 of 7 tests) of the findings for cetirizine and in 13% (2 of 16 test findings) for terfenadine. The other two 2nd generation drugs studied showed no impairment; (astemizole was not studied).

3.3.**2. PSYCHOMOTOR SKILLS** (Figure 6, Table 6 in Appendix A)

A total of 35 studies evaluated the impairing effects of antihistamines on psychomotor skills and yielded 70 test findings. For the 1st generation drugs, 44% (22 of 50) of the findings showed significant impairment whereas none of the 20 findings for the 2nd generation drugs demonstrated significant impairment. (However, only astemizole, cetirizine and terfenadine were studied). Again, there is considerable variability in the type of psychomotor skills and specific task demands evaluated in these studies. Thus, this behavioral category does not appear particularly sensitive to detecting impairment. Of note, analysis of the specific subcategories revealed that tasks measuring balance (e.g., body sway, hand steadiness) seemed most sensitive to impairment by the 1st generation drugs (10 of 15 findings, or 67% versus none of the 4 tests for the 2nd generation drugs). In contrast, tasks requiring dexterity (e.g., picking up beads and other fine-motor tasks) were notably insensitive: none of the findings (4 each) for either the 1st generation or the 2nd generation drugs showed significant performance deficits. In addition, finger tapping tests were found to show significant impairment for 50% (8 of 16) of the findings for 1st generation drugs versus none of the 3 tests for the 2nd generation drugs.

3.3.**3. PERCEPTION**(Figure 7, Table 7 in Appendix A)

This category reflects varied tasks of perception (e.g., visual discrimination, time estimation) including singular visual search tasks (i.e., those *not* performed in the context of divided attention). No clear conclusions can be made for this category, however, since the available data from this review are quite limited: 14 studies produced a total of 26 test findings. For the 1st generation drugs, 35% (6 of 17) of the findings for the 1st generation drugs evidenced significant impairment of perceptual tasks whereas no impairment was reported in any of the 9 tests for the 2nd generation drugs (which only included astemizole, cetirizine and terfenadine). Looking at the figures for the individual 1st generation drugs, however, it appears that diphenhydramine was more often impairing than not (56% or 5 of 9 test findings) for perceptual tasks.

3.3.**4. VISUAL FUNCTIONS & CRITICAL FLICKER FUSION** (Figures 8A & 8B, Table 8)

Measures of visual functions included saccadic eye movements, smooth pursuit, dynamic visual acuity, visual field, pupillary diameter and extraocular muscle control. Such measures were examined in 16 studies, producing 31 test findings regarding impairment. Significant impairment was found in 10 of the 15 tests (67%) for the 1st generation drugs versus only 1 of the 16 tests (6%) for the 2nd generation drugs. It should be pointed out, however, that the single finding of significant impairment for the 2nd generation drugs involved dynamic visual acuity and loratadine 40 mg, a dose which is much higher than the recommended 10 mg dose. It also should be noted that the most often studied 1st generation drug for this visual function category was tripolidine 10 mg which was found to cause significant impairment in 89% (8 of 9) of the tests. Since all of these test findings came from the same group of investigators, however, one cannot tease apart the effect of tripolidine versus the inherent greater sensitivity (i.e., via decreased variability) afforded by using a single, standardized measure, namely dynamic visual acuity, and by the same group of investigators.

Some investigators have classified critical flicker fusion (CFF) as a measure of information processing while others consider it to reflect a more basic visual perception task. In this review, the CFF task simply was analyzed separately as a subset of the visual functions category. A total of 29 studies examined CFF, producing 52 test findings. Significantly impaired CFF was found in 52% (15 of 29) of the test finding for the 1st generation drugs. In contrast, the 2nd generation drugs were only found to impair CFF in one of the 23 times tested (4%); this single finding involved terfenadine 60 mg. As was the case with visual functions, the significant impairment by 1st generation drugs was most apparent in the studies of tripolidine (100% of the 10 tests). Again, the consistency of these findings may be due partly to the fact that they largely came from the same investigators who were using a more homogenous set of standardized CFF measures and methods.

3.3.**5. COGNITIVE TASKS** (Figure 9, Table 9 in Appendix A)

The category of cognitive tasks includes tasks of complex psychomotor skills (e.g., card sorting), memory (auditory and visual), trail-making tests and a variety of tasks requiring problem solving (arithmetic, numerical and logical reasoning) and cognitive flexibility (Stroop color/word task). As such, this category of cognitive tasks, like psychomotor skills, reflects a wide range of tasks and measures with the result of increased variability and concomitant decreased sensitivity to detecting impairment. Of the 63 studies which examined cognitive tasks, a total of 201 test findings evaluated impairment. For the 1st generation drugs, only 37% (46 of 126) of the test findings showed statistically significant impairment as compared to only 3% (2 of 75 tests) for the 2nd generation drugs. Moreover, the two cases of impairment for the 2nd generation drugs involved higher than recommended doses, cetirizine 20 mg and loratadine 40 mg, and both tested digit symbol substitution skills.

Given the large number of test findings and the wide variety of tasks represented, specific subsets of cognitive tasks also were analyzed. Results showed that digit symbol substitution tests were found to be impaired by 1st generation drugs in 38% (17 of 45) of the test findings versus only 7% (2 of 28 findings) for the 2nd generation drugs. Memory tasks were impaired in 39% (13 of 33) of the tests of 1st generation drugs whereas no significant memory impairment was found in any of the 13 tests for the 2nd generation drugs. Trail-making tasks appeared to provide the most sensitive measures in this category, albeit with rather limited data available in this review, with 50% (5 of 10) of the findings for the 1st generation drugs showing significant impairment versus none of the 5 tests for the 2nd generation drugs.

3.3.**6. DIVIDED ATTENTION** (Figure 10, Table 10 in Appendix A)

Divided attention tasks were examined in 28 studies, producing 52 test findings concerning impairment. Typically, the divided-attention task consisted of the concurrent performance of a tracking and visual search task. In other cases, some investigators employed other types of dual tasks such as simultaneous tracking and continuous memory tasks. As expected, given the complex demands of most divided-attention tasks, this behavioral category was found to be relatively sensitive for detecting significant impairment. The 1st generation drugs were found to impair divided-attention skills in 69% (20 of 29) of the findings versus 13% (3 of 23 test findings) for the 2nd generation drugs. The most frequently studied 1st generation drug, diphenhydramine, was found to impair divided-attention tasks in 77% (13 of 17) of test findings. For the 2nd generation drugs, one finding of significant impairment was found for each of the following drugs: cetirizine (from a total of 6 tests), loratadine (of 8 tests) and terfenadine (of 8 tests); all of these significant findings occurred at the recommended doses. Interestingly, two cases of an apparent performance-*enhancing* effect (i.e., performance was significantly *better* after the active drug relative to placebo) also were reported for loratadine 10 mg (Kay et al., 1997) and terfenadine 60 mg (Moskowitz & Burns, 1988). This suggests there may be a possible arousing or stimulating effect of these specific 2nd-generation drugs.

3.3.**7. VIGILANCE TASKS** (Figure 11, Table 11 in Appendix A)

Vigilance was evaluated in 25 studies, producing a total of 46 test findings. As clearly shown in the figures, both for each drug as well as for the overall findings by drug generation, nearly all of the 1st generation drugs consistently were found to cause significant impairment of the measures of sustained attention. In marked contrast, not one of the 2nd generation drugs showed any evidence of impairment. By generation, the older drugs were found to impair vigilance 86% of the times tested (25 of 29 findings) whereas all 17 tests for the new drugs found no evidence of any significant impairment. Such findings attest to the sensitivity of vigilance tasks to detect CNS sedation.

Moreover, an interesting finding concerning vigilance comes from an earlier study in our laboratory (Moskowitz & Burns, 1988). In brief, that study found an apparent alerting or stimulating effect evidenced in the terfenadine 60 mg treatment condition which showed *better* vigilance performance (i.e., faster response times) relative to the placebo control. As noted earlier, fexofenadine has a chemical structure nearly identical to that of terfenadine's active metabolite. The single study of fexofenadine (Vermeeren & O'Hanlon, 1998; Ref#122) also examined vigilance but found neither impairment nor improved performance. The authors of that study suggested that such findings indicate that fexofenadine does not act pharmacologically like classic stimulants since typically the "latter enhance signal detection performance in vigilance tests." Of note, as discussed for some of the other behavioral categories, there are a number of findings in this review of other apparently alerting or stimulating effects reported for terfenadine. Since the safety implications of this issue need to be evaluated in more depth, additional studies of the 2nd-generation drugs are eagerly awaited. This is particularly important for fexofenadine, since it is only beginning to be studied and terfenadine is no longer on the market.

3.3.**8. TRACKING** (Figures 12A & 12B, Table 12 in Appendix A)

A total of 80 test findings was produced by the 39 studies which evaluated tracking performance. This behavioral category included measures of different types of tracking tasks, including pursuit, compensatory, critical and adaptive tracking. Significant impairment was reported for 69% (33 of 48 tests) versus 19% (6 of 32 tests), respectively, of the findings for the 1st and 2nd generation drugs. As seen in Figure 12A, for the individual drugs, all five of the 1st generation drugs demonstrated significant impairment for nearly all test findings reviewed. In contrast, for the five 2nd-generation drugs tested, only cetirizine and fexofenadine were found to impair tracking. Specifically, two of the three findings for cetirizine, and both of the two findings for fexofenadine, showed significantly impaired tracking performance.

Focusing next on the subset of 26 studies which evaluated *either critical or adaptive tracking* (Figure 12B), the 52 test findings for this specific subcategory revealed significant impairment for over 90% (28 of 31) of the findings for the 1st generation drugs, in contrast to 19% (4 of 21 findings) for the 2nd generation drugs. Moreover, two of the three findings of no impairment for the older drugs actually showed trends ($p < 0.08$). Therefore, if a less stringent criterion for statistical significance is allowed, the findings of impairment by the 1st generation drugs increase to 97% (30 of 31 findings). Clearly, consistent with what prior investigators and reviewers have reported, the current review's findings confirm that critical and adaptive tracking tasks appear to provide sensitive measures of driving-related performance.

3.3.**9. REACTION TIME** (Figure 13, Table 13 in Appendix A)

This category included simple and complex reaction time tasks, as well as some that were not easily classified into either category since the published task descriptions often were quite limited if not lacking. Overall, there were 50 studies which included reaction time tasks, producing 98 test findings for this behavioral category. For the 1st generation drugs, 48% (29 of 61) of the test findings were found to show significant slowing of reaction time; this compares to 11% (4 of 37 findings) for the 2nd generation drugs. As seen in Figure 13 for the individual drugs, diphenhydramine and tripolidine, respectively, had the most notable impairing effects (54% or 13 of 24 findings, and 50% or 6 of 12 findings), whereas cetirizine was the only 2nd generation drug showing significant impairment (40%, 4 of 10 findings).

Looking at the subcategories, the simple reaction time tasks appeared to be somewhat more sensitive to detecting impairment than were the complex (or choice) reaction time tasks, at least for the 1st generation drugs. Specifically, 42% (11 of 26) of the findings showed significant slowing of choice reaction time versus 60% (15 of 25 test findings) for simple reaction time. Perhaps the relative insensitivity of complex (or choice) reaction time tasks is due to the greater variation in the specific measures employed across studies. In contrast, there may be less variability in the measures of simple reaction time. However, for the 2nd generation drugs, no distinction was seen for the findings of significant slowing of simple reaction time (11% or 1 of 9 findings) versus complex reaction time (12% or 3 of 26 findings).

3.3.**10. PHYSIOLOGICAL MEASURES OF SEDATION** (Figures 14A & 14B, Table 14)

Physiological measures of sedation included spectral analysis of electroencephalograph (EEG) waves, evoked response potentials (ERP's such as P300, etc.), as well as the highly standardized Multiple Sleep Latency Test (MSLT) which utilizes EEG frequencies to detect the onset of sleep. A total of 23 studies evaluated one or more of these various objective measures

of sedation, producing 56 test findings. Significant objective sedation was reported for 79% (22 of 28) of the findings for the 1st generation drugs versus 14% (4 of 28 findings) for the 2nd generation drugs. As clearly evident in Figure 14A, all five of the older drugs showed significant sedation in most cases and three of the four new drugs also showed some sedation (there were no data for this category from the single fexofenadine study).

If we next focus only on the subset of the MSLT measures, as shown in Figure 14B, the results are quite striking. Now 100% of the 9 test findings for the 1st generation drugs shows significant sedation as compared to only 9% (1 of 11) of the findings for the 2nd generation. While admittedly small numbers of test findings are available, it is interesting that the single finding of significant objective sedation found for the new drugs is due to cetirizine which, consistent with the findings from many of the other behavioral categories in this review, seems to stand out in the group of otherwise *relatively* "non-sedating" new drugs.

4. SUMMARY AND DISCUSSION

4.1. Impairment as a function of Behavioral Tasks (Figure 15)

An overall summary of the acute dose impairment results, as a function of H1-antagonist generation and behavioral category (or subjective sedation), is presented in Figure 15. As clearly shown, the most sensitive objective measures for detecting sedation and impairment appear to be: the Multiple Sleep Latency Test, critical or adaptive tracking, vigilance, divided attention and some driving measures. On the other hand, the categories of cognitive tasks, perception and psychomotor skills all seem to lack sensitivity overall. This may be due, at least partly, to the greater variability across types of the tasks and measures employed in the studies reviewed. Finally, the subjective measures of sedation appear to be relatively sensitive, at least for the 1st-generation drugs.

Also apparent in Figure 15, and as expected, the 1st-generation drugs generally were found to impair and sedate substantially more often than did the 2nd-generation drugs. However, it is important to emphasize that some findings of statistically significant impairment also were reported for the 2nd-generation drugs, specifically for subjective sedation as well as for all of the behavioral categories except psychomotor skills, perceptual tasks, and vigilance. The greater heterogenity of measures employed across studies for these tasks may partially explain the lack of any significant findings at least for the first two categories. In contrast, however, despite the use of a considerably more homogenous group of vigilance measures across studies, the overall results still showed no significant impairment of vigilance by the 2nd-generation drugs. This is an important finding, given that histaminergic pathways are widespread in the CNS and appear to be related to mechanisms that support alertness and vigilance during the wakeful state (Nicholson et al. 1985). Thus, the newer, 2nd-generation histamine-antagonist drugs which claim to be “non-sedating” actually may reflect a true pharmacological advance at least in terms of eliminating any disruption of vigilance.

On the other hand, the repeated reports of apparent arousal or stimulating effects noted with terfenadine and some of the other 2nd-generation drugs suggest that additional study is needed. Although the newer H1-antagonists appear to be relatively devoid of impairing effects, the findings of faster response times and apparent performance enhancement clearly warrant closer scrutiny. What are the specific pharmacodynamic actions for such effects? And what, if any, are the driving safety implications? Only carefully designed studies, using sensitive and validated measures, can address this issue by examining if such increased arousal is associated, or not, with any concomitant disruption of the ability to continue to focus on the primary driving task. Or, is such increased arousal indicative of influences on physiological systems that are not primarily CNS?

4.2. Comparison with Impairment Findings for Alcohol

As noted earlier, alcohol’s effects often are used as a benchmark for evaluating the degree of impairment by medicinal drugs. Therefore, a comparison of the results of this review with those from the first author’s recent review of the effects of low to moderate BAC’s on driving (Moskowitz & Fiorentino, 2000) is in order. Although neither of the current reviews specifically examined the magnitude of impairment associated with alcohol or the H1-antagonists, the

relative sensitivity of the various behavioral categories was summarized in each review. In brief, there are several areas of consistency, as well as discrepancy, across the findings from these two reviews. First, both reviews found support for the sensitivity of the following behavioral categories for detecting driving-related performance impairment: Multiple Sleep Latency Test (i.e., measure of wakefulness or arousal), tracking, vigilance and divided attention. Second, critical flicker fusion and simple reaction time were found to be insensitive measures for detecting alcohol's impairing effects, at least for low to moderate doses. In contrast, these two measures did appear to be relatively sensitive to the impairing effects of the 1st-generation antagonists. This suggests that different behavioral mechanisms may be involved. Thus, experimental studies of the effects of a given drug class must include specific measures related to that drug's actions, and not simply rely on the standard test batteries employed for assessing alcohol's effects.

Finally, in addition to examining impairment as a function of the behavioral tasks, as described above, there also are a number of issues which were not addressed in the current review since relevant studies were limited in availability. These issues are summarized briefly below:

4.3. Repeated Dosing And Tolerance Effects

There was a rather limited number of studies in this review which examined repeated doses. Moreover, they ranged from studies of two doses in one day to three or four doses per day over the course of two weeks. Thus, the wide variability of dosing schedules, as well as the limited number of repeated dose studies available for review, do not permit a systematic evaluation of the effects of repeated doses. Nonetheless, this is a very important issue since most individuals needing a medication do not simply take a single dose of a drug. Partial tolerance to sedation and impairment have been reported after repeated doses of the 1st-generation antihistamines in some studies (e.g., Bye et al., 1977; Walsh et al., 1994) but not in others (e.g., Alford et al., 1989; Brookhuis et al., 1993; Goetz et al., 1989). And evidence both for impairment (e.g., Volkerts et al., 1992) as well as for improved performance (e.g., Vermeeren & O'Hanlon, 1998) have been reported after chronic daily dosing with some of the 2nd-generation antihistamines, apparently due to drug accumulation. In the future, more studies will need to examine more systematically the effects of repeated doses of antihistamines.

4.4. Timing of Acute Doses Tested

Most studies tested for impairment or sedation within the window of expected peak drug effects, typically at two to three hours post-dose. Some studies utilized repeated test batteries over a five to eight hour period. However, in certain cases the lack of significant findings appeared due to testing either too early, or too late, to capture the peak drug effects. For example, two of the significant findings of impairment by cetirizine only occurred on specific measures and at much later times in the testing session, namely between 6 and 8 hours post-dose (Gengo et al., 1990; Walsh et al., 1992). Such effects clearly would be missed if the testing had only included a more limited number of measures or only earlier post-dose times as many of the other studies had done. Thus, future studies must assess the effects of antihistamines at the optimal post-dose times and employ a comprehensive, standardized test battery of the most sensitive and valid measures of sedation and driving-related impairment.

4.5. Specific Populations Tested

The typical subject population used in the majority of the studies reviewed was healthy volunteers, usually young to middle-aged men. Such a sample is appropriate as an initial step in a research program. However, more systematic research studies are needed to explore further the effects of antihistamines on other populations, including women, the elderly, and symptomatic versus asymptomatic allergy patients. In the latter case, studies are needed to evaluate whether the underlying allergy symptoms might actually contribute to impaired performance and, if so, if an antihistamine might improve performance (cf. Burns et al., 1994).

The effect of gender also may influence the test findings in terms of an inherent confound, namely women being relatively more susceptible to a given drug dose, due to their smaller body size. Indeed, of the very few significant findings of impairment by terfenadine, one was reported in a study which only tested women, and found that only the highest dose, 240 mg, caused driving-related impairment (e.g., Bhatti & Hindmarch, 1989).

Driving is a complex task requiring the integration of visual, psychomotor and cognitive skills. Age, and the various medical conditions and medications that often accompany aging, may compromise many of the skills needed to operate a motor vehicle safely. Elderly drivers are known to have a greater crash fatality risk (i.e., more fatalities when in a crash). A recent study of 3,238 drivers aged 65 and older specifically found that cognitive test performance remained significantly associated with crash risk even after controlling for driver age, race and measures of driving exposure (Stutts et al., 1998). Such findings support the validity of the various driving-related cognitive measures employed in the studies reviewed. However, there were relatively few studies which examined the effects of antihistamines on older subjects. Clearly, this area demands further study.

4.6. Clinical Efficacy Versus Side Effect Profile

Finally, another issue needing further study concerns the design of comprehensive and well-controlled studies which compare several antihistamines, with each drug tested at its indicated therapeutic dose, for clinical efficacy (i.e., using wheal and flare tests, the standard skin reaction measures of peripheral allergic effects), subjective sedation, and behavioral toxicity, all within the same study. In the current review, there is only one example of the use of such an exemplary design. It is the study by Simons et al. (1996; Ref#114) which evaluated the effects of five 2nd-generation H1-antagonists (astemizole, cetirizine, loratadine, terfenadine, ketotifen) in comparison to placebo and to the 1st-generation drug, diphenhydramine, as the positive control. The results showed that:

1) compared to placebo, the 1st-generation drug caused both significant subjective sedation and objective impairment;
2) the 2nd-generation drugs were *relatively* devoid of significant sedation or impairment, with the exception of cetirizine which caused significant sedation; and
3) even the 2nd-generation drugs showed some evidence of sedation or impairment relative to placebo, although the magnitude of the effects generally were not statistically significant.

It should be noted that the Simons et al. (1996) study is limited by its use of only a single objective measure of impairment, namely the evoked response potential. The results of that single study are notable, however, in that they closely mirror the findings of this current review of the findings across many studies. Thus, despite the limitations noted of the studies in this review, the overall findings do appear to be representative of the effects of the antihistamines.

5. CONCLUSIONS

5.1. There is some slight, but ambiguous, evidence from epidemiological studies of a connection between antihistamine use and traffic collision rates. Of note, these epidemiological studies were done primarily when the use of 1st-generation (but not 2nd-generation) antihistamines was prevalent.

5.2 There is overwhelming evidence from the experimental literature that the 1st-generation antihistamines produce objective signs of skills performance impairment as well as subjective symptoms of sedation.

5.3 The 2nd-generation antihistamines show low incidence of objective skills performance impairment and in the majority of cases no evidence of subjective sedation.

5.4 While 2nd-generation antihistamines represent a major triumph for the pharmaceutical industry in reducing potential side effects, there still remains some evidence that all antihistamines, even the 2nd- generation drugs, can have objective skills impairment consequences at least in some cases.

5.5 Within both the 1st- and 2nd-generation antihistamine groupings, there is considerable variation in objective evidence of impairment. Additionally, for the 1st-generation antihistamines, there is considerable variation in subjective effects, such as sedation. Within each generation of antihistamines, there clearly are drugs that are to be preferred for use to avoid side effects.

5.6. It would appear that proper selection of a 2nd-generation antihistamine would produce little skills performance impairment and only a small effect on traffic collisions.

5.7. Methodologically, it is apparent that among the many diverse techniques for investigating driving-related impairment, some methods and behavioral domains are more sensitive to the effects of antihistamines. Obviously, reports of the rate of impairment can be manipulated by a failure to use sensitive measures or test at appropriate post-dose times. In future studies of antihistamines, therefore, it would be hoped that more utilization will be made of the most methodologically-sound techniques so as to permit a better comparison between different drugs.

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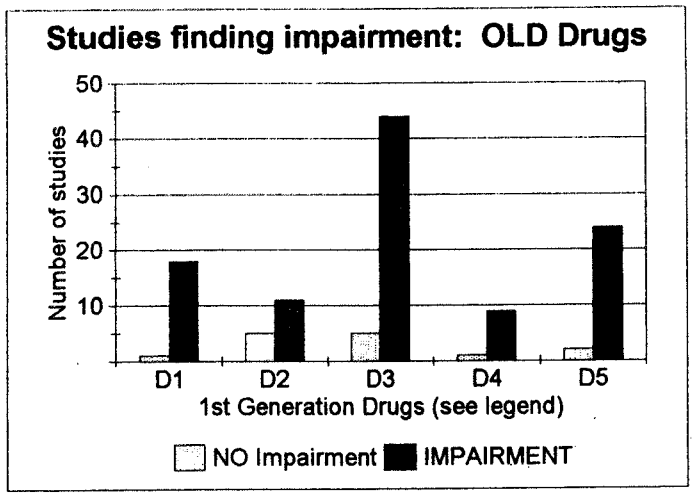
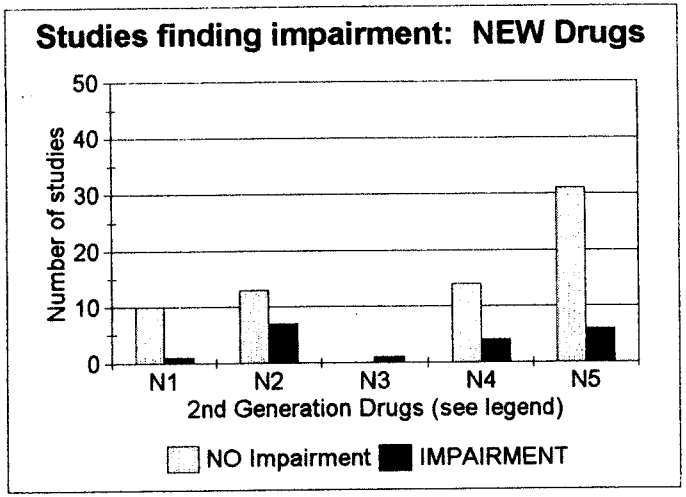
FIGURES

(Appearing as a complete set, from #1 through #15)





DRUG code:	GENERIC NAME:
D1	CHLORPHENIRAMINE
D2	CLEMASTINE
D3	DIPHENHYDRAMINE
D4	HYDROXYZINE
D5	TRIPOLIDINE

DRUG code:	GENERIC NAME:
N1	ASTEMIZOLE
N2	CETIRIZINE
N3	FEXOFENADINE
N4	LORATADINE
N5	TERFENADINE

FIGURE 1. Impairment Findings by Study

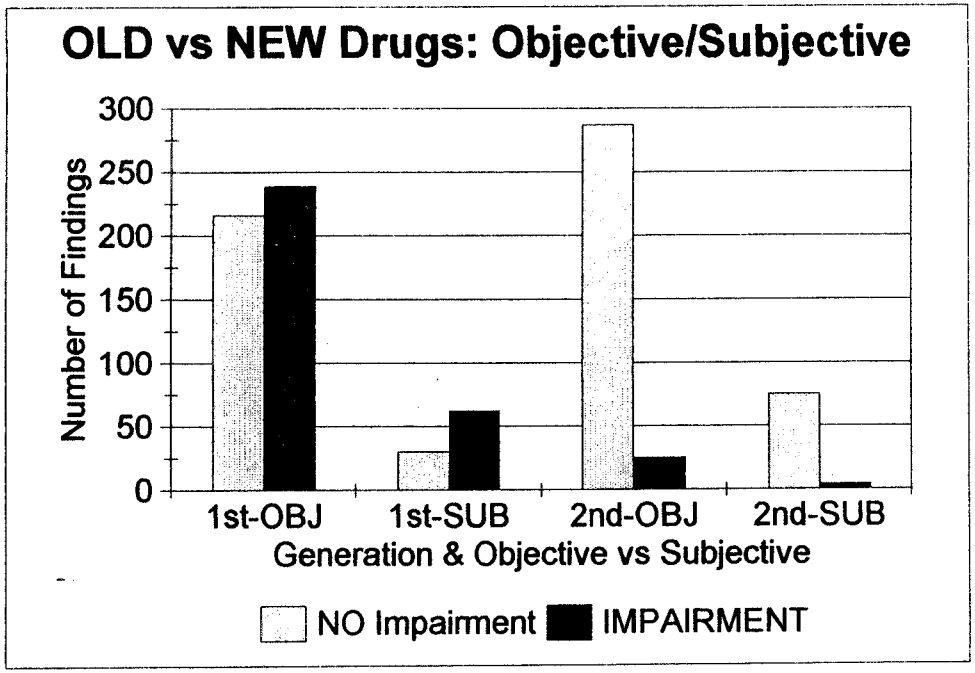


FIGURE 2. Acute Doses Only

FIGURE 3A.

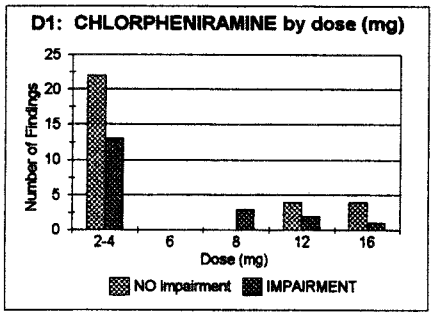
Results shown for:
TASK CATEGORY: **OBJECTIVE MEASURES**
SC#: 1-10

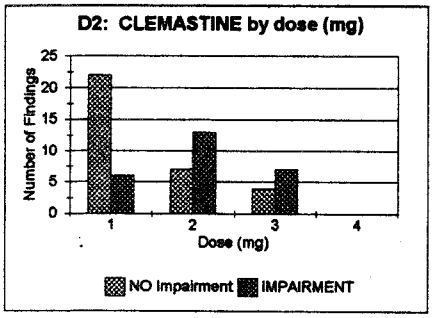
DOSING: ACUTE

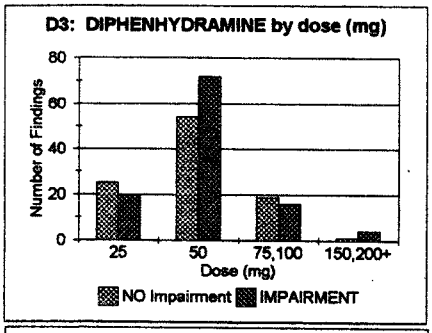
Total # Tests: 767

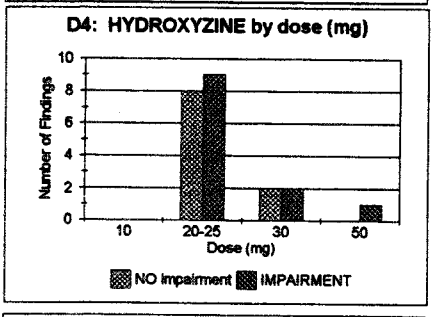
ANTIHISTAMINES: H1-RECEPTOR ANTAGONISTS by DRUG GENERATION:

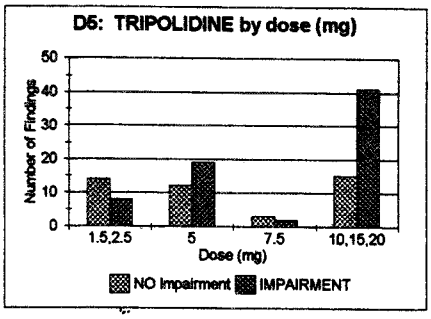
1st GENERATION DRUGS:



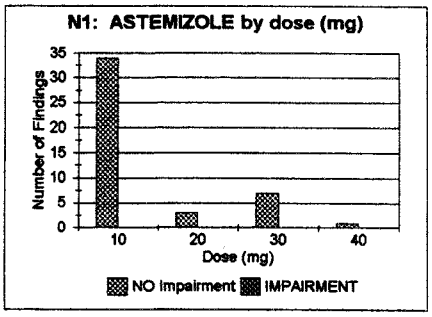


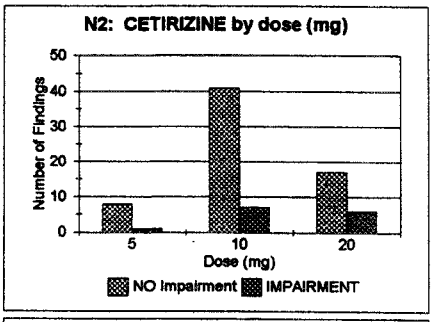


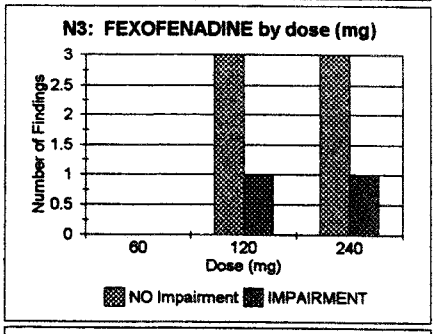


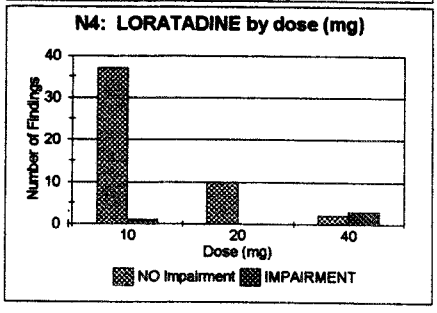


2nd GENERATION DRUGS:









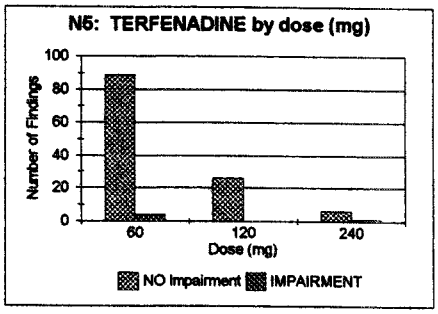
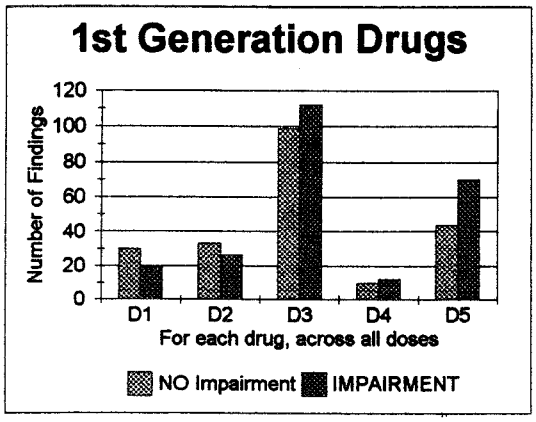


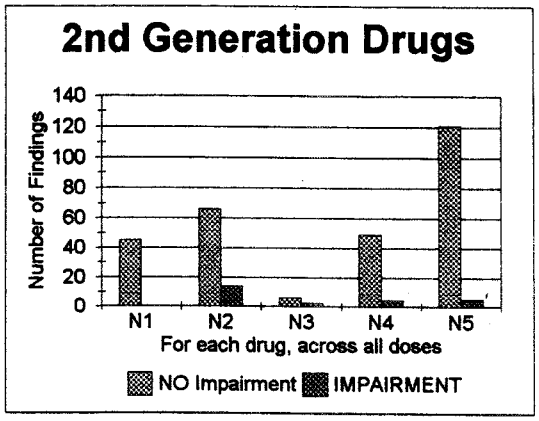
FIGURE 3B.

Results shown for:
TASK CATEGORY:
OBJECTIVE MEASURES
SC#: 1-10

DOSING: **ACUTE**

Total # Tests: 767





DRUG code:	GENERIC NAME:
D1	CHLORPHENIRAMINE
D2	CLEMASTINE
D3	DIPHENHYDRAMINE
D4	HYDROXYZINE
D5	TRIPOLIDINE

DRUG code:	GENERIC NAME:
N1	ASTEMIZOLE
N2	CETIRIZINE
N3	FEXOFENADINE
N4	LORATADINE
N5	TERFENADINE

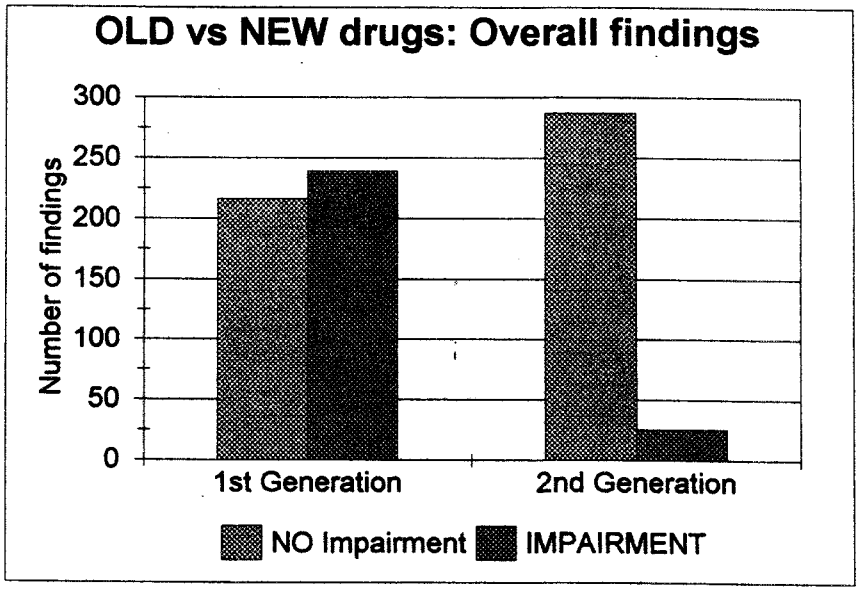


FIGURE 4A.

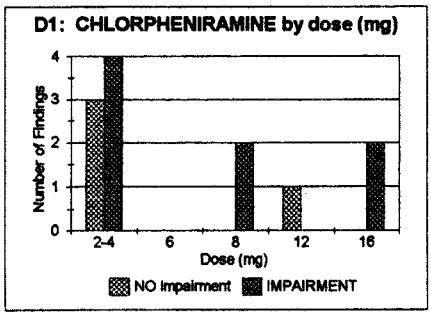
Results shown for:
TASK CATEGORY: **SUBJECTIVE SEDATION**
SC#: 99

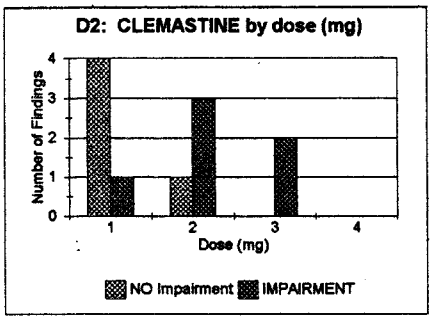
DOSING: ACUTE

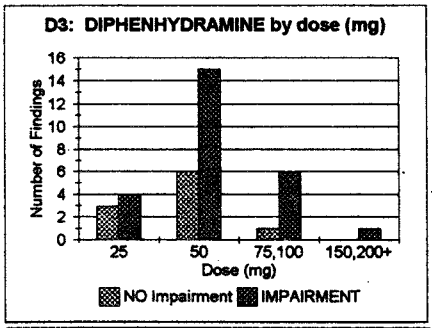
Total # Tests: 171

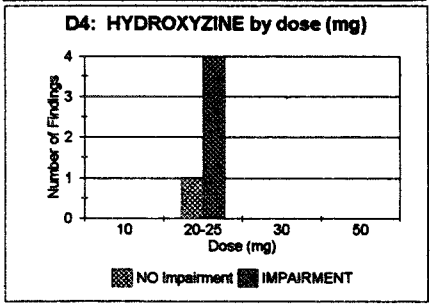
ANTIHISTAMINES: H1-RECEPTOR ANTAGONISTS by DRUG GENERATION:

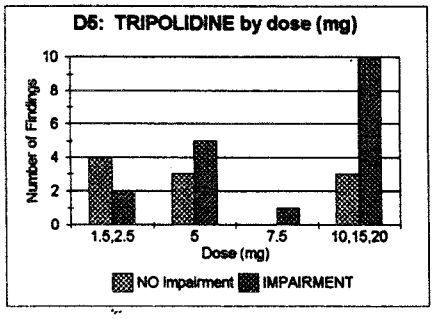
1st GENERATION DRUGS:



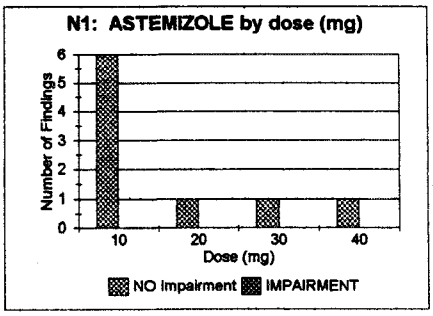


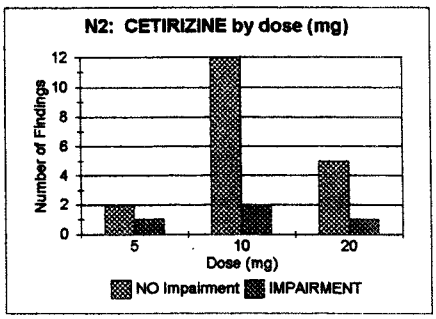


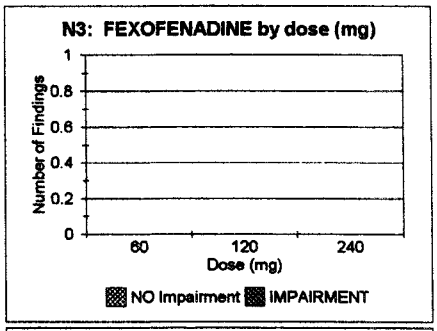


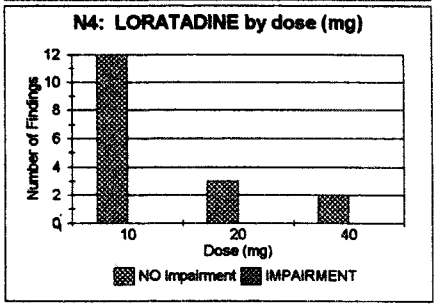


2nd GENERATION DRUGS:









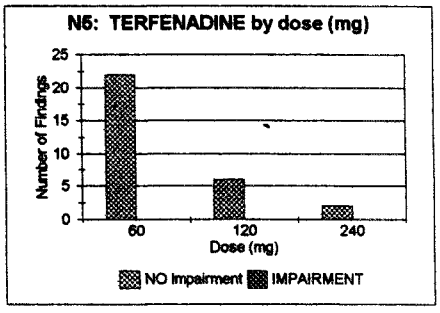
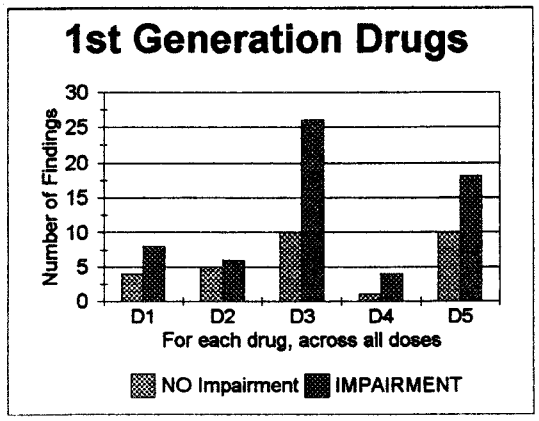
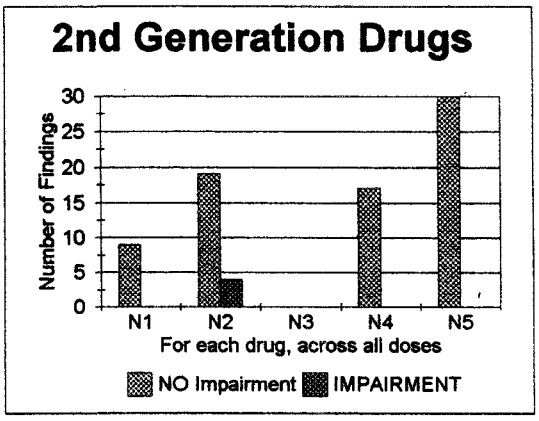


FIGURE 4B.

Results shown for:
TASK CATEGORY: **SUBJECTIVE SEDATION**
SC#: 99

DOSING: Total # Tests:
ACUTE 171





DRUG code:	GENERIC NAME:
D1	CHLORPHENIRAMINE
D2	CLEMASTINE
D3	DIPHENHYDRAMINE
D4	HYDROXYZINE
D5	TRIPOLIDINE

DRUG code:	GENERIC NAME:
N1	ASTEMIZOLE
N2	CETIRIZINE
N3	FEXOFENADINE
N4	LORATADINE
N5	TERFENADINE

SUBJECTIVE SEDATION

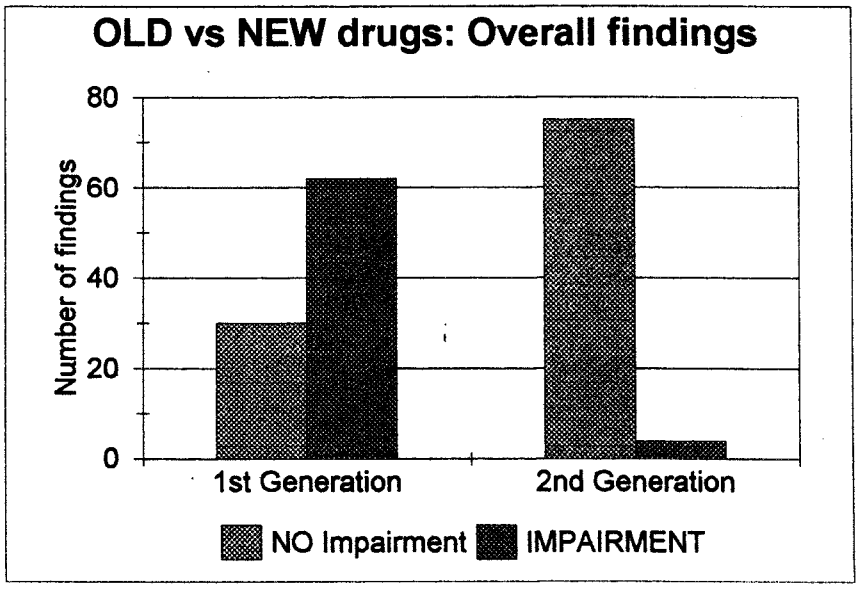
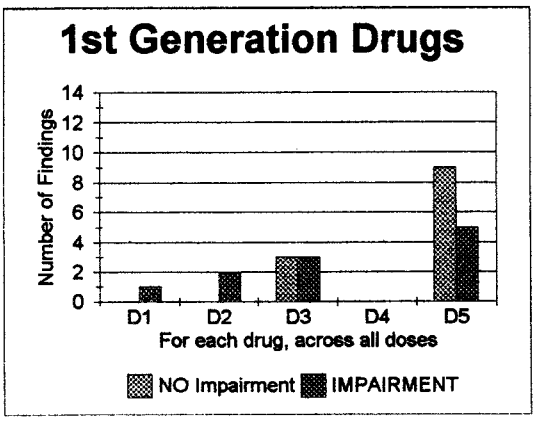
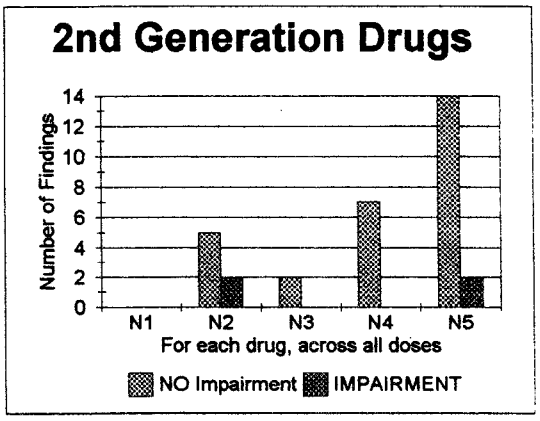


FIGURE 5.

Results shown for:
TASK CATEGORY:
DRIVING and PILOTING
SC#: 1C, 1R, 1S, 1?

DOSING: Total # Tests:
ACUTE 55





DRUG code:	GENERIC NAME:
D1	CHLORPHENIRAMINE
D2	CLEMASTINE
D3	DIPHENHYDRAMINE
D4	HYDROXYZINE
D5	TRIPOLIDINE

DRUG code:	GENERIC NAME:
N1	ASTEMIZOLE
N2	CETIRIZINE
N3	FEXOFENADINE
N4	LORATADINE
N5	TERFENADINE

DRIVING and PILOTING

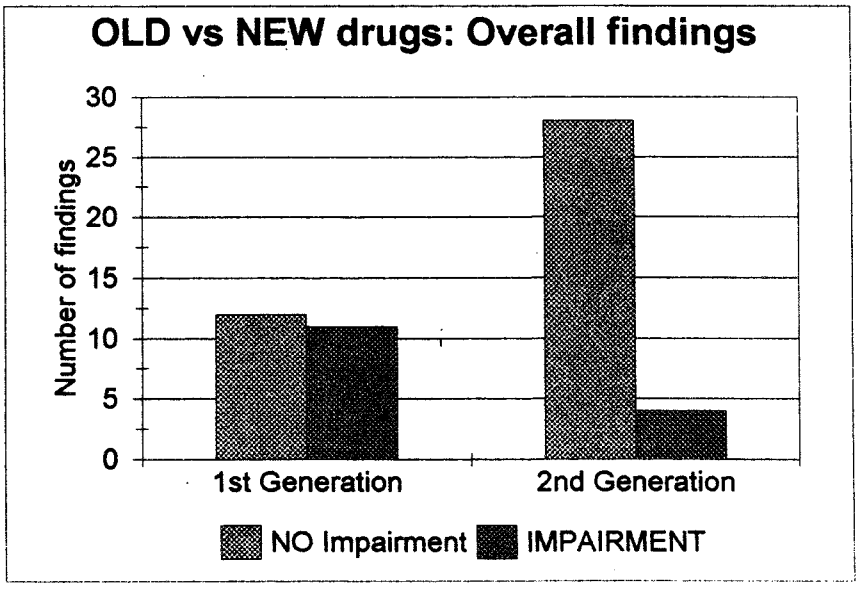
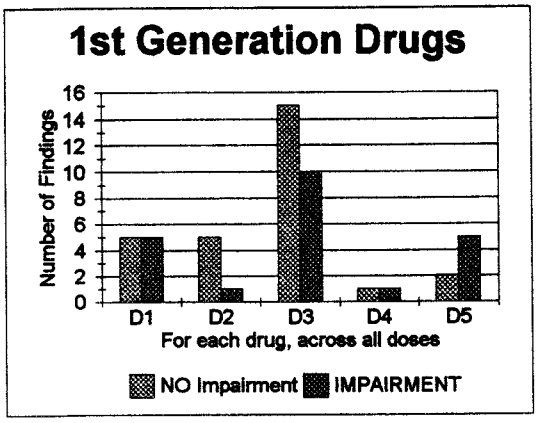
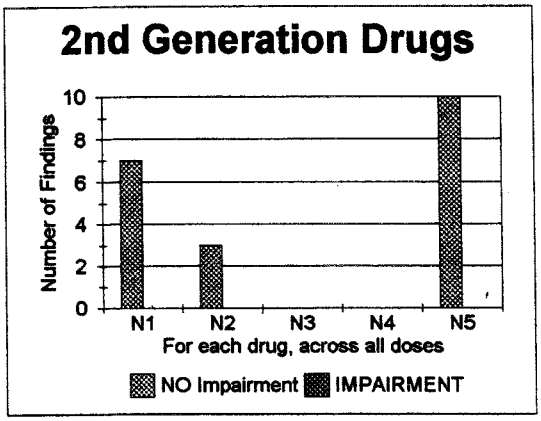


FIGURE 6.

Results shown for:
TASK CATEGORY:
PSYCHOMOTOR TASKS
SC#: 2 (2,2B,2D,2T)

DOSING: Total # Tests:
ACUTE 70





DRUG code:	GENERIC NAME:
D1	CHLORPHENIRAMINE
D2	CLEMASTINE
D3	DIPHENHYDRAMINE
D4	HYDROXYZINE
D5	TRIPOLIDINE

DRUG code:	GENERIC NAME:
N1	ASTEMIZOLE
N2	CETIRIZINE
N3	FEXOFENADINE
N4	LORATADINE
N5	TERFENADINE

PSYCHOMOTOR TASKS

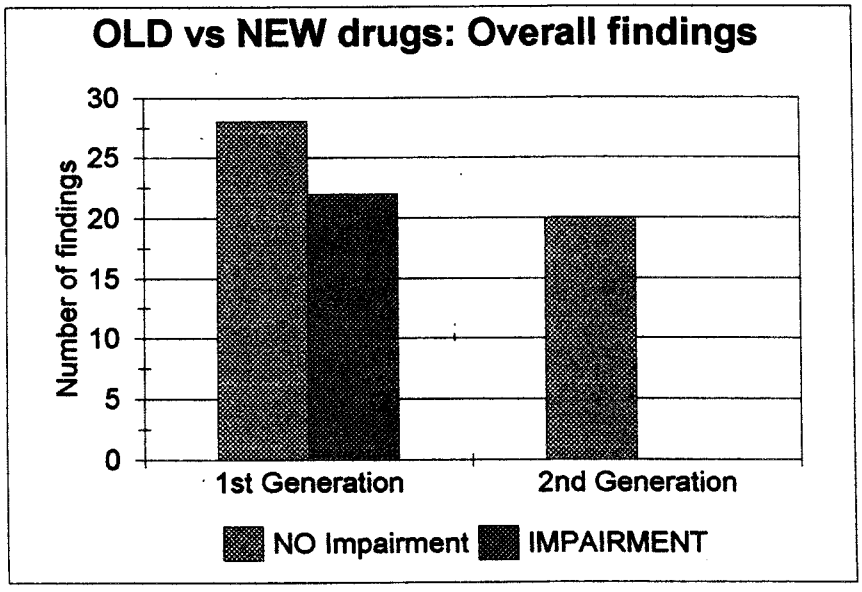
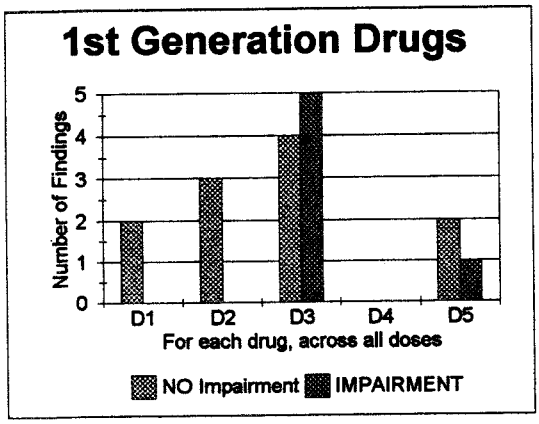


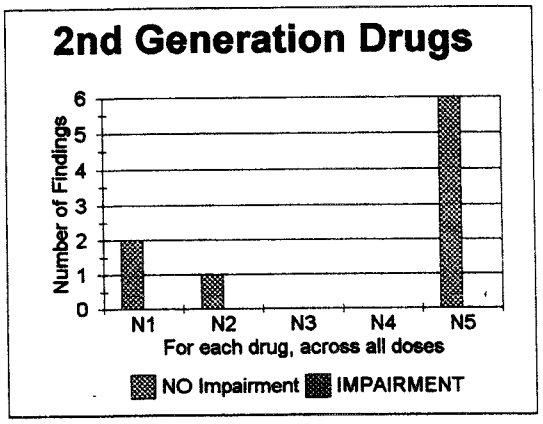
FIGURE 7.

Results shown for:
TASK CATEGORY: **PERCEPTION (& Visual Search)**
SC#: 3

DOSING: **ACUTE**

Total # Tests: 26





DRUG code:	GENERIC NAME:
D1	CHLORPHENIRAMINE
D2	CLEMASTINE
D3	DIPHENHYDRAMINE
D4	HYDROXYZINE
D5	TRIPOLIDINE

DRUG code:	GENERIC NAME:
N1	ASTEMIZOLE
N2	CETIRIZINE
N3	FEXOFENADINE
N4	LORATADINE
N5	TERFENADINE

PERCEPTION (& Visual Search)

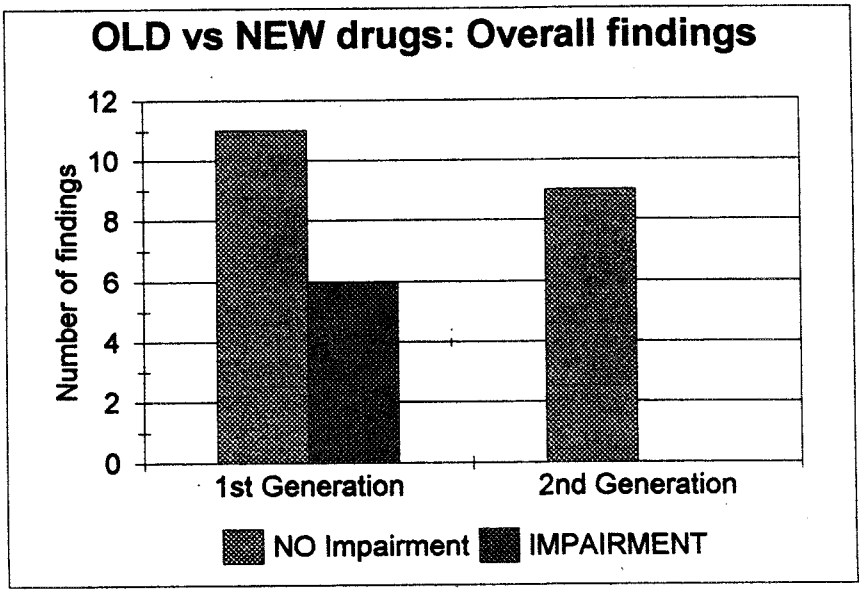
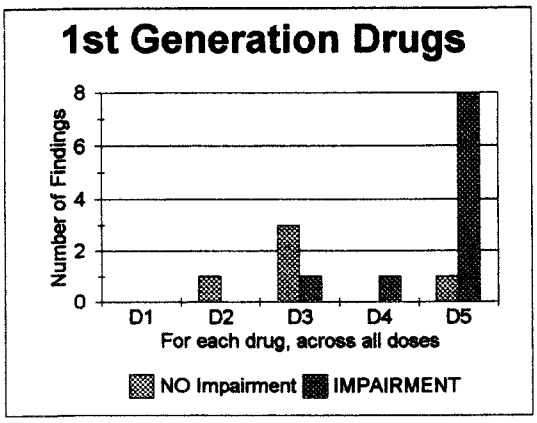


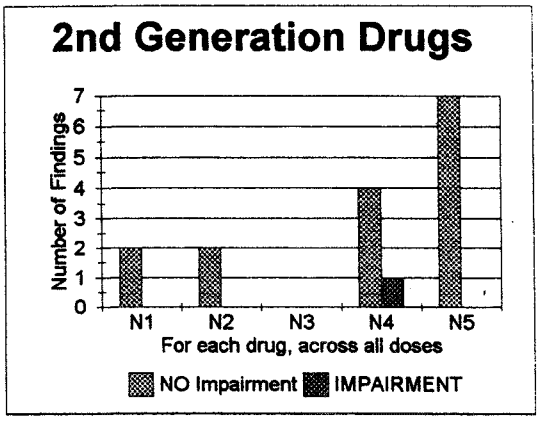
FIGURE 8A.

Results shown for:
TASK CATEGORY:
VISUAL FUNCTIONS
SC#: 4

DOSING: **ACUTE**

Total # Tests: 31





DRUG code:	GENERIC NAME:
D1	CHLORPHENIRAMINE
D2	CLEMASTINE
D3	DIPHENHYDRAMINE
D4	HYDROXYZINE
D5	TRIPOLIDINE

DRUG code:	GENERIC NAME:
N1	ASTEMIZOLE
N2	CETIRIZINE
N3	FEXOFENADINE
N4	LORATADINE
N5	TERFENADINE

VISUAL FUNCTIONS

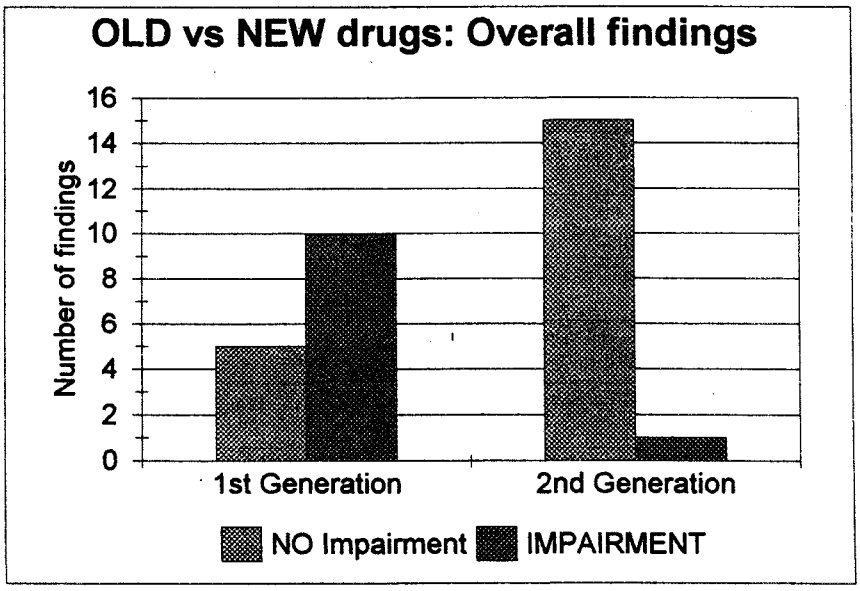
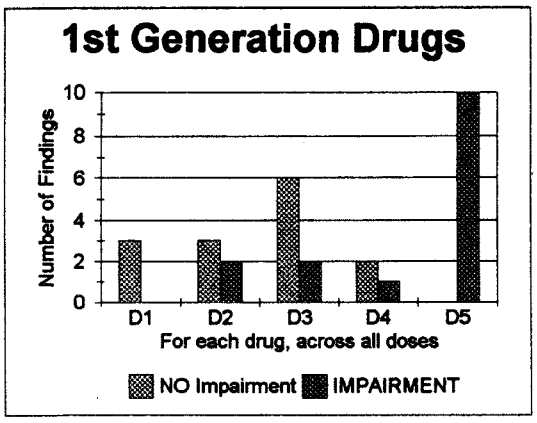


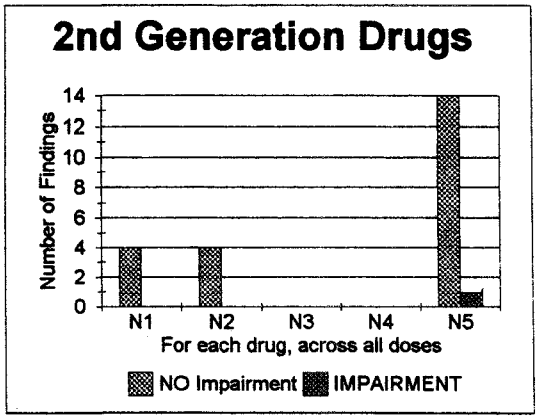
FIGURE 8B.

Results shown for:
TASK CATEGORY: **CRITICAL FLICKER FUSION**
SC#: 4C

DOSING: ACUTE

Total # Tests: 52





DRUG code:	GENERIC NAME:
D1	CHLORPHENIRAMINE
D2	CLEMASTINE
D3	DIPHENHYDRAMINE
D4	HYDROXYZINE
D5	TRIPOLIDINE

DRUG code:	GENERIC NAME:
N1	ASTEMIZOLE
N2	CETIRIZINE
N3	FEXOFENADINE
N4	LORATADINE
N5	TERFENADINE

CRITICAL FLICKER FUSION

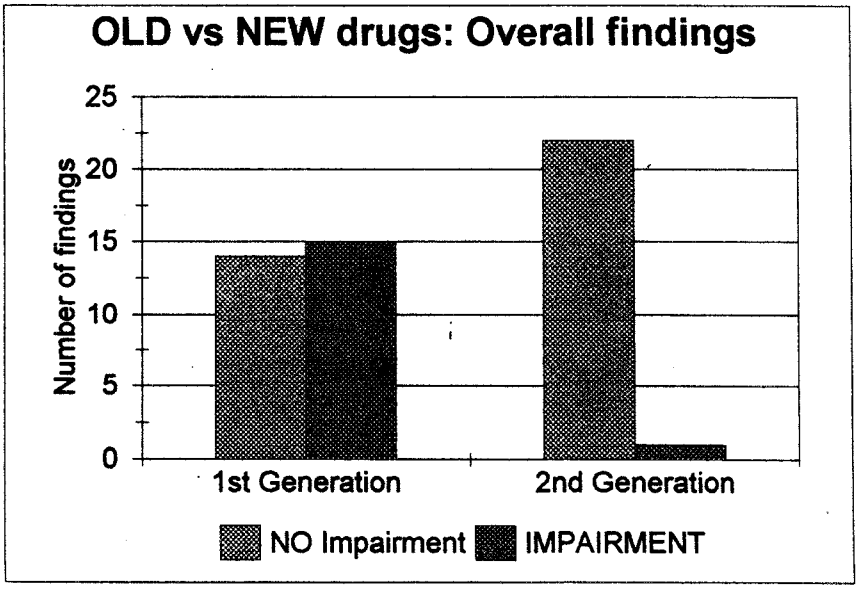
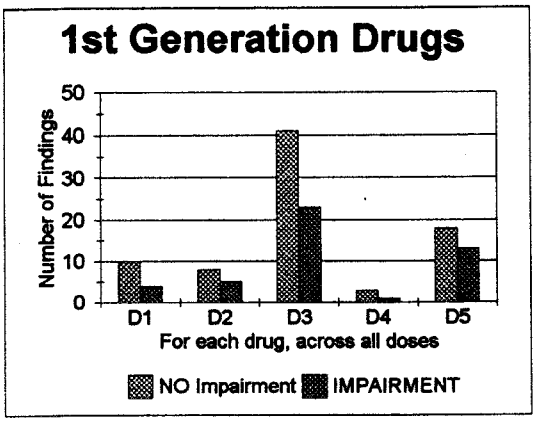
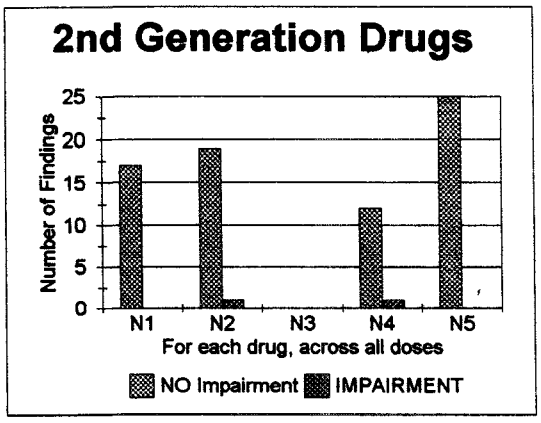


FIGURE 9.

Results shown for:
TASK CATEGORY:
COGNITIVE TASKS
SC#: 5 (5D,5M,5T)

DOSING: Total # Tests:
ACUTE 201





DRUG code:	GENERIC NAME:
D1	CHLORPHENIRAMINE
D2	CLEMASTINE
D3	DIPHENHYDRAMINE
D4	HYDROXYZINE
D5	TRIPOLIDINE

DRUG code:	GENERIC NAME:
N1	ASTEMIZOLE
N2	CETIRIZINE
N3	FEXOFENADINE
N4	LORATADINE
N5	TERFENADINE

COGNITIVE TASKS

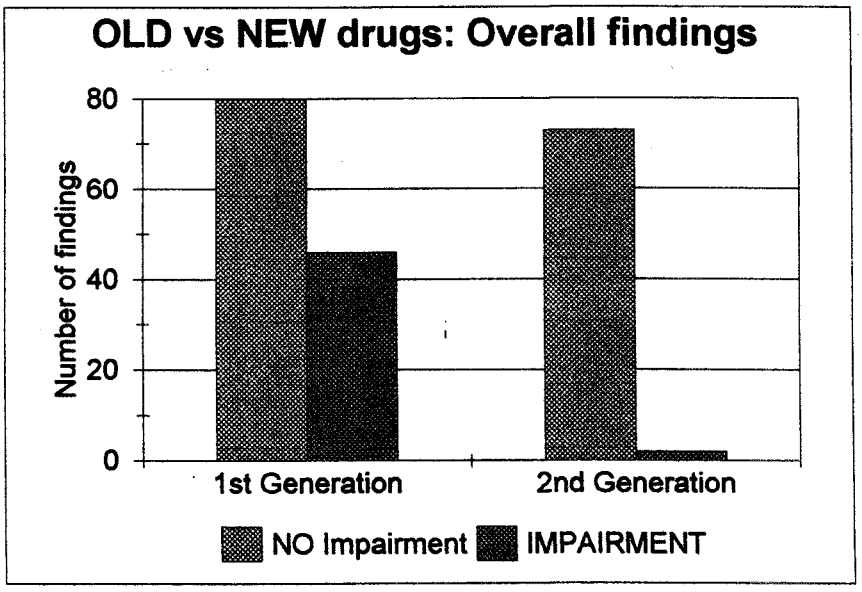
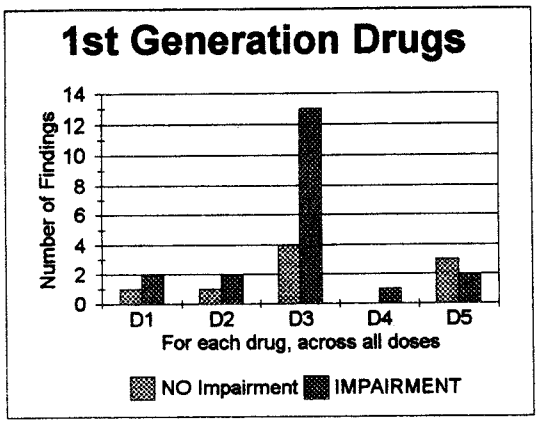
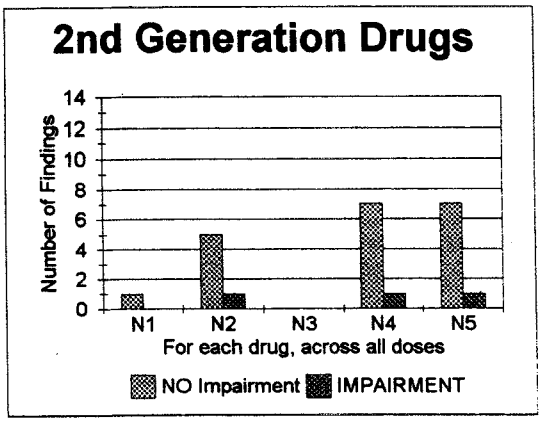


FIGURE 10.

Results shown for:
TASK CATEGORY:
DIVIDED ATTENTION
SC#: 6

DOSING: Total # Tests:
ACUTE 52





DRUG code:	GENERIC NAME:
D1	CHLORPHENIRAMINE
D2	CLEMASTINE
D3	DIPHENHYDRAMINE
D4	HYDROXYZINE
D5	TRIPOLIDINE

DRUG code:	GENERIC NAME:
N1	ASTEMIZOLE
N2	CETIRIZINE
N3	FEXOFENADINE
N4	LORATADINE
N5	TERFENADINE

DIVIDED ATTENTION

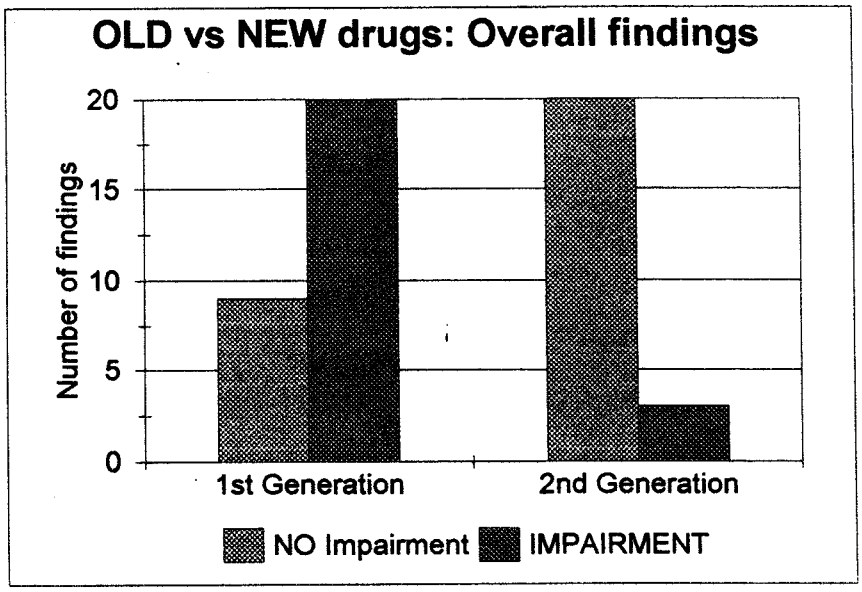
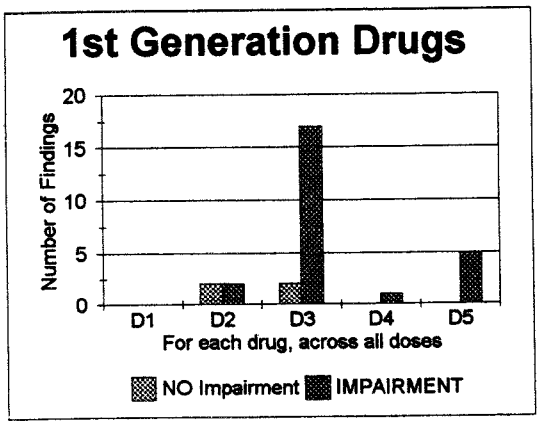
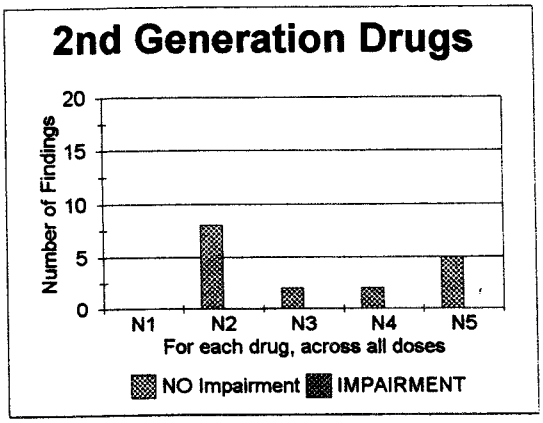


FIGURE 11.

Results shown for:
TASK CATEGORY:
VIGILANCE
SC#: 7 (7?)

DOSING: Total # Tests:
ACUTE 46





DRUG code:	GENERIC NAME:
D1	CHLORPHENIRAMINE
D2	CLEMASTINE
D3	DIPHENHYDRAMINE
D4	HYDROXYZINE
D5	TRIPOLIDINE

DRUG code:	GENERIC NAME:
N1	ASTEMIZOLE
N2	CETIRIZINE
N3	FEXOFENADINE
N4	LORATADINE
N5	TERFENADINE

VIGILANCE

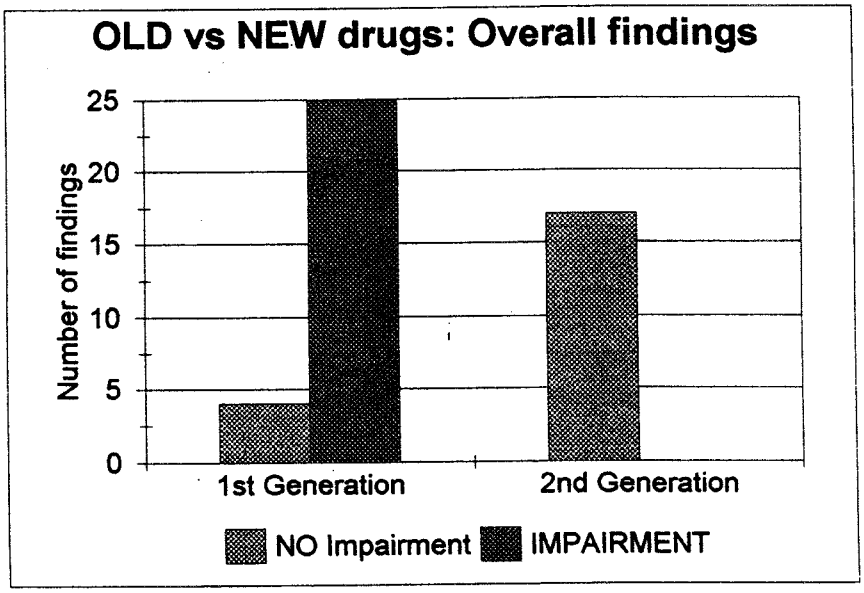
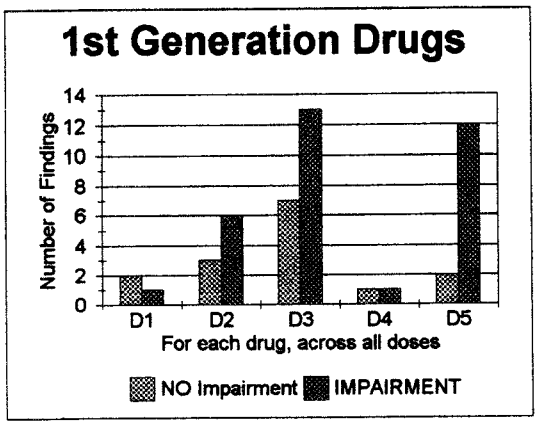
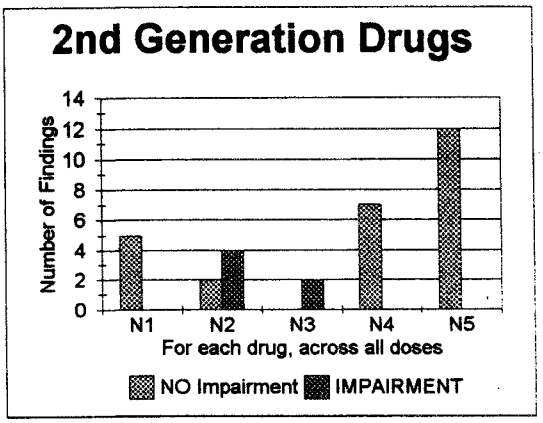


FIGURE 12A.

Results shown for:
TASK CATEGORY: **TRACKING**
SC#: 8 (8, 8Cr)

DOSING: **ACUTE**
Total # Tests: 80





DRUG code:	GENERIC NAME:
D1	CHLORPHENIRAMINE
D2	CLEMASTINE
D3	DIPHENHYDRAMINE
D4	HYDROXYZINE
D5	TRIPOLIDINE

DRUG code:	GENERIC NAME:
N1	ASTEMIZOLE
N2	CETIRIZINE
N3	FEXOFENADINE
N4	LORATADINE
N5	TERFENADINE

TRACKING

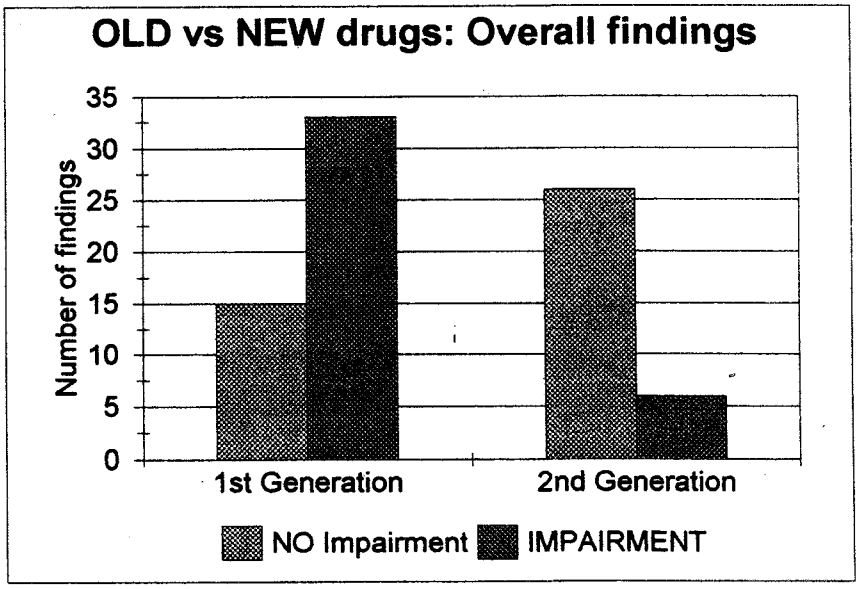
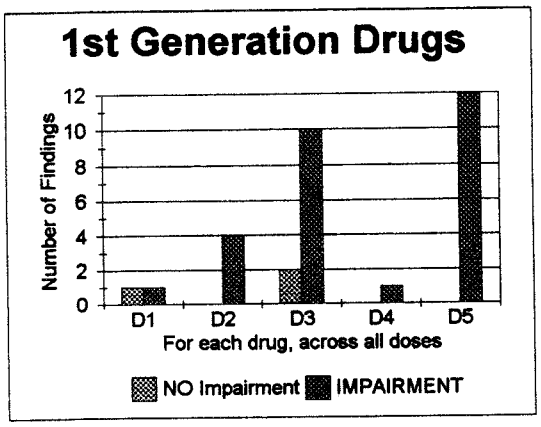


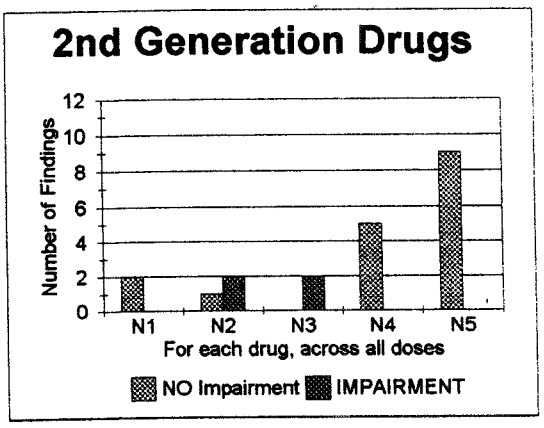
FIGURE 12B.

Results shown for:
TASK CATEGORY: **TRACKING - Critical and Adaptive**
SC#: 8Cr

DOSING: **ACUTE**

Total # Tests: 52





DRUG code:	GENERIC NAME:
D1	CHLORPHENIRAMINE
D2	CLEMASTINE
D3	DIPHENHYDRAMINE
D4	HYDROXYZINE
D5	TRIPOLIDINE

DRUG code:	GENERIC NAME:
N1	ASTEMIZOLE
N2	CETIRIZINE
N3	FEXOFENADINE
N4	LORATADINE
N5	TERFENADINE

TRACKING - Critical and Adaptive

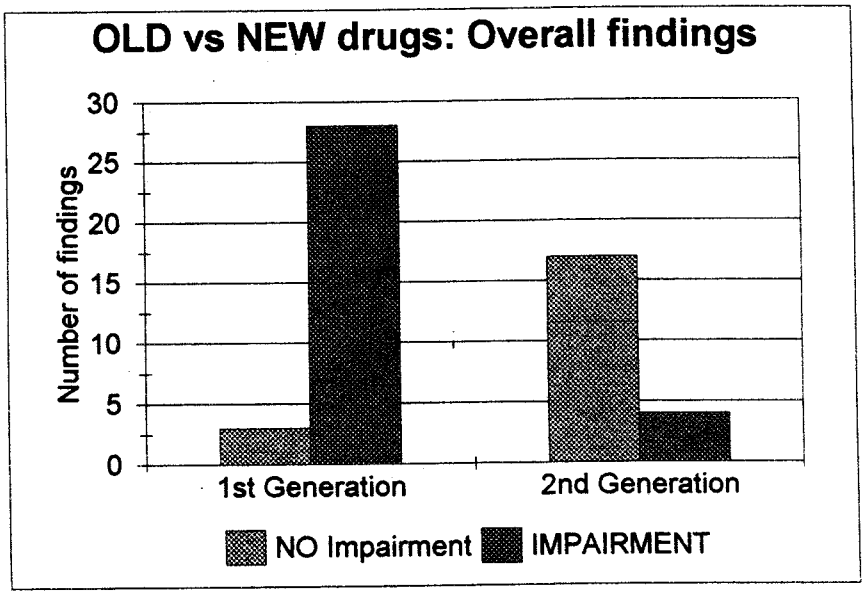
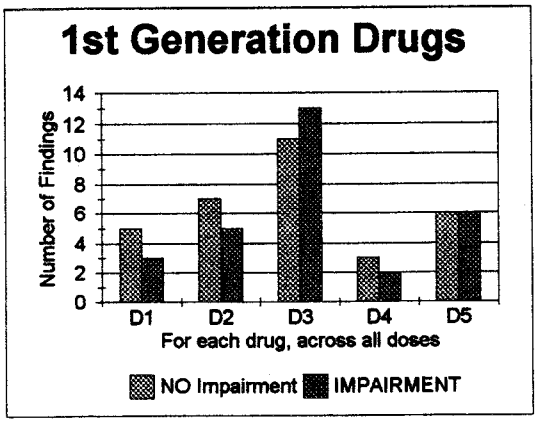
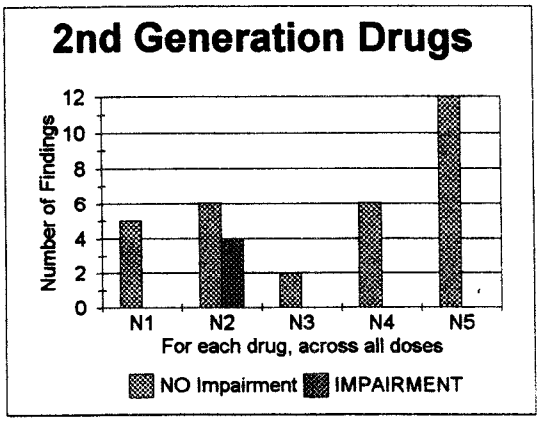


FIGURE 13.

Results shown for:
TASK CATEGORY:
REACTION TIME
SC#: 9 (9, 9S,9C)

DOSING: Total # Tests:
ACUTE 98





DRUG code:	GENERIC NAME:
D1	CHLORPHENIRAMINE
D2	CLEMASTINE
D3	DIPHENHYDRAMINE
D4	HYDROXYZINE
D5	TRIPOLIDINE

DRUG code:	GENERIC NAME:
N1	ASTEMIZOLE
N2	CETIRIZINE
N3	FEXOFENADINE
N4	LORATADINE
N5	TERFENADINE

REACTION TIME

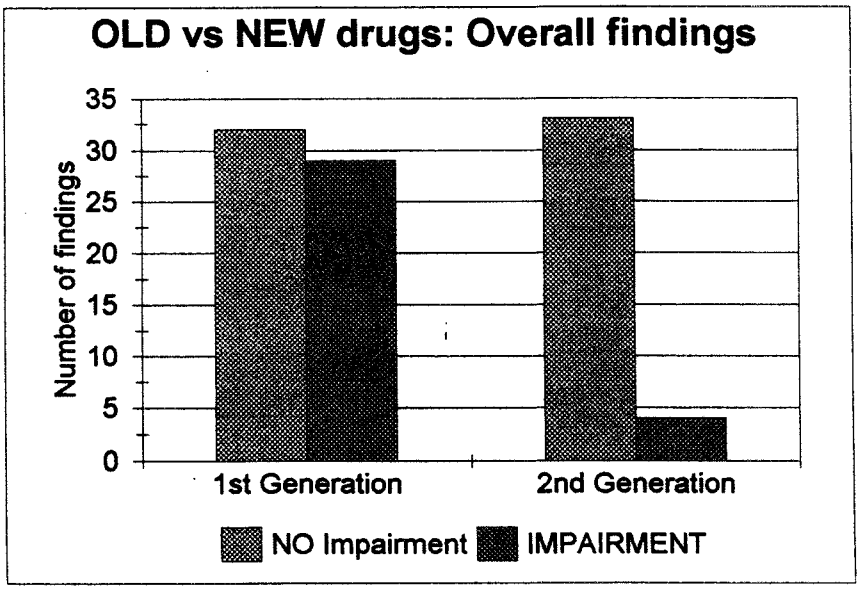
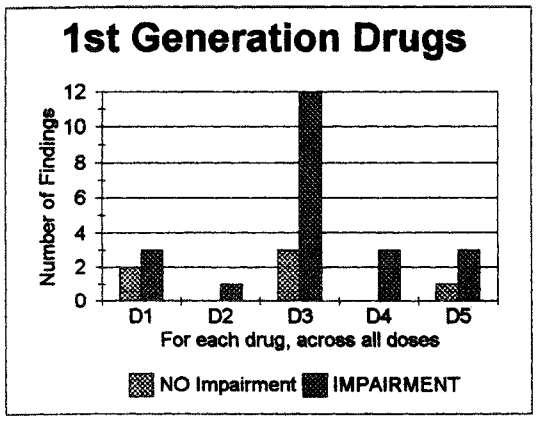


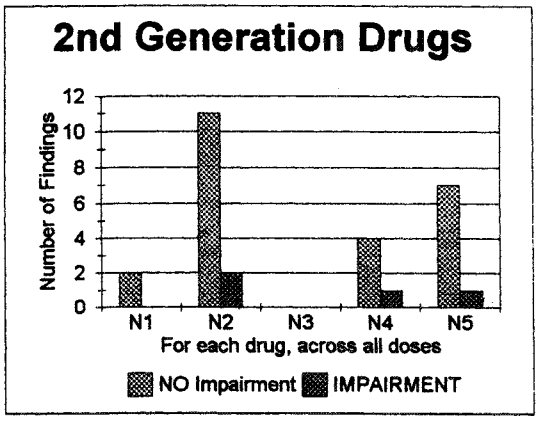
FIGURE 14A.

Results shown for:
TASK CATEGORY:
PHYSIOLOGICAL SEDATION
SC#: 10 (10, 10M)
EEG, ERP, MSLT

DOSING: **ACUTE**

Total # Tests: 56





DRUG code:	GENERIC NAME:
D1	CHLORPHENIRAMINE
D2	CLEMASTINE
D3	DIPHENHYDRAMINE
D4	HYDROXYZINE
D5	TRIPOLIDINE

DRUG code:	GENERIC NAME:
N1	ASTEMIZOLE
N2	CETIRIZINE
N3	FEXOFENADINE
N4	LORATADINE
N5	TERFENADINE

PHYSIOLOGICAL SEDATION

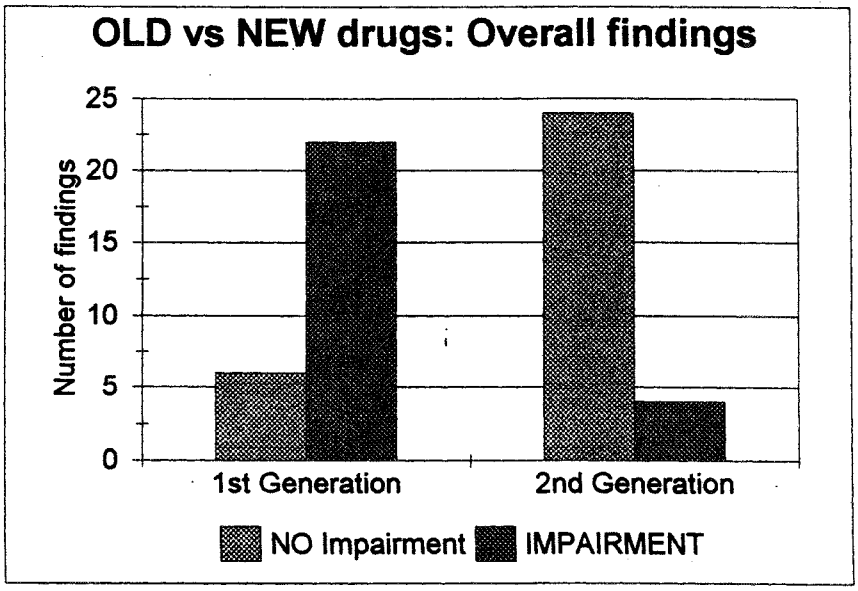
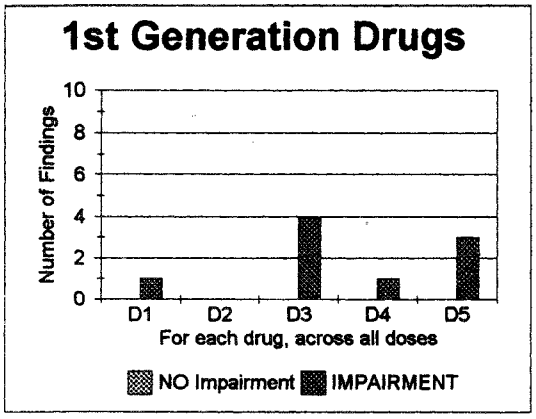


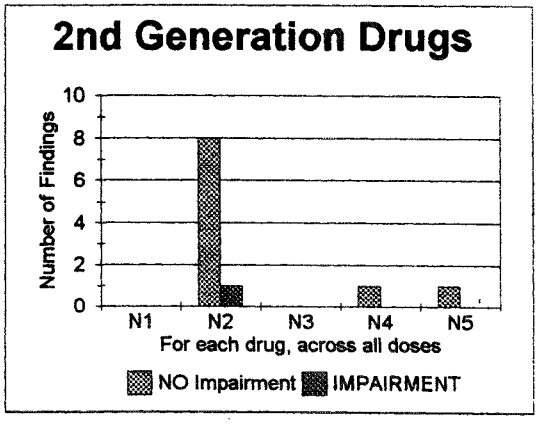
FIGURE 14B.

Results shown for:
TASK CATEGORY:
Multiple Sleep Latency Test
SC#: 10M
(subcode of Physiological)

DOSING: **ACUTE**

Total # Tests: 20

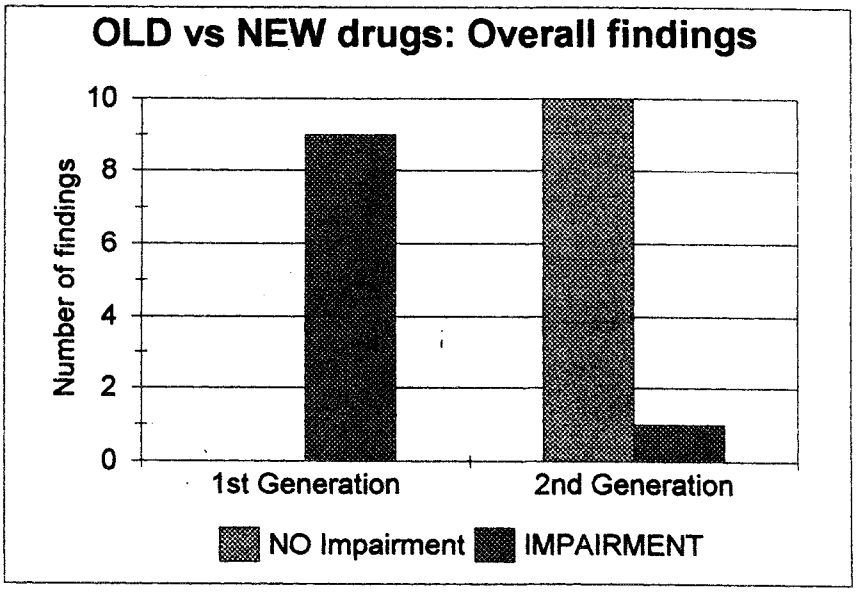


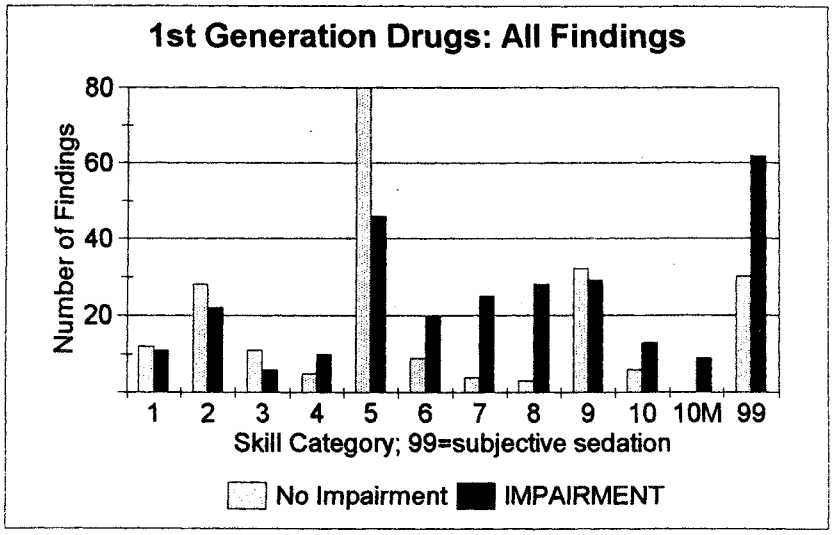


DRUG code:	GENERIC NAME:
D1	CHLORPHENIRAMINE
D2	CLEMASTINE
D3	DIPHENHYDRAMINE
D4	HYDROXYZINE
D5	TRIPOLIDINE

DRUG code:	GENERIC NAME:
N1	ASTEMIZOLE
N2	CETIRIZINE
N3	FEXOFENADINE
N4	LORATADINE
N5	TERFENADINE

Multiple Sleep Latency Test





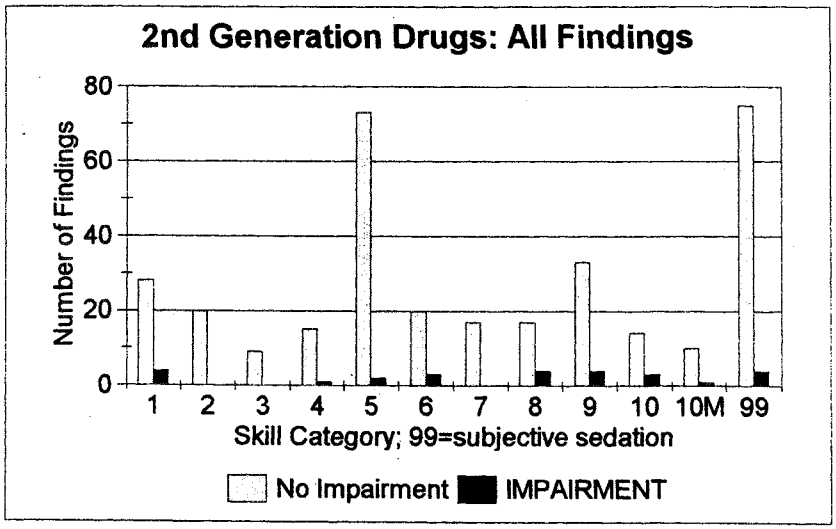


FIGURE 15. Overall Summary

SC#:	SKILL CATEGORIES:
1	DRIVING & PILOTING
2	PSYCHOMOTOR
3	PERCEPTION
4	VISUAL FUNCTIONS, but not CFF
5	COGNITIVE TASKS
6	DIVIDED ATTENTION
7	VIGILANCE
8	TRACKING - only critical & adaptive
9	REACTION TIME
10	PHYSIOLOGICAL - EEG,ERP
10M	Multiple Sleep Latency Test
99	SEDATION - SUBJECTIVE

APPENDICES

Appendix A
Tables of Impairment Findings by Behavioral Category (Listings by Study & Drug)

Appendix B
EXAMPLE of an Impairment Summary Sheet (YES/NO Counts) by Behavioral Category

Appendix C
EXAMPLE of a Study Summary Sheet (n=138 studies from 130 references)

Appendix D
Summary Table of Impairment Findings by Study (includes all 10 Drugs)

Appendix A

Tables of Impairment Findings by Behavioral Category

(Listings by Study & Drug)

SEDATION - SUBJECTIVE MEASURES - Summary of impairment findings as a function of DRUG and Dose - ACUTE DOSING only

TABLE 4.

Sheet: SEDATION

SC#99 Page 2: sorted by Generation, DRUG, Dose, Ref#, Measure

Ref#	REFERENCE	MEASURE of Subjective Sedation	SC#	Gen	DRUG	Dose: mg	IMPAIRMENT? YES	NO
				1st	**Generation Drugs:**			
8	Biehl (1979)	SEDATION - VAS of mood adjectives	99	1	CHLORPHENIRAMINE	4		NO
26	Clarke & Nicholson (1978)	SEDATION - VAS	99	1	CHLORPHENIRAMINE	4		NO
35	Dhorranintra et al. (1990)	SEDATION - VAS & Alertness rating	99	1	CHLORPHENIRAMINE	4	YES	
61	Kulshrestha et al. (1978)	SEDATION - VAS for Sedation	99	1	CHLORPHENIRAMINE	4	YES	
76	Nicholson (1979)	SEDATION - VAS	99	1	CHLORPHENIRAMINE	4		NO
120	Unchern et al. (1986)	SEDATION - 7-pt ratings & Sx report	99	1	CHLORPHENIRAMINE	4	YES	
131B	Witek, Jr. et al. (1995)	SEDATION - VAS (PC), SSS	99	1	CHLORPHENIRAMINE	4	YES	
69	Meador et al. (1989)	SEDATION - reported occurrences	99	1	CHLORPHENIRAMINE	8	YES	
83	Nicholson et al. (1991)	SEDATION - VAS, Stanford (SSS)	99	1	CHLORPHENIRAMINE	10	YES	
63	Lee et al. (1988)	SEDATION - factor 1 of Mood ratings	99	1	CHLORPHENIRAMINE	12		NO bP
25	Chapman & Rawlins (1982)	SEDATION - VAS	99	1	CHLORPHENIRAMINE	16	YES	
59	Khosla et al. (1993)	SEDATION - VAS	99	1	CHLORPHENIRAMINE	16	YES	
26	Clarke & Nicholson (1978)	SEDATION - VAS	99	1	CLEMASTINE	1		NO
42	Gaillard et al. (1988)	SEDATION - VAS scales	99	1	CLEMASTINE	1		NO wP
91	Peck et al. (1975)	SEDATION - VAS set of states	99	1	CLEMASTINE	1		NO
97	Reinberg et al. (1978)	SEDATION - (~VAS rectangle 22cm)	99	1	CLEMASTINE	1		NO
112	Seppala et al. (1981)	SEDATION - VAS series	99	1	CLEMASTINE	1	YES	
53	Hopes et al. (1992)	SEDATION - Adjective checklists	99	1	CLEMASTINE	2	YES	
87	Patat et al. (1994)	SEDATION - VAS series (LARS)	99	1	CLEMASTINE	2		NO wP
91	Peck et al. (1975)	SEDATION - VAS set of states	99	1	CLEMASTINE	2	YES	
124	Vuurman et al. (1994)	SEDATION - VAS, Bond & Lader	99	1	CLEMASTINE	2	YES	
64	Levander et al. (1985)	SEDATION - VAS; 3/6 sets = sedation	99	1	CLEMASTINE	3	YES	
97	Reinberg et al. (1978)	SEDATION - (~VAS rectangle 22cm)	99	1	CLEMASTINE	3	YES	
27	Cohen et al. (1984)	SEDATION - VAS; on drive day	99	1	DIPHENHYDRAMINE	25		NO
27	Cohen et al. (1984)	SEDATION - VAS; on lab day	99	1	DIPHENHYDRAMINE	25	YES	
30	Curran et al. (1998)	SEDATION - VAS	99	1	DIPHENHYDRAMINE	25		NO
38	Fine et al. (1994)	SEDATION - POMS (PC)	99	1	DIPHENHYDRAMINE	25	YES	
120	Unchern et al. (1986)	SEDATION - 7-pt ratings & Sx report	99	1	DIPHENHYDRAMINE	25	YES	
134	Scavone et al. (1998)	SEDATION - VAS lines	99	1	DIPHENHYDRAMINE	25		NO
131B	Witek, Jr. et al. (1995)	SEDATION - VAS (PC), SSS	99	1	DIPHENHYDRAMINE	25	YES	
4	Berlinger et al. (1982)	SEDATION - VAS sed, mood adjectives	99	1	DIPHENHYDRAMINE	50		NO
20	Burns et al. (1999 - ms)	SEDATION - VAS	99	1	DIPHENHYDRAMINE	50		NO
24	Carruthers et al. (1978)	SEDATION - VAS	99	1	DIPHENHYDRAMINE	50	YES	
27	Cohen et al. (1984)	SEDATION - VAS; on drive day	99	1	DIPHENHYDRAMINE	50		NO
27	Cohen et al. (1984)	SEDATION - VAS; on lab day	99	1	DIPHENHYDRAMINE	50	YES	
29	Cohen et al. (1987)	SEDATION - VAS	99	1	DIPHENHYDRAMINE	50	YES	
30	Curran et al. (1998)	SEDATION - VAS	99	1	DIPHENHYDRAMINE	50	YES	
39	Fink et al. (1979)	SEDATION - Alertness rating	99	1	DIPHENHYDRAMINE	50	YES	
44	Gengo et al. (1990)	SEDATION - VAS, Stanford (SSS)	99	1	DIPHENHYDRAMINE	50	YES	
57	Kaye et al. (1997)	SEDATION - Stanford SSS, VAS, Moods	99	1	DIPHENHYDRAMINE	50	YES	
66	Lines et al. (1997)	SEDATION - VAS; Bond & Lader Factor 1	99	1	DIPHENHYDRAMINE	50		NO
110	Schweitzer et al. (1994)	SEDATION - VAS	99	1	DIPHENHYDRAMINE	50	YES	
114	Simons et al. (1996)	SEDATION - VAS based on SSS	99	1	DIPHENHYDRAMINE	50	YES	
116	Spector et al. (1980)	SEDATION - VAS (mean of 8)	99	1	DIPHENHYDRAMINE	50	YES	
119	Tharion et al. (1994)	SEDATION - POMS, Sx Q	99	1	DIPHENHYDRAMINE	50		NO
127	Wilkinson & Moskowitz (1990)	SEDATION - POMS	99	1	DIPHENHYDRAMINE	50	YES	
129	Wilkinson et al. (1999 - ms)	SEDATION - VAS	99	1	DIPHENHYDRAMINE	50		NO
130A	Witek, Jr. et al. (1992)	SEDATION - VAS (PC), SSS	99	1	DIPHENHYDRAMINE	50	YES	
130B	Witek, Jr. et al. (1992)	SEDATION - VAS (PC), SSS	99	1	DIPHENHYDRAMINE	50	YES	
131A	Witek, Jr. et al. (1995)	SEDATION - VAS (PC), SSS	99	1	DIPHENHYDRAMINE	50	YES	
131B	Witek, Jr. et al. (1995)	SEDATION - VAS (PC), SSS	99	1	DIPHENHYDRAMINE	50	YES	
27	Cohen et al. (1984)	SEDATION - VAS; on drive day	99	1	DIPHENHYDRAMINE	100	YES	
27	Cohen et al. (1984)	SEDATION - VAS; on lab day	99	1	DIPHENHYDRAMINE	100	YES	
68	Mattila et al. (1986)	SEDATION - VAS	99	1	DIPHENHYDRAMINE	100	YES	
70	Mohs et al. (1978)	SEDATION - reported occurrences	99	1	DIPHENHYDRAMINE	100	YES	
71	Moser et al. (1978)	SEDATION - 9-pt VAS: tired, dull	99	1	DIPHENHYDRAMINE	100	YES	
94	Preston et al. (1992)	SEDATION - DEQ: Alert-Sleepy scale	99	1	DIPHENHYDRAMINE	100		NO
106	Saarialho-Kere et al. (1989)	SEDATION - VAS set of states	99	1	DIPHENHYDRAMINE	100	YES	
94	Preston et al. (1992)	SEDATION - DEQ: Alert-Sleepy scale	99	1	DIPHENHYDRAMINE	200	YES	
64	Levander et al. (1985)	SEDATION - VAS; 3/6 sets = sedation	99	1	HYDROXYZINE	20	YES	
65	Levander et al. (1991)	SEDATION - VAS; 3/7 sets = sedation	99	1	HYDROXYZINE	20	YES	
43	Gengo et al. (1987)	SEDATION - VAS	99	1	HYDROXYZINE	25	YES	
111	Seidel et al. (1987)	SEDATION - VAS, Stanford (SSS), POMS	99	1	HYDROXYZINE	25		NO
125	Walsh et al. (1992)	SEDATION - VAS	99	1	HYDROXYZINE	25	YES	
91	Peck et al. (1975)	SEDATION - VAS set of states	99	1	TRIPOLIDINE	1.25	YES	
21	Bye et al. (1974)	SEDATION - VAS	99	1	TRIPOLIDINE	2.5		NO
28	Cohen et al. (1985)	SEDATION - VAS	99	1	TRIPOLIDINE	2.5	YES	
48	Hamilton et al. (1982)	SEDATION - VAS	99	1	TRIPOLIDINE	2.5		NO
76	Nicholson (1979)	SEDATION - VAS	99	1	TRIPOLIDINE	2.5		NO

82	Nicholson & Stone (1986)	SEDATION - VAS	99	1	TRIPOLIDINE	2.5		NO
21	Bye et al. (1974)	SEDATION - VAS	99	1	TRIPOLIDINE	5	YES	
22	Bye et al. (1977)	SEDATION - VAS	99	1	TRIPOLIDINE	5	YES	
28	Cohen et al. (1985)	SEDATION - VAS	99	1	TRIPOLIDINE	5	YES	
82	Nicholson & Stone (1986)	SEDATION - VAS	99	1	TRIPOLIDINE	5		NO
83	Nicholson et al. (1991)	SEDATION - VAS, Stanford (SSS)	99	1	TRIPOLIDINE	5		NO
91	Peck et al. (1975)	SEDATION - VAS set of states	99	1	TRIPOLIDINE	5	YES	
121	Valk et al. (1997)	SEDATION - Stanford (SSS)	99	1	TRIPOLIDINE	5	YES	
123	Volkerts et al. (1992)	SEDATION - ~VAS (interval scale)	99	1	TRIPOLIDINE	5		NO
117	Swire et al. (1989)	SEDATION - VAS set of states (Bond & Lader)	99	1	TRIPOLIDINE	7.5	YES	
12	Bradley & Nicholson (1986)	SEDATION - VAS Mood assessments	99	1	TRIPOLIDINE	10	YES	
14	Bradley & Nicholson (1987)	SEDATION - VAS Mood assessments	99	1	TRIPOLIDINE	10	YES	
15	Brookhuis et al. (1993)	SEDATION - mental activation (sed)	99	1	TRIPOLIDINE	10		NO
58	Kerr et al. (1994)	SEDATION - VAS	99	1	TRIPOLIDINE	10	YES	
76	Nicholson (1979)	SEDATION - VAS	99	1	TRIPOLIDINE	10		NO
77	Nicholson & Stone (1982)	SEDATION - VAS	99	1	TRIPOLIDINE	10	YES	
78	Nicholson et al. (1982)	SEDATION - VAS	99	1	TRIPOLIDINE	10		NO wP
79	Nicholson & Stone (1983)	SEDATION - VAS	99	1	TRIPOLIDINE	10	YES	
80	Nicholson & Stone (1984)	SEDATION - VAS	99	1	TRIPOLIDINE	10	YES	
82	Nicholson & Stone (1986)	SEDATION - VAS	99	1	TRIPOLIDINE	10	YES	
104	Rombaut et al. (1991)	SEDATION - VAS set of states	99	1	TRIPOLIDINE	10	YES	
13A	Bradley et al. (1987)	SEDATION - VAS Mood assessments	99	1	TRIPOLIDINE	10	YES	
13B	Bradley et al. (1987)	SEDATION - VAS Mood assessments	99	1	TRIPOLIDINE	10	YES	

SEDATION - SUBJECTIVE MEASURES - Summary of impairment findings as a function of DRUG and Dose - ACUTE DOSING only

cont'd... Sheet: SEDATION
SC#99 Page 2: sorted by Generation, DRUG, Dose, Ref#, Measure

Ref#	REFERENCE	MEASURE of Subjective Sedation	SC#	Gen	DRUG	Dose: mg	IMPAIRMENT? YES	NO
				2nd	Generation Drugs:			
34	Dhorranintra et al. (1986)	SEDATION - VAS & Alertness rating	99	2	ASTEMIZOLE	10		NO
51	Hindmarch & Easton (1986)	SEDATION - VAS set (LARS)	99	2	ASTEMIZOLE	10		NO
77	Nicholson & Stone (1982)	SEDATION - VAS	99	2	ASTEMIZOLE	10		NO
78	Nicholson et al. (1982)	SEDATION - VAS	99	2	ASTEMIZOLE	10		NO
113	Seppala & Savolainen (1982)	SEDATION - VAS series	99	2	ASTEMIZOLE	10		NO
114	Simons et al. (1996)	SEDATION - VAS based on SSS	99	2	ASTEMIZOLE	10		NO wB
77	Nicholson & Stone (1982)	SEDATION - VAS	99	2	ASTEMIZOLE	20		NO
113	Seppala & Savolainen (1982)	SEDATION - VAS series	99	2	ASTEMIZOLE	30		NO
25	Chapman & Rawlins (1982)	SEDATION - VAS	99	2	ASTEMIZOLE	40		NO
44	Gengo et al. (1990)	SEDATION - VAS, Stanford (SSS)	99	2	CETIRIZINE	5		NO
84	Nicholson & Turner (1998)	SEDATION - VAS, Stanford (SSS)	99	2	CETIRIZINE	5	YES	
111	Seidel et al. (1987)	SEDATION - VAS, Stanford (SSS), POMS	99	2	CETIRIZINE	5		NO
6	Betts et al. (1989)	SEDATION - VAS set	99	2	CETIRIZINE	10		NO
36	Doms et al. (1988)	SEDATION - VAS & ratings	99	2	CETIRIZINE	10		NO
43	Gengo et al. (1987)	SEDATION - VAS	99	2	CETIRIZINE	10		NO
44	Gengo et al. (1990)	SEDATION - VAS, Stanford (SSS)	99	2	CETIRIZINE	10		NO
65	Levander et al. (1991)	SEDATION - VAS; 3/7 sets = sedation	99	2	CETIRIZINE	10		NO
84	Nicholson & Turner (1998)	SEDATION - VAS, Stanford (SSS)	99	2	CETIRIZINE	10	YES	
89	Pechadre et al. (1988)	SEDATION - VAS	99	2	CETIRIZINE	10		NO
90	Pechadre et al. (1991)	SEDATION - VAS	99	2	CETIRIZINE	10		NO
95	Ramaekers et al. (1992)	SEDATION - VAS	99	2	CETIRIZINE	10		NO wP
110	Schweitzer et al. (1994)	SEDATION - VAS	99	2	CETIRIZINE	10		NO
111	Seidel et al. (1987)	SEDATION - VAS, Stanford (SSS), POMS	99	2	CETIRIZINE	10		NO
114	Simons et al. (1996)	SEDATION - VAS based on SSS	99	2	CETIRIZINE	10	YES	
123	Volkerts et al. (1992)	SEDATION - ~VAS (interval scale)	99	2	CETIRIZINE	10		NO
125	Walsh et al. (1992)	SEDATION - VAS	99	2	CETIRIZINE	10		NO wP
6	Betts et al. (1989)	SEDATION - VAS set	99	2	CETIRIZINE	20		NO
33	De Roeck et al. (1990)	SEDATION - Stanford Sleepiness Scale	99	2	CETIRIZINE	20		NO?
43	Gengo et al. (1987)	SEDATION - VAS	99	2	CETIRIZINE	20		NO
44	Gengo et al. (1990)	SEDATION - VAS, Stanford (SSS)	99	2	CETIRIZINE	20		NO
84	Nicholson & Turner (1998)	SEDATION - VAS, Stanford (SSS)	99	2	CETIRIZINE	20	YES	
111	Seidel et al. (1987)	SEDATION - VAS, Stanford (SSS), POMS	99	2	CETIRIZINE	20		NO
14	Bradley & Nicholson (1987)	SEDATION - VAS Mood assessments	99	2	LORATADINE	10		NO
37	Englisch et al. (1996)	SEDATION - VAS	99	2	LORATADINE	10		NO
42	Gaillard et al. (1988)	SEDATION - VAS scales	99	2	LORATADINE	10		NO
57	Kaye et al. (1997)	SEDATION - Stanford SSS, VAS, Moods	99	2	LORATADINE	10		NO
75	Neves-Pinto et al. (1992)	SEDATION - reported Sx per list	99	2	LORATADINE	10		NO
90	Pechadre et al. (1991)	SEDATION - VAS	99	2	LORATADINE	10		NO
95	Ramaekers et al. (1992)	SEDATION - VAS	99	2	LORATADINE	10		NO
109	Schaffler et al. (1994)	SEDATION - VAS; wakefulness	99	2	LORATADINE	10		NO
114	Simons et al. (1996)	SEDATION - VAS based on SSS	99	2	LORATADINE	10		NO wB
121	Valk et al. (1997)	SEDATION - Stanford (SSS)	99	2	LORATADINE	10		NO
127	Wilkinson & Moskowitz (1990)	SEDATION - POMS	99	2	LORATADINE	10		NO
133	Corner et al. (1998)	SEDATION - VAS lines in 50 set	99	2	LORATADINE	10		NO
14	Bradley & Nicholson (1987)	SEDATION - VAS Mood assessments	99	2	LORATADINE	20		NO
33	De Roeck et al. (1990)	SEDATION - Stanford Sleepiness Scale	99	2	LORATADINE	20		NO
133	Corner et al. (1998)	SEDATION - VAS lines in 50 set	99	2	LORATADINE	20		NO
14	Bradley & Nicholson (1987)	SEDATION - VAS Mood assessments	99	2	LORATADINE	40		NO
90	Pechadre et al. (1991)	SEDATION - VAS	99	2	LORATADINE	40		NO
6	Betts et al. (1989)	SEDATION - VAS set	99	2	TERFENADINE	60		NO
7	Bhatti & Hindmarch (1989)	SEDATION - VAS	99	2	TERFENADINE	60		NO
26	Clarke & Nicholson (1978)	SEDATION - VAS	99	2	TERFENADINE	60		NO bP
39	Fink et al. (1979)	SEDATION - Alertness rating	99	2	TERFENADINE	60		NO
42	Gaillard et al. (1988)	SEDATION - VAS scales	99	2	TERFENADINE	60		NO
58	Kerr et al. (1994)	SEDATION - VAS	99	2	TERFENADINE	60		NO
61	Kulshrestha et al. (1978)	SEDATION - VAS for Sedation	99	2	TERFENADINE	60		NO
69	Meador et al. (1989)	SEDATION - reported occurrences	99	2	TERFENADINE	60		NO
71	Moser et al. (1978)	SEDATION - 9-pt VAS: tired, dull	99	2	TERFENADINE	60		NO
77	Nicholson & Stone (1982)	SEDATION - VAS	99	2	TERFENADINE	60		NO
78	Nicholson et al. (1982)	SEDATION - VAS	99	2	TERFENADINE	60		NO
79	Nicholson & Stone (1983)	SEDATION - VAS	99	2	TERFENADINE	60		NO
82	Nicholson & Stone (1986)	SEDATION - VAS	99	2	TERFENADINE	60		NO
89	Pechadre et al. (1988)	SEDATION - VAS	99	2	TERFENADINE	60		NO
97	Reinberg et al. (1978)	SEDATION - (~VAS rectangle 22cm)	99	2	TERFENADINE	60		NO bP
114	Simons et al. (1996)	SEDATION - VAS based on SSS	99	2	TERFENADINE	60		NO wB
117	Swire et al. (1989)	SEDATION - VAS set of states (Bond & Lader)	99	2	TERFENADINE	60		NO
119	Tharion et al. (1994)	SEDATION - POMS, Sx Q	99	2	TERFENADINE	60		NO
120	Unchern et al. (1986)	SEDATION - 7-pt ratings & Sx report	99	2	TERFENADINE	60		NO
123	Volkerts et al. (1992)	SEDATION - ~VAS (interval scale)	99	2	TERFENADINE	60		NO

130A	Witek, Jr. et al. (1992)	SEDATION - VAS (PC), SSS	99	2	TERFENADINE	60	NO
131A	Witek, Jr. et al. (1995)	SEDATION - VAS (PC), SSS	99	2	TERFENADINE	60	NO
6	Betts et al. (1989)	SEDATION - VAS set	99	2	TERFENADINE	120	NO
7	Bhatti & Hindmarch (1989)	SEDATION - VAS	99	2	TERFENADINE	120	NO
71	Moser et al. (1978)	SEDATION - 9-pt VAS: tired, dull	99	2	TERFENADINE	120	NO
74	Murri et al. (1986)	SEDATION - Stanford (SSS)	99	2	TERFENADINE	120	NO
82	Nicholson & Stone (1986)	SEDATION - VAS	99	2	TERFENADINE	120	NO
123	Volkerts et al. (1992)	SEDATION - ~VAS (interval scale)	99	2	TERFENADINE	120	NO
7	Bhatti & Hindmarch (1989)	SEDATION - VAS	99	2	TERFENADINE	240	NO
71	Moser et al. (1978)	SEDATION - 9-pt VAS: tired, dull	99	2	TERFENADINE	240	NO

TABLE 5. DRIVING SC#1 **DRIVING and PILOTING TASKS - Summary of impairment findings as a function of DRUG and Dose - ACUTE DOSING only**

sorted by Generation, Drug, Dose, Ref#, SC#

Ref#	REFERENCE	TASK (or Subjective SEDATION)	SC#	TaskDUR	Gen	DRUG	Dose: mg	IMPAIRMENT? YES	NO
				1st		**Generation Drugs:**			
8	Biehl (1979)	DRIVING SIMULATOR - very basic	1S	???	1	CHLORPHENIRAMINE	4	**YES**	
124	Vuurman et al. (1994)	DRIVING - Actual, Highway circuit	1R	~ 1hr	1	CLEMASTINE	2	**YES**	
122	Vermeeren & O'Hanlon (1998)	DRIVING - Actual, Highway circuit	1R	~ 1hr	1	CLEMASTINE	3	**YES**	
27	Cohen et al. (1984)	DRIVING - off-road, circuit	1C	15 min	1	DIPHENHYDRAMINE	25		NO
27	Cohen et al. (1984)	DRIVING - off-road, circuit	1C	15 min	1	DIPHENHYDRAMINE	50		NO
44	Gengo et al. (1990)	DRIVING SIMULATOR - Doron, 2 diff. runs	1S	7 min runs	1	DIPHENHYDRAMINE	50	**YES**	
96	Ramaekers et al. (1994)	DRIVING - Actual, Car following test	1R	12 min	1	DIPHENHYDRAMINE	50	**YES**	
96	Ramaekers et al. (1994)	DRIVING - Actual, Highway circuit	1R	~1hr	1	DIPHENHYDRAMINE	50	**YES**	
27	Cohen et al. (1984)	DRIVING - off-road, circuit	1C	15 min	1	DIPHENHYDRAMINE	100		NO
55	Irving & Jones (1992)	HAZARD PERCEPTION - Sim traffic scenes	1?	12 min?	1	TRIPOLIDINE	2.5		NO
55	Irving & Jones (1992)	SPEED PERCEPTION - Sim traffic scenes	1?	12 min	1	TRIPOLIDINE	2.5		NO
55	Irving & Jones (1992)	DRIVING - Actual, Closed course	1C	15 min	1	TRIPOLIDINE	2.5		NO
55	Irving & Jones (1992)	DRIVING - SIMULATOR	1S	15 min	1	TRIPOLIDINE	2.5		NO
55	Irving & Jones (1992)	SPEED PERCEPTION - Sim traffic scenes	1?	12 min	1	TRIPOLIDINE	5		NO
55	Irving & Jones (1992)	HAZARD PERCEPTION - Sim traffic scenes	1?	12 min?	1	TRIPOLIDINE	5		NO
55	Irving & Jones (1992)	DRIVING - Actual, Closed course	1C	15 min	1	TRIPOLIDINE	5		NO
55	Irving & Jones (1992)	DRIVING - SIMULATOR	1S	15 min	1	TRIPOLIDINE	5		NO
121	Valk et al. (1997)	Multi-Attribute Task Battery (MAT) - on PC	1S	10 min	1	TRIPOLIDINE	5	**YES**	
123	Volkerts et al. (1992)	DRIVING - Actual, Highway circuit	1R	75 min	1	TRIPOLIDINE	5	**YES**	
15	Brookhuis et al. (1993)	DRIVING - on road; weaving test	1R		1	TRIPOLIDINE	10		NO
15	Brookhuis et al. (1993)	DRIVING - on road; car-following test	1R		1	TRIPOLIDINE	10	**YES**	
86A	O'Hanlon et al. (1988)	DRIVING - Actual, Highway circuit	1R	1hr+?	1	TRIPOLIDINE	10	**YES**	
99A	Riedel et al. (1990)	DRIVING - Actual, Highway 100km circuit	1R	1 hr	1	TRIPOLIDINE	10	**YES**	
				2nd		**Generation Drugs:**			
44	Gengo et al. (1990)	DRIVING SIMULATOR - Doron, 2 diff. runs	1S	7 min runs	2	CETIRIZINE	5		NO
6	Betts et al. (1989)	DRIVING circuit - slalom & gap acceptance	1C		2	CETIRIZINE	10		NO
44	Gengo et al. (1990)	DRIVING SIMULATOR - Doron, 2 diff. runs	1S	7 min runs	2	CETIRIZINE	10		NO
95	Ramaekers et al. (1992)	DRIVING - Actual, Circuit on highway	1R	~1hr	2	CETIRIZINE	10	**YES**	
123	Volkerts et al. (1992)	DRIVING - Actual, Highway circuit	1R	75 min	2	CETIRIZINE	10		NO
6	Betts et al. (1989)	DRIVING circuit - slalom & gap acceptance	1C		2	CETIRIZINE	20	**YES**	
44	Gengo et al. (1990)	DRIVING SIMULATOR - Doron, 2 diff. runs	1S	7 min runs	2	CETIRIZINE	20		NO
122	Vermeeren & O'Hanlon (1998)	DRIVING - Actual, Highway circuit	1R	~ 1hr	2	FEXOFENADINE	120		NO
122	Vermeeren & O'Hanlon (1998)	DRIVING - Actual, Highway circuit	1R	~ 1hr	2	FEXOFENADINE	240		NO
75	Neves-Pinto et al. (1992)	FLIGHT SIMULATOR - observer ratings	1S		2	LORATADINE	10		NO
95	Ramaekers et al. (1992)	DRIVING - Actual, Circuit on highway	1R	~1hr	2	LORATADINE	10		NO
121	Valk et al. (1997)	Multi-Attribute Task Battery (MAT) - on PC	1S	10 min	2	LORATADINE	10		NO
86A	O'Hanlon et al. (1988)	DRIVING - Actual, Highway circuit	1R	1hr+?	2	LORATADINE	10		NO
99A	Riedel et al. (1990)	DRIVING - Actual, Highway 100km circuit	1R	1 hr	2	LORATADINE	10		NO
99B	Riedel et al. (1990)	DRIVING - Actual, Highway 100km circuit	1R	1 hr	2	LORATADINE	10		NO
99A	Riedel et al. (1990)	DRIVING - Actual, Highway 100km circuit	1R	1 hr	2	LORATADINE	20		NO
6	Betts et al. (1989)	DRIVING circuit - slalom & gap acceptance	1C		2	TERFENADINE	60		NO
7	Bhatti et al. (1989)	SIMULATED DRIVING TASK (SDT)	1S	?	2	TERFENADINE	60		NO
96	Ramaekers et al. (1994)	DRIVING - Actual, Highway circuit	1R	~1hr	2	TERFENADINE	60	**YES**	
96	Ramaekers et al. (1994)	DRIVING - Actual, Car following test	1R	12 min	2	TERFENADINE	60		NO
123	Volkerts et al. (1992)	DRIVING - Actual, Highway circuit	1R	75 min	2	TERFENADINE	60		NO
86A	O'Hanlon et al. (1988)	DRIVING - Actual, Highway circuit	1R	1hr+?	2	TERFENADINE	60		NO
99A	Riedel et al. (1990)	DRIVING - Actual, Highway 100km circuit	1R	1 hr	2	TERFENADINE	60		NO
6	Betts et al. (1989)	DRIVING circuit - slalom & gap acceptance	1C		2	TERFENADINE	120		NO
7	Bhatti et al. (1989)	SIMULATED DRIVING TASK (SDT)	1S	?	2	TERFENADINE	120		NO
96	Ramaekers et al. (1994)	DRIVING - Actual, Highway circuit	1R	~1hr	2	TERFENADINE	120		NO
96	Ramaekers et al. (1994)	DRIVING - Actual, Car following test	1R	12 min	2	TERFENADINE	120		NO
123	Volkerts et al. (1992)	DRIVING - Actual, Highway circuit	1R	75 min	2	TERFENADINE	120		NO
99B	Riedel et al. (1990)	DRIVING - Actual, Highway 100km circuit	1R	1 hr	2	TERFENADINE	120		NO
7	Bhatti et al. (1989)	SIMULATED DRIVING TASK (SDT)	1S	?	2	TERFENADINE	240	**YES**	
96	Ramaekers et al. (1994)	DRIVING - Actual, Highway circuit	1R	~1hr	2	TERFENADINE	240		NO
96	Ramaekers et al. (1994)	DRIVING - Actual, Car following test	1R	12 min	2	TERFENADINE	240		NO

YES:

Summary: 1st generation drugs: **47.83%**

2nd generation drugs: **12.50%**

Sheet: Psychomotor TABLE 6. **PSYCHOMOTOR TASKS - Summary of impairment findings as a function of DRUG and Dose - ACUTE DOSING only**

Page 2: sorted by Generation, DRUG, Dose, Ref#, SC#.

Ref#	REFERENCE	TASK	SC#	Duration	Gen	DRUG	Dose: mg	IMPAIRMENT? YES	NO
					1st	**Generation Drugs:**			
8	Biehl (1979)	FINGER TAPPING	2T	30sec	1	CHLORPHENIRAMINE	4	YES	
35	Dhorranintra et al. (1990)	Glass Bead Picking (percept-motor)	2D	brief	1	CHLORPHENIRAMINE	4		NO
40	Franks et al. (1978)	Vienna Determination Apparatus	2?		1	CHLORPHENIRAMINE	4	YES	
40	Franks et al. (1978)	STANDING STEADINESS	2B		1	CHLORPHENIRAMINE	4	YES	
40	Franks et al. (1978)	MANUAL DEXTERITY	2D		1	CHLORPHENIRAMINE	4		NO
120	Unchern et al. (1986)	Plug Board (put pins in holes)	2D	20 sec x2	1	CHLORPHENIRAMINE	4		NO
131B	Witek, Jr. et al. (1995)	Hand Steadiness (PC)	2B	v. brief	1	CHLORPHENIRAMINE	4		NO
63	Lee et al. (1988)	FINGER TAPPING	2T	v. brief	1	CHLORPHENIRAMINE	12	YES	
25	Chapman & Rawlins (1982)	Letter Cancellation	2	v.brief	1	CHLORPHENIRAMINE	16	YES	
59	Khosla et al. (1993)	Digit Cancellation Task (DCT)	2	v brief	1	CHLORPHENIRAMINE	16		NO wB
31	Day et al. (1972)	HAND-EYE COORDINATION	2		1	CLEMASTINE	1		NO
41	Franks et al. (1979)	STANDING STEADINESS	2B		1	CLEMASTINE	1		NO
41	Franks et al. (1979)	MANUAL DEXTERITY	2D		1	CLEMASTINE	1		NO
97	Reinberg et al. (1978)	EYE-HAND SKILL Test (bearings in tube)	2D	v. brief	1	CLEMASTINE	1		NO
64	Levander et al. (1985)	FINGER TAPPING - index; alternating 2 fingers	2T	v. brief	1	CLEMASTINE	3	YES	
97	Reinberg et al. (1978)	EYE-HAND SKILL Test (bearings in tube)	2D	v. brief	1	CLEMASTINE	3		NO
27	Cohen et al. (1984)	BODY SWAY - antero-posterior	2B	3 min	1	DIPHENHYDRAMINE	25	YES	
30	Curran et al. (1998)	SYMBOL COPYING - motor comp of DSST	2	90 sec	1	DIPHENHYDRAMINE	25		NO
30	Curran et al. (1998)	DIGIT CANCELLATION	2	brief	1	DIPHENHYDRAMINE	25		NO
30	Curran et al. (1998)	FINGER TAPPING	2T	60 sec	1	DIPHENHYDRAMINE	25		NO
120	Unchern et al. (1986)	Plug Board (put pins in holes)	2D	20 sec x2	1	DIPHENHYDRAMINE	25		NO
131B	Witek, Jr. et al. (1995)	Hand Steadiness (PC)	2B	v. brief	1	DIPHENHYDRAMINE	25	YES	
4	Berlinger et al. (1982)	FINGER TAPPING	2T	2 min	1	DIPHENHYDRAMINE	50		NO
24	Carruthers et al. (1978)	FINGER TAPPING	2T	50 sec	1	DIPHENHYDRAMINE	50		NO
27	Cohen et al. (1984)	BODY SWAY - antero-posterior	2B	3 min	1	DIPHENHYDRAMINE	50	YES	
29	Cohen et al. (1987)	BODY SWAY - antero-posterior	2B	2 min	1	DIPHENHYDRAMINE	50		NO
30	Curran et al. (1998)	DIGIT CANCELLATION	2	brief	1	DIPHENHYDRAMINE	50		NO
30	Curran et al. (1998)	SYMBOL COPYING - motor comp of DSST	2	90 sec	1	DIPHENHYDRAMINE	50		NO
30	Curran et al. (1998)	FINGER TAPPING	2T	60 sec	1	DIPHENHYDRAMINE	50	YES	
56	Katz et al. (1998)	FINGER TAPPING	2T	brief	1	DIPHENHYDRAMINE	50		NO
116	Spector et al. (1980)	FINGER TAPPING - alternating area	2T	3.5min	1	DIPHENHYDRAMINE	50		NO
130A	Witek, Jr. et al. (1992)	Hand Steadiness (PC)	2B	v. brief	1	DIPHENHYDRAMINE	50	YES	
130B	Witek, Jr. et al. (1992)	Hand Steadiness (PC)	2B	v. brief	1	DIPHENHYDRAMINE	50	YES	
131A	Witek, Jr. et al. (1995)	Hand Steadiness (PC)	2B	v. brief	1	DIPHENHYDRAMINE	50	YES	
131B	Witek, Jr. et al. (1995)	Hand Steadiness (PC)	2B	v. brief	1	DIPHENHYDRAMINE	50	YES	
27	Cohen et al. (1984)	BODY SWAY - antero-posterior	2B	3 min	1	DIPHENHYDRAMINE	100	YES	
71	Moser et al. (1978)	PSYCHOMOTOR TASKS (set of 5)	2		1	DIPHENHYDRAMINE	100		NO
94	Preston et al. (1992)	BALANCE - Time keep foot raised; eyes closed	2B	2 min	1	DIPHENHYDRAMINE	100		NO
106	Saarialho-Kere et al. (1989)	BODY SWAY	2B	v. brief	1	DIPHENHYDRAMINE	100		NO
106	Saarialho-Kere et al. (1989)	FINGER TAPPING	2T	1 min	1	DIPHENHYDRAMINE	100		NO
94	Preston et al. (1992)	BALANCE - Time keep foot raised; eyes closed	2B	2 min	1	DIPHENHYDRAMINE	200	YES	
64	Levander et al. (1985)	FINGER TAPPING - index; alternating 2 fingers	2T	v. brief	1	HYDROXYZINE	20	YES	
65	Levander et al. (1991)	FINGER TAPPING - index; alternating 2 fingers	2T	v. brief	1	HYDROXYZINE	20		NO
21	Bye et al. (1974)	FINGER TAPPING	2T	1 min	1	TRIPOLIDINE	2.5	YES	
48	Hamilton et al. (1982)	FINGER TAPPING	2T	60 sec	1	TRIPOLIDINE	2.5		NO
21	Bye et al. (1974)	FINGER TAPPING	2T	1 min	1	TRIPOLIDINE	5	YES	
22	Bye et al. (1977)	FINGER TAPPING	2T	60 sec	1	TRIPOLIDINE	5	YES	
78	Nicholson et al. (1982)	CANCELLATION Task - (P&P, letters)	2	5 min	1	TRIPOLIDINE	10		NO
80	Nicholson & Stone (1984)	SYMBOL COPYING - motor comp of DSST	2	1 min	1	TRIPOLIDINE	10	YES	
82	Nicholson & Stone (1986)	SYMBOL COPYING - motor comp of DSST	2	1 min	1	TRIPOLIDINE	10	YES	
					2nd	**Generation Drugs:**			
34	Dhorranintra et al. (1986)	Glass Bead Picking (percept-motor)	2D	brief	2	ASTEMIZOLE	10		NO
78	Nicholson et al. (1982)	CANCELLATION Task - (P&P, letters)	2	5 min	2	ASTEMIZOLE	10		NO
113	Seppala & Savolainen (1982)	BODY SWAY - lateral & sagittal; electronic.	2B	40 sec	2	ASTEMIZOLE	10		NO
113	Seppala & Savolainen (1982)	FINGER TAPPING - hand counter	2T	30 sec	2	ASTEMIZOLE	10		NO
113	Seppala & Savolainen (1982)	BODY SWAY - lateral & sagittal; electronic.	2B	40 sec	2	ASTEMIZOLE	30		NO
113	Seppala & Savolainen (1982)	FINGER TAPPING - hand counter	2T	30 sec	2	ASTEMIZOLE	30		NO
25	Chapman & Rawlins (1982)	Letter Cancellation	2	v.brief	2	ASTEMIZOLE	40		NO
36	Doms et al. (1988)	Bourdon Wiersma Test - p/p attention	2	5 min	2	CETIRIZINE	10		NO
36	Doms et al. (1988)	Crawford Small Parts Dexterity Test	2D	?	2	CETIRIZINE	10		NO
65	Levander et al. (1991)	FINGER TAPPING - index; alternating 2 fingers	2T	v. brief	2	CETIRIZINE	10		NO
71	Moser et al. (1978)	PSYCHOMOTOR TASKS (set of 5)	2		2	TERFENADINE	60		NO
78	Nicholson et al. (1982)	CANCELLATION Task - (P&P, letters)	2	5 min	2	TERFENADINE	60		NO
82	Nicholson & Stone (1986)	SYMBOL COPYING - motor comp of DSST	2	1 min	2	TERFENADINE	60		NO
97	Reinberg et al. (1978)	EYE-HAND SKILL Test (bearings in tube)	2D	v. brief	2	TERFENADINE	60		NO
120	Unchern et al. (1986)	Plug Board (put pins in holes)	2D	20 sec x2	2	TERFENADINE	60		NO
130A	Witek, Jr. et al. (1992)	Hand Steadiness (PC)	2B	v. brief	2	TERFENADINE	60		NO
131A	Witek, Jr. et al. (1995)	Hand Steadiness (PC)	2B	v. brief	2	TERFENADINE	60		NO
71	Moser et al. (1978)	PSYCHOMOTOR TASKS (set of 5)	2		2	TERFENADINE	120		NO
82	Nicholson & Stone (1986)	SYMBOL COPYING - motor comp of DSST	2	1 min	2	TERFENADINE	120		NO
71	Moser et al. (1978)	PSYCHOMOTOR TASKS (set of 5)	2		2	TERFENADINE	240		NO

Sheet: PERCEPTION SC#3

TABLE 7 **PERCEPTION - Summary of impairment findings as a function of DRUG and Dose - ACUTE DOSING only**

Page 2: sorted by Generation, DRUG, Dose, Ref#, SC#.

Ref#	REFERENCE	TASK	SC#	Duration	Gen	DRUG	Dose: mg	IMPAIRMENT? YES	NO
					1st	**Generation Drugs:**			
8	Biehl (1979)	TACHISTOSCOPE - 4 slides of 16 ltrs	3	very brief	1	CHLORPHENIRAMINE	4		NO
40	Franks et al. (1978)	PERCEPTUAL SPEED	3		1	CHLORPHENIRAMINE	4		NO
41	Franks et al. (1979)	PERCEPTUAL SPEED	3		1	CLEMASTINE	1		NO
112	Seppala et al. (1981)	TIME ANTICIPATION - Est speed of moving light	3?	v. brief	1	CLEMASTINE	1		NO
112	Seppala et al. (1981)	VISUAL SEARCH - (they say "D-A"?)	3VS	5 min	1	CLEMASTINE	1		NO
56	Katz et al. (1998)	Pattern Recognition - spatial perception	3	brief	1	DIPHENHYDRAMINE	25		NO
18A	Burns & Moskowitz (1993)	VISUAL SEARCH - SCRI	3VS	6 min	1	DIPHENHYDRAMINE	25	**YES**	
18B	Burns & Moskowitz (1993)	VISUAL SEARCH - SCRI	3VS	6 min	1	DIPHENHYDRAMINE	25		NO
73	Moskowitz & Burns (1988)	VISUAL SEARCH - SCRI	3VS	6 min	1	DIPHENHYDRAMINE	50	**YES**	
108	Sands et al. (1997)	Pattern Recognition - spatial perception	3?	brief	1	DIPHENHYDRAMINE	50	**YES**	
108	Sands et al. (1997)	Pattern Recognition - spatial perception	3?	brief	1	DIPHENHYDRAMINE	75	**YES**	
70	Mohs et al. (1978)	TIME PRODUCTION Task (time estimates)	3	5-10 min	1	DIPHENHYDRAMINE	100	**YES**	
70	Mohs et al. (1978)	VISUAL SEARCH (t-scope, digits)	3VS	20 min	1	DIPHENHYDRAMINE	100		NO
106	Saarialho-Kere et al. (1989)	VISUAL SEARCH - (they say "D-A"?)	3VS	5 min	1	DIPHENHYDRAMINE	100		NO
21	Bye et al. (1974)	VISUAL SEARCH	3VS	30 min	1	TRIPOLIDINE	2.5		NO
21	Bye et al. (1974)	VISUAL SEARCH	3VS	30 min	1	TRIPOLIDINE	5		NO
123	Volkerts et al. (1992)	Visual Discrimination (Letter or Digit)	3	~10 min	1	TRIPOLIDINE	5	**YES**	
					2nd	**Generation Drugs:**			
113	Seppala & Savolainen (1982)	TIME ANTICIPATION - Est speed of moving light	3?	v. brief	2	ASTEMIZOLE	10		NO
113	Seppala & Savolainen (1982)	TIME ANTICIPATION - Est speed of moving light	3?	v. brief	2	ASTEMIZOLE	30		NO
123	Volkerts et al. (1992)	Visual Discrimination (Letter or Digit)	3	~10 min	2	CETIRIZINE	10		NO
73	Moskowitz & Burns (1988)	VISUAL SEARCH - SCRI	3VS	6 min	2	TERFENADINE	60		NO bP
123	Volkerts et al. (1992)	Visual Discrimination (Letter or Digit)	3	~10 min	2	TERFENADINE	60		NO
18A	Burns & Moskowitz (1993)	VISUAL SEARCH - SCRI	3VS	6 min	2	TERFENADINE	60		NO
18B	Burns & Moskowitz (1993)	VISUAL SEARCH - SCRI	3VS	6 min	2	TERFENADINE	60		NO
123	Volkerts et al. (1992)	Visual Discrimination (Letter or Digit)	3	~10 min	2	TERFENADINE	120		NO
18B	Burns & Moskowitz (1993)	VISUAL SEARCH - SCRI	3VS	6 min	2	TERFENADINE	120		NO

SC#4 **VISUAL FUNCTIONS & CFF - Summary of impairment findings as a function of DRUG and Dose - ACUTE DOSING only**
Sheet: VISUAL_CFF

VISUAL FUNCTIONS TABLE 8A.

Page 2: sorted by SC#, Generation, DRUG, Dose, Ref#

Ref#	REFERENCE	TASK (or Subjective SEDATION)	SC#	Duration	Gen	DRUG	Dose: mg	IMPAIRMENT? YES	NO
					1st	**Generation Drugs:**			
31	Day et al. (1972)	VISUAL FUNCTION TESTS (5 types)	4		1	CLEMASTINE	1		NO
29	Cohen et al. (1987)	SACCADIC EYE MOVEMENTS	4	~5 min?	1	DIPHENHYDRAMINE	50	**YES**	
29	Cohen et al. (1987)	SMOOTH PURSUIT EYE MOVEMENTS	4	~5 min?	1	DIPHENHYDRAMINE	50		NO
68	Mattila et al. (1986)	MADDOX WING (extraocular muscles)	4	v. brief	1	DIPHENHYDRAMINE	100		NO wB
106	Saarialho-Kere et al. (1989)	MADDOX WING (extraocular muscles)	4	v. brief	1	DIPHENHYDRAMINE	100		NO
9	Blom et al. (1992)	SACCADIC EYE MOVEMENT - SEM-K	4		1	HYDROXYZINE	30	**YES**	
12	Bradley & Nicholson (1986)	DYNAMIC VISUAL ACUITY	4	~5 min	1	TRIPOLIDINE	10	**YES**	
14	Bradley & Nicholson (1987)	DYNAMIC VISUAL ACUITY	4	~5 min	1	TRIPOLIDINE	10	**YES**	
78	Nicholson et al. (1982)	DYNAMIC VISUAL ACUITY - DVA (Landolt C rings)	4	v. brief	1	TRIPOLIDINE	10	**YES**	
78	Nicholson et al. (1982)	PUPILLARY DIAMETER (TV pupillometer)	4	v. brief	1	TRIPOLIDINE	10		NO
79	Nicholson & Stone (1983)	DYNAMIC VISUAL ACUITY - DVA (Landolt C rings)	4	v. brief	1	TRIPOLIDINE	10	**YES**	
80	Nicholson & Stone (1984)	DYNAMIC VISUAL ACUITY - DVA (Landolt C rings)	4	v. brief	1	TRIPOLIDINE	10	**YES**	
82	Nicholson & Stone (1986)	DYNAMIC VISUAL ACUITY - DVA (Landolt C rings)	4	v. brief	1	TRIPOLIDINE	10	**YES**	
13A	Bradley et al. (1987)	DYNAMIC VISUAL ACUITY	4	~5 min	1	TRIPOLIDINE	10	**YES**	
13B	Bradley et al. (1987)	DYNAMIC VISUAL ACUITY	4	~5 min	1	TRIPOLIDINE	10	**YES**	
					2nd	**Generation Drugs:**			
78	Nicholson et al. (1982)	DYNAMIC VISUAL ACUITY - DVA (Landolt C rings)	4	v. brief	2	ASTEMIZOLE	10		NO
78	Nicholson et al. (1982)	PUPILLARY DIAMETER (TV pupillometer)	4	v. brief	2	ASTEMIZOLE	10		NO
6	Betts et al. (1989)	VISION TEST (Visual field index)	4		2	CETIRIZINE	10		NO
6	Betts et al. (1989)	VISION TEST (Visual field index)	4		2	CETIRIZINE	20		NO
14	Bradley & Nicholson (1987)	DYNAMIC VISUAL ACUITY	4	~5 min	2	LORATADINE	10		NO
37	Englisch et al. (1996)	VISUAL FUNCTIONS - in Oculodynamic test	4	20 min	2	LORATADINE	10		NO
109	Schaffler et al. (1994)	Oculodynamic Test (ODT)- EOG measures	4	20 min	2	LORATADINE	10		NO
14	Bradley & Nicholson (1987)	DYNAMIC VISUAL ACUITY	4	~5 min	2	LORATADINE	20		NO
14	Bradley & Nicholson (1987)	DYNAMIC VISUAL ACUITY	4	~5 min	2	LORATADINE	40	**YES**	
6	Betts et al. (1989)	VISION TEST (Visual field index)	4		2	TERFENADINE	60		NO
78	Nicholson et al. (1982)	PUPILLARY DIAMETER (TV pupillometer)	4	v. brief	2	TERFENADINE	60		NO
78	Nicholson et al. (1982)	DYNAMIC VISUAL ACUITY - DVA (Landolt C rings)	4	v. brief	2	TERFENADINE	60		NO
79	Nicholson & Stone (1983)	DYNAMIC VISUAL ACUITY - DVA (Landolt C rings)	4	v. brief	2	TERFENADINE	60		NO
82	Nicholson & Stone (1986)	DYNAMIC VISUAL ACUITY - DVA (Landolt C rings)	4	v. brief	2	TERFENADINE	60		NO
6	Betts et al. (1989)	VISION TEST (Visual field index)	4		2	TERFENADINE	120		NO
82	Nicholson & Stone (1986)	DYNAMIC VISUAL ACUITY - DVA (Landolt C rings)	4	v. brief	2	TERFENADINE	120		NO

SC#4 **VISUAL FUNCTIONS & CFF - Summary of Impairment findings as a function of DRUG and Dose - ACUTE DOSING only**
Sheet: VISUAL_CFF

continued... **CRITICAL FLICKER FUSION**

TABLE 8B.

Page 2: sorted by SC#, Generation, DRUG, Dose, Ref#

Ref#	REFERENCE	TASK (or Subjective SEDATION)	SC#	Duration	Gen	DRUG	Dose: mg	IMPAIRMENT? YES	NO
					1st	**Generation Drugs:**			
61	Kulshrestha et al. (1978)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	CHLORPHENIRAMINE	4		NO
63	Lee et al. (1988)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	CHLORPHENIRAMINE	12		NO
59	Khosla et al. (1993)	CRITICAL FLICKER FUSION (CFF)	4C	v brief	1	CHLORPHENIRAMINE	16		NO wB
93	Pishkin et al. (1983)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	CLEMASTINE	1		NO
112	Seppala et al. (1981)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	CLEMASTINE	1		NO
87	Patat et al. (1994)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	CLEMASTINE	2	YES	
93	Pishkin et al. (1983)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	CLEMASTINE	2		NO
124	Vuurman et al. (1994)	CRITICAL FLICKER FUSION - CFF	4C	6 min	1	CLEMASTINE	2	YES	
30	Curran et al. (1998)	CRITICAL FLICKER FUSION - CFF	4C	brief	1	DIPHENHYDRAMINE	25		NO
30	Curran et al. (1998)	CRITICAL FLICKER FUSION - CFF	4C	brief	1	DIPHENHYDRAMINE	50		NO
39	Fink et al. (1979)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	DIPHENHYDRAMINE	50		NO
93	Pishkin et al. (1983)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	DIPHENHYDRAMINE	50		NO
119	Tharion et al. (1994)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	DIPHENHYDRAMINE	50		NO
68	Mattila et al. (1986)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	DIPHENHYDRAMINE	100	YES	
71	Moser et al. (1978)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	DIPHENHYDRAMINE	100		NO
106	Saarialho-Kere et al. (1989)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	DIPHENHYDRAMINE	100	YES	
43	Gengo et al. (1987)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	HYDROXYZINE	25	YES	
93	Pishkin et al. (1983)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	HYDROXYZINE	25		NO
9	Blom et al. (1992)	CRITICAL FLICKER FUSION	4C		1	HYDROXYZINE	30		NO
117	Swire et al. (1989)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	TRIPOLIDINE	7.5	YES	
12	Bradley & Nicholson (1986)	CRITICAL FLICKER FUSION - CFF	4C	~5 min	1	TRIPOLIDINE	10	YES	
58	Kerr et al. (1994)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	TRIPOLIDINE	10	YES	
78	Nicholson et al. (1982)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	TRIPOLIDINE	10	YES	
79	Nicholson & Stone (1983)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	TRIPOLIDINE	10	YES	
80	Nicholson & Stone (1984)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	TRIPOLIDINE	10	YES	
82	Nicholson & Stone (1986)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	TRIPOLIDINE	10	YES	
104	Rombaut et al. (1991)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	1	TRIPOLIDINE	10	YES	
13A	Bradley et al. (1987)	CRITICAL FLICKER FUSION - CFF	4C	~5 min	1	TRIPOLIDINE	10	YES	
13B	Bradley et al. (1987)	CRITICAL FLICKER FUSION - CFF	4C	~5 min	1	TRIPOLIDINE	10	YES	
					2nd	**Generation Drugs:**			
51	Hindmarch & Easton (1986)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	ASTEMIZOLE	10		NO
78	Nicholson et al. (1982)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	ASTEMIZOLE	10		NO
113	Seppala & Savolainen (1982)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	ASTEMIZOLE	10		NO
113	Seppala & Savolainen (1982)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	ASTEMIZOLE	30		NO
43	Gengo et al. (1987)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	CETIRIZINE	10		NO
100	Riedel et al. (1990)	CRITICAL FLICKER FUSION - CFF	4C		2	CETIRIZINE	10		NO
43	Gengo et al. (1987)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	CETIRIZINE	20		NO
100	Riedel et al. (1990)	CRITICAL FLICKER FUSION - CFF	4C		2	CETIRIZINE	20		NO
7	Bhatti & Hindmarch (1989)	CRITICAL FLICKER FUSION (CFF)	4C	very brief	2	TERFENADINE	60		NO
39	Fink et al. (1979)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	TERFENADINE	60		NO
58	Kerr et al. (1994)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	TERFENADINE	60	YES	
61	Kulshrestha et al. (1978)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	TERFENADINE	60		NO
71	Moser et al. (1978)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	TERFENADINE	60		NO
78	Nicholson et al. (1982)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	TERFENADINE	60		NO
79	Nicholson & Stone (1983)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	TERFENADINE	60		NO
82	Nicholson & Stone (1986)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	TERFENADINE	60		NO
117	Swire et al. (1989)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	TERFENADINE	60		NO
124	Vuurman et al. (1994)	CRITICAL FLICKER FUSION - CFF	4C	6 min	2	TERFENADINE	60		NO
7	Bhatti & Hindmarch (1989)	CRITICAL FLICKER FUSION (CFF)	4C	very brief	2	TERFENADINE	120		NO
71	Moser et al. (1978)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	TERFENADINE	120		NO
82	Nicholson & Stone (1986)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	TERFENADINE	120		NO
7	Bhatti & Hindmarch (1989)	CRITICAL FLICKER FUSION (CFF)	4C	very brief	2	TERFENADINE	240		NO
71	Moser et al. (1978)	CRITICAL FLICKER FUSION - CFF	4C	v. brief	2	TERFENADINE	240		NO

TABLE 9.

Ref#	REFERENCE	TASK (or Subjective SEDATION)	SC#	Duration	Gen	DRUG	Dose, mg	IMPAIRMENT? YES	NO
					1st	**Generation Drugs:**			
8	Biehl (1979)	CONCENTRATION TEST (KLT) - math	5	15 min	1	CHLORPHENIRAMINE	4		NO
35	Dhorranintra et al. (1990)	CARD SORTING test (CNS problem solving)	5	brief	1	CHLORPHENIRAMINE	4		NO
40	Franks et al. (1978)	NUMERICAL REASONING	5		1	CHLORPHENIRAMINE	4	YES	
120	Unchern et al. (1986)	Arithmetic (p&p ??)	5	v. brief	1	CHLORPHENIRAMINE	4		NO
120	Unchern et al. (1986)	Card Sorting Task (4 piles #1-10 each)	5	v. brief	1	CHLORPHENIRAMINE	4	YES	
120	Unchern et al. (1986)	Digit Span ("Recall Memory; F & Backward)	5M	v. brief	1	CHLORPHENIRAMINE	4		NO
120	Unchern et al. (1986)	Line Test (p&p: draw ~= tracking)	5T	30sec X2	1	CHLORPHENIRAMINE	4	YES	
120	Unchern et al. (1986)	T-Maze (p&p: draw ~= tracking)	5T	3 sec	1	CHLORPHENIRAMINE	4		NO bP
131B	Witek, Jr. et al. (1995)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	CHLORPHENIRAMINE	4		NO
83	Nicholson et al. (1991)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	CHLORPHENIRAMINE	10	YES	
63	Lee et al. (1988)	DSST (WAIS) & Symbol Copying (SCT)	5D	90 sec each	1	CHLORPHENIRAMINE	12		NO
63	Lee et al. (1988)	MEMORY - STM, words & delay recall	5M	brief	1	CHLORPHENIRAMINE	12		NO
59	Khosla et al. (1993)	Card Sorting Task (CST)	5	v brief	1	CHLORPHENIRAMINE	16		NO
59	Khosla et al. (1993)	DIGIT SYMBOL Substitution - DSST	5D	v brief	1	CHLORPHENIRAMINE	16		NO wB
41	Franks et al. (1979)	VERBAL FLUENCY	5		1	CLEMASTINE	1		NO
41	Franks et al. (1979)	NUMERICAL REASONING	5		1	CLEMASTINE	1		NO
91	Peck et al. (1975)	DIGIT SYMBOL Substitution - DSST (WAIS)	5D	90 sec	1	CLEMASTINE	1	YES	
91	Peck et al. (1975)	MEMORY - STM, 8-digit series x90	5M	15 min	1	CLEMASTINE	1		NO
97	Reinberg et al. (1978)	Random# ADDITION TEST (P&P)	5	brief	1	CLEMASTINE	1		NO
53	Hopes et al. (1992)	Matching Paradigm - Info. Processing	5	10 min?	1	CLEMASTINE	2	YES	
87	Patat et al. (1994)	DIGIT SYMBOL Substitution - DSST (WAIS)	5D	90 sec	1	CLEMASTINE	2		NO
87	Patat et al. (1994)	MEMORY tests - LTM, pictures & delay recall; STM, 1	5M	brief	1	CLEMASTINE	2		NO
91	Peck et al. (1975)	DIGIT SYMBOL Substitution - DSST (WAIS)	5D	90 sec	1	CLEMASTINE	2	YES	
91	Peck et al. (1975)	MEMORY - STM, 8-digit series x90	5M	15 min	1	CLEMASTINE	2		NO
124	Vuurman et al. (1994)	MEMORY - letters, Sternberg CRT	5M	12 min	1	CLEMASTINE	2	YES	
64	Levander et al. (1985)	TRAIL MAKING - PC-based (~TrailsB)	5T	v. brief	1	CLEMASTINE	3		NO
97	Reinberg et al. (1978)	Random# ADDITION TEST (P&P)	5	brief	1	CLEMASTINE	3	YES	
16	Burns (1990)	VISUAL BACKWARD MASKING -SCRI	5	10+ min	1	DIPHENHYDRAMINE	25		NO
17	Burns & Moskowitz (1980)	VISUAL BACKWARD MASKING - SCRI	5	10+ min	1	DIPHENHYDRAMINE	25		NO
30	Curran et al. (1998)	WORD RECOGNITION (visual, during ERP)	5	~ 20 min?	1	DIPHENHYDRAMINE	25		NO
30	Curran et al. (1998)	DIGIT SYMBOL Substitution - DSST	5D	90 sec	1	DIPHENHYDRAMINE	25		NO
30	Curran et al. (1998)	MEMORY - immediate & delayed recall	5M	brief	1	DIPHENHYDRAMINE	25		NO
120	Unchern et al. (1986)	Arithmetic (p&p ??)	5	v. brief	1	DIPHENHYDRAMINE	25	YES	
120	Unchern et al. (1986)	Card Sorting Task (4 piles #1-10 each)	5	v. brief	1	DIPHENHYDRAMINE	25		NO
120	Unchern et al. (1986)	Digit Span ("Recall Memory; F & Backward)	5M	v. brief	1	DIPHENHYDRAMINE	25		NO
120	Unchern et al. (1986)	Line Test (p&p: draw ~= tracking)	5T	30sec X2	1	DIPHENHYDRAMINE	25	YES	
120	Unchern et al. (1986)	T-Maze (p&p: draw ~= tracking)	5T	3 sec	1	DIPHENHYDRAMINE	25	YES	
134	Scavone et al. (1998)	DIGIT SYMBOL Substitution - DSST	5D	?	1	DIPHENHYDRAMINE	25		NO
134	Scavone et al. (1998)	MEMORY - word list, aquisition & recall	5M	?	1	DIPHENHYDRAMINE	25		NO
131B	Witek, Jr. et al. (1995)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	DIPHENHYDRAMINE	25		NO
4	Berlinger et al. (1982)	CARD SORTING TEST B	5	very brief	1	DIPHENHYDRAMINE	50	YES	
4	Berlinger et al. (1982)	CARD SORTING TEST A	5	very brief	1	DIPHENHYDRAMINE	50		NO
19	Burns et al. (1994)	VISUAL BACKWARD MASKING - SCRI	5	10+ min	1	DIPHENHYDRAMINE	50		NO
19	Burns et al. (1994)	S-R CONFLICT (SRC) - SCRI	5	~10 min	1	DIPHENHYDRAMINE	50	YES	
24	Carruthers et al. (1978)	CARD SORTING tasks	5	v. brief	1	DIPHENHYDRAMINE	50		NO
30	Curran et al. (1998)	WORD RECOGNITION (visual, during ERP)	5	~ 20 min?	1	DIPHENHYDRAMINE	50		NO
30	Curran et al. (1998)	DIGIT SYMBOL Substitution - DSST	5D	90 sec	1	DIPHENHYDRAMINE	50		NO
30	Curran et al. (1998)	MEMORY - immediate & delayed recall	5M	brief	1	DIPHENHYDRAMINE	50		NO
44	Gengo et al. (1990)	DIGIT SYMBOL Substitution - DSST	5D	90 sec	1	DIPHENHYDRAMINE	50	YES	
44	Gengo et al. (1990)	Trails B Maze Tracking - p/p test	5T	v. brief	1	DIPHENHYDRAMINE	50		NO
56	Katz et al. (1998)	DIGIT SYMBOL Substitution - DSST (WAIS-R)	5D	90 sec	1	DIPHENHYDRAMINE	50		NO
56	Katz et al. (1998)	MEMORY - Buschke task - word lists	5M	20 min	1	DIPHENHYDRAMINE	50		NO
56	Katz et al. (1998)	DIGIT SPAN - STM for verbal digits (WAIS-R)	5M	brief	1	DIPHENHYDRAMINE	50	YES	
56	Katz et al. (1998)	Trails A & B	5T	brief	1	DIPHENHYDRAMINE	50		NO
57	Kay et al. (1997)	DIGIT SYMBOL Coding - CogScreen	5D	brief	1	DIPHENHYDRAMINE	50		NO
57	Kay et al. (1997)	WORKING MEMORY - CogScreen	5M	brief	1	DIPHENHYDRAMINE	50	YES	
66	Lines et al. (1997)	DIGIT SYMBOL Substitution - DSST (~WAIS)	5D	90 sec	1	DIPHENHYDRAMINE	50		NO
66	Lines et al. (1997)	Verbal MEMORY; immed. & delay recall; PC	5M	brief	1	DIPHENHYDRAMINE	50		NO
98	Rice & Synder (1993)	Following Directions Test - CCAB	5	v. brief	1	DIPHENHYDRAMINE	50	YES	
98	Rice & Synder (1993)	Manikan - WRPAB	5	v. brief	1	DIPHENHYDRAMINE	50		NO
98	Rice & Synder (1993)	Logical Reasoning - WRPAB	5	v. brief	1	DIPHENHYDRAMINE	50		NO
98	Rice & Synder (1993)	Pattern Comparison - WRPAB	5	v. brief	1	DIPHENHYDRAMINE	50	YES	
98	Rice & Synder (1993)	Serial ADDITION/SUBTRACTION - WRPAB	5	v. brief	1	DIPHENHYDRAMINE	50	YES	
98	Rice & Synder (1993)	Interval Production - WRPAB	5	v. brief	1	DIPHENHYDRAMINE	50		NO
98	Rice & Synder (1993)	Time Wall - WRPAB	5	v. brief	1	DIPHENHYDRAMINE	50		NO
98	Rice & Synder (1993)	Code Substitution - WRPAB	5D	v. brief	1	DIPHENHYDRAMINE	50		NO
108	Sands et al. (1997)	DIGIT SYMBOL Substitution - DSST (WAIS-R)	5D	90 sec	1	DIPHENHYDRAMINE	50	YES	
108	Sands et al. (1997)	DIGIT SPAN - STM for verbal digits (WAIS-R)	5M	brief	1	DIPHENHYDRAMINE	50		NO

108	Sands et al. (1997)	MEMORY - Buschke Task (word lists)	5M	20 min	1	DIPHENHYDRAMINE	50	YES	
108	Sands et al. (1997)	Trails A & B	5T	brief	1	DIPHENHYDRAMINE	50	YES	
116	Spector et al. (1980)	CARD SORTING TESTS (A&B)	5	v. brief	1	DIPHENHYDRAMINE	50		NO
119	Tharion et al. (1994)	Baddeley Grammatical Reasoning (BGRT)	5	3 min	1	DIPHENHYDRAMINE	50		NO
119	Tharion et al. (1994)	DIGIT SYMBOL Substitution - DSST (WAIS)	5D	90 sec	1	DIPHENHYDRAMINE	50		NO
130A	Witek, Jr. et al. (1992)	Grammatical Reasoning (PC)	5	v. brief	1	DIPHENHYDRAMINE	50		NO
130A	Witek, Jr. et al. (1992)	Arithmetic task (PC)	5	v. brief	1	DIPHENHYDRAMINE	50		NO
130B	Witek, Jr. et al. (1992)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	DIPHENHYDRAMINE	50		NO
131A	Witek, Jr. et al. (1995)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	DIPHENHYDRAMINE	50		NO
131B	Witek, Jr. et al. (1995)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	DIPHENHYDRAMINE	50		NO
108	Sands et al. (1997)	DIGIT SYMBOL Substitution - DSST (WAIS-R)	5D	90 sec	1	DIPHENHYDRAMINE	75	YES	
108	Sands et al. (1997)	DIGIT SPAN - STM for verbal digits (WAIS-R)	5M	brief	1	DIPHENHYDRAMINE	75		NO
108	Sands et al. (1997)	MEMORY - Buschke Task (word lists)	5M	20 min	1	DIPHENHYDRAMINE	75	YES	
108	Sands et al. (1997)	Trails A & B	5T	brief	1	DIPHENHYDRAMINE	75	YES	
68	Mattila et al. (1986)	DIGIT SYMBOL Substitution - DSST	5D	3 min	1	DIPHENHYDRAMINE	100	YES	
68	Mattila et al. (1986)	DIGIT SPAN (Backward, verbally)	5M	v. brief	1	DIPHENHYDRAMINE	100	YES	
94	Preston et al. (1992)	DIGIT SYMBOL Substitution - DSST (PC)	5D	v. brief	1	DIPHENHYDRAMINE	100		NO
94	Preston et al. (1992)	MEMORY - Picture Recog/Recall	5M	v. brief	1	DIPHENHYDRAMINE	100		NO
94	Preston et al. (1992)	Enter & Recall Test - Digits (PC)	5M	v. brief	1	DIPHENHYDRAMINE	100	YES	
106	Saarialho-Kere et al. (1989)	DIGIT SYMBOL Substitution - DSST	5D	3 min	1	DIPHENHYDRAMINE	100		NO
94	Preston et al. (1992)	DIGIT SYMBOL Substitution - DSST (PC)	5D	v. brief	1	DIPHENHYDRAMINE	200	YES	
94	Preston et al. (1992)	MEMORY - Picture Recog/Recall	5M	v. brief	1	DIPHENHYDRAMINE	200	YES	
94	Preston et al. (1992)	Enter & Recall Test - Digits (PC)	5M	v. brief	1	DIPHENHYDRAMINE	200	YES	
64	Levander et al. (1985)	TRAIL MAKING - PC-based (~TrailsB)	5T	v. brief	1	HYDROXYZINE	20		NO
65	Levander et al. (1991)	Perceptual MAZE Test - PC-based	5	v. brief	1	HYDROXYZINE	20		NO
43	Gengo et al. (1987)	Stroop color/word test - PC version	5	brief	1	HYDROXYZINE	25	YES	
9	Blom et al. (1992)	STERNBERG MEMORY & CRT - SRT-C	5M		1	HYDROXYZINE	30		NO
21	Bye et al. (1974)	DIGIT SYMBOL Substitution (DSST)	5D	90 sec	1	TRIPOLIDINE	2.5		NO
48	Hamilton et al. (1982)	DIGIT SYMBOL Substitution - DSST	5D	90 sec	1	TRIPOLIDINE	2.5		NO
82	Nicholson & Stone (1986)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	TRIPOLIDINE	2.5		NO
91	Peck et al. (1975)	DIGIT SYMBOL Substitution - DSST (WAIS)	5D	90 sec	1	TRIPOLIDINE	2.5		NO
91	Peck et al. (1975)	MEMORY - STM, 8-digit series x90	5M	15 min	1	TRIPOLIDINE	2.5		NO
21	Bye et al. (1974)	DIGIT SYMBOL Substitution (DSST)	5D	90 sec	1	TRIPOLIDINE	5		NO
22	Bye et al. (1977)	DIGIT SYMBOL Substitution (DSST)	5D	90 sec	1	TRIPOLIDINE	5	YES	
22	Bye et al. (1977)	MEMORY - STM for 8-digit numbers	5M	15 min	1	TRIPOLIDINE	5	YES	
82	Nicholson & Stone (1986)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	TRIPOLIDINE	5		NO
83	Nicholson et al. (1991)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	TRIPOLIDINE	5		NO
91	Peck et al. (1975)	DIGIT SYMBOL Substitution - DSST (WAIS)	5D	90 sec	1	TRIPOLIDINE	5	YES	
91	Peck et al. (1975)	MEMORY - STM, 8-digit series x90	5M	15 min	1	TRIPOLIDINE	5		NO
123	Volkerts et al. (1992)	Letter Matching Task	5	~10 min	1	TRIPOLIDINE	5		NO wP
123	Volkerts et al. (1992)	MEMORY - Digit Scanning (Sternberg)	5M	~13 min	1	TRIPOLIDINE	5	YES	
117	Swire et al. (1989)	DIGIT SYMBOL Substitution - DSST (WAIS)	5D	90 sec	1	TRIPOLIDINE	7.5	YES	
117	Swire et al. (1989)	DIGIT SPAN - STM for verbal digits (WAIS)	5M	v. brief	1	TRIPOLIDINE	7.5		NO
12	Bradley & Nicholson (1986)	DIGIT SYMBOL SUBSTITUTION - DSS	5D	~5 min	1	TRIPOLIDINE	10		NO
14	Bradley & Nicholson (1987)	DIGIT SYMBOL SUBSTITUTION - DSS	5D	~5 min	1	TRIPOLIDINE	10	YES	
14	Bradley & Nicholson (1987)	MEMORY - STM - digits visually	5M	8 min	1	TRIPOLIDINE	10	YES	
58	Kerr et al. (1994)	Stroop task - color/word (PC-based)	5	?	1	TRIPOLIDINE	10		NO
58	Kerr et al. (1994)	Sternberg STM - MEMORY, digits visual (PC-based)	5M	v. brief	1	TRIPOLIDINE	10		NO
77	Nicholson & Stone (1982)	ARITHMETIC Test (p&p)	5	10 min	1	TRIPOLIDINE	10		NO
77	Nicholson & Stone (1982)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	TRIPOLIDINE	10		NO
78	Nicholson et al. (1982)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	TRIPOLIDINE	10		NO
79	Nicholson & Stone (1983)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	TRIPOLIDINE	10	YES	
80	Nicholson & Stone (1984)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	TRIPOLIDINE	10	YES	
82	Nicholson & Stone (1986)	DIGIT SYMBOL Substitution - DSST	5D	2 min	1	TRIPOLIDINE	10	YES	
104	Rombaut et al. (1991)	MEMORY - Word recognition (PC)	5M	v. brief	1	TRIPOLIDINE	10		NO
104	Rombaut et al. (1991)	MEMORY - STM, Sternberg (PC)	5M	v. brief	1	TRIPOLIDINE	10	YES	
13A	Bradley et al. (1987)	DIGIT SYMBOL SUBSTITUTION - DSS	5D	~5 min	1	TRIPOLIDINE	10	YES	
13B	Bradley et al. (1987)	DIGIT SYMBOL SUBSTITUTION - DSS	5D	~5 min	1	TRIPOLIDINE	10	YES	

					2nd	Generation Drugs:			
34	Dhorranintra et al. (1986)	CARD SORTING test (CNS problem solving)	5	brief	2	ASTEMIZOLE	10		NO
51	Hindmarch & Easton (1986)	Stroop task - color/word (PC-based)	5		2	ASTEMIZOLE	10		NO
77	Nicholson & Stone (1982)	ARITHMETIC Test (p&p)	5	10 min	2	ASTEMIZOLE	10		NO
77	Nicholson & Stone (1982)	DIGIT SYMBOL Substitution - DSST	5D	2 min	2	ASTEMIZOLE	10		NO
78	Nicholson et al. (1982)	DIGIT SYMBOL Substitution - DSST	5D	2 min	2	ASTEMIZOLE	10		NO
98	Rice & Synder (1993)	Logical Reasoning - WRPAB	5	v. brief	2	ASTEMIZOLE	10		NO
98	Rice & Synder (1993)	Manikan - WRPAB	5	v. brief	2	ASTEMIZOLE	10		NO
98	Rice & Synder (1993)	Interval Production - WRPAB	5	v. brief	2	ASTEMIZOLE	10		NO
98	Rice & Synder (1993)	Serial ADDITION/SUBTRACTION - WRPAB	5	v. brief	2	ASTEMIZOLE	10		NO
98	Rice & Synder (1993)	Following Directions Test - CCAB	5	v. brief	2	ASTEMIZOLE	10		NO
98	Rice & Synder (1993)	Time Wall - WRPAB	5	v. brief	2	ASTEMIZOLE	10		NO
98	Rice & Synder (1993)	Pattern Comparison - WRPAB	5	v. brief	2	ASTEMIZOLE	10		NO
98	Rice & Synder (1993)	Code Substitution - WRPAB	5D	v. brief	2	ASTEMIZOLE	10		NO
113	Seppala & Savolainen (1982)	DIGIT SYMBOL Substitution - DSST	5D	3 min	2	ASTEMIZOLE	10		NO
77	Nicholson & Stone (1982)	ARITHMETIC Test (p&p)	5	10 min	2	ASTEMIZOLE	20		NO
77	Nicholson & Stone (1982)	DIGIT SYMBOL Substitution - DSST	5D	2 min	2	ASTEMIZOLE	20		NO
113	Seppala & Savolainen (1982)	DIGIT SYMBOL Substitution - DSST	5D	3 min	2	ASTEMIZOLE	30		NO
44	Gengo et al. (1990)	DIGIT SYMBOL Substitution - DSST	5D	90 sec	2	CETIRIZINE	5		NO
44	Gengo et al. (1990)	Trails B Maze Tracking - p/p test	5T	v. brief	2	CETIRIZINE	5		NO
84	Nicholson & Turner (1998)	DIGIT SYMBOL Substitution - DSST	5D	2 min	2	CETIRIZINE	5		NO
36	Doms et al. (1988)	Attention & concen. test - p/p	5	?	2	CETIRIZINE	10		NO
36	Doms et al. (1988)	Fieldmarking test - p/p concentration	5	10 min?	2	CETIRIZINE	10		NO
36	Doms et al. (1988)	Learning & memory test - p/p	5M	?	2	CETIRIZINE	10		NO
43	Gengo et al. (1987)	Stroop color/word test - PC version	5	brief	2	CETIRIZINE	10		NO
44	Gengo et al. (1990)	DIGIT SYMBOL Substitution - DSST	5D	90 sec	2	CETIRIZINE	10		NO
44	Gengo et al. (1990)	Trails B Maze Tracking - p/p test	5T	v. brief	2	CETIRIZINE	10		NO
65	Levander et al. (1991)	Perceptual MAZE Test - PC-based	5	v. brief	2	CETIRIZINE	10		NO
84	Nicholson & Turner (1998)	DIGIT SYMBOL Substitution - DSST	5D	2 min	2	CETIRIZINE	10		NO
100	Riedel et al. (1990)	MEMORY - 15 words	5M		2	CETIRIZINE	10		NO
123	Volkerts et al. (1992)	Letter Matching Task	5	~10 min	2	CETIRIZINE	10		NO
123	Volkerts et al. (1992)	MEMORY - Digit Scanning (Sternberg)	5M	~13 min	2	CETIRIZINE	10		NO
33	De Roeck et al. (1990)	DIGIT SYMBOL Substitution - DSST	5D	90 sec?	2	CETIRIZINE	20		NO?
43	Gengo et al. (1987)	Stroop color/word test - PC version	5	brief	2	CETIRIZINE	20		NO
44	Gengo et al. (1990)	DIGIT SYMBOL Substitution - DSST	5D	90 sec	2	CETIRIZINE	20	YES	
44	Gengo et al. (1990)	Trails B Maze Tracking - p/p test	5T	v. brief	2	CETIRIZINE	20		NO
84	Nicholson & Turner (1998)	DIGIT SYMBOL Substitution - DSST	5D	2 min	2	CETIRIZINE	20		NO
100	Riedel et al. (1990)	MEMORY - 15 words	5M		2	CETIRIZINE	20		NO
14	Bradley & Nicholson (1987)	DIGIT SYMBOL SUBSTITUTION - DSS	5D	~5 min	2	LORATADINE	10		NO
14	Bradley & Nicholson (1987)	MEMORY - STM - digits visually	5M	8 min	2	LORATADINE	10		NO
57	Kay et al. (1997)	DIGIT SYMBOL Coding - CogScreen	5D	brief	2	LORATADINE	10		NO
57	Kay et al. (1997)	WORKING MEMORY - CogScreen	5M	brief	2	LORATADINE	10		NO
133	Comer et al. (1998)	Repeated Aquisition & Rapid Info Tasks	5	3, 10min	2	LORATADINE	10		NO
133	Comer et al. (1998)	DIGIT SYMBOL Substitution - DSST	5D	3 min	2	LORATADINE	10		NO
14	Bradley & Nicholson (1987)	DIGIT SYMBOL SUBSTITUTION - DSS	5D	~5 min	2	LORATADINE	20		NO
14	Bradley & Nicholson (1987)	MEMORY - STM - digits visually	5M	8 min	2	LORATADINE	20		NO
33	De Roeck et al. (1990)	DIGIT SYMBOL Substitution - DSST	5D	90 sec?	2	LORATADINE	20		NO
133	Comer et al. (1998)	Repeated Aquisition & Rapid Info Tasks	5	3, 10min	2	LORATADINE	20		NO
133	Comer et al. (1998)	DIGIT SYMBOL Substitution - DSST	5D	3 min	2	LORATADINE	20		NO
14	Bradley & Nicholson (1987)	DIGIT SYMBOL SUBSTITUTION - DSS	5D	~5 min	2	LORATADINE	40	YES	
14	Bradley & Nicholson (1987)	MEMORY - STM - digits visually	5M	8 min	2	LORATADINE	40		NO
58	Kerr et al. (1994)	Stroop task - color/word (PC-based)	5	?	2	TERFENADINE	60		NO
58	Kerr et al. (1994)	Sternberg STM - MEMORY, digits visual (PC-based)	5M	v. brief	2	TERFENADINE	60		NO
77	Nicholson & Stone (1982)	ARITHMETIC Test (p&p)	5	10 min	2	TERFENADINE	60		NO
77	Nicholson & Stone (1982)	DIGIT SYMBOL Substitution - DSST	5D	2 min	2	TERFENADINE	60		NO
78	Nicholson et al. (1982)	DIGIT SYMBOL Substitution - DSST	5D	2 min	2	TERFENADINE	60		NO
79	Nicholson & Stone (1983)	DIGIT SYMBOL Substitution - DSST	5D	2 min	2	TERFENADINE	60		NO
82	Nicholson & Stone (1986)	DIGIT SYMBOL Substitution - DSST	5D	2 min	2	TERFENADINE	60		NO
97	Reinberg et al. (1978)	Random# ADDITION TEST (P&P)	5	brief	2	TERFENADINE	60		NO
117	Swire et al. (1989)	DIGIT SYMBOL Substitution - DSST (WAIS)	5D	90 sec	2	TERFENADINE	60		NO
117	Swire et al. (1989)	DIGIT SPAN - STM for verbal digits (WAIS)	5M	v. brief	2	TERFENADINE	60		NO
119	Tharion et al. (1994)	Baddeley Grammatical Reasoning (BGRT)	5	3 min	2	TERFENADINE	60		NO
119	Tharion et al. (1994)	DIGIT SYMBOL Substitution - DSST (WAIS)	5D	90 sec	2	TERFENADINE	60		NO
120	Unchern et al. (1986)	Card Sorting Task (4 piles #1-10 each)	5	v. brief	2	TERFENADINE	60		NO
120	Unchern et al. (1986)	Arithmetic (p&p ??)	5	v. brief	2	TERFENADINE	60		NO
120	Unchern et al. (1986)	Digit Span ("Recall Memory; F & Backward)	5M	v. brief	2	TERFENADINE	60		NO
120	Unchern et al. (1986)	Line Test (p&p: draw ~= tracking)	5T	30sec X2	2	TERFENADINE	60		NO
120	Unchern et al. (1986)	T-Maze (p&p: draw ~= tracking)	5T	3 sec	2	TERFENADINE	60		NO
123	Volkerts et al. (1992)	Letter Matching Task	5	~10 min	2	TERFENADINE	60		NO
123	Volkerts et al. (1992)	MEMORY - Digit Scanning (Sternberg)	5M	~13 min	2	TERFENADINE	60		NO
130A	Witek, Jr. et al. (1992)	Arithmetic task (PC)	5	v. brief	2	TERFENADINE	60		NO
130A	Witek, Jr. et al. (1992)	Grammatical Reasoning (PC)	5	v. brief	2	TERFENADINE	60		NO
131A	Witek, Jr. et al. (1995)	DIGIT SYMBOL Substitution - DSST	5D	2 min	2	TERFENADINE	60		NO
82	Nicholson & Stone (1986)	DIGIT SYMBOL Substitution - DSST	5D	2 min	2	TERFENADINE	120		NO
123	Volkerts et al. (1992)	Letter Matching Task	5	~10 min	2	TERFENADINE	120		NO
123	Volkerts et al. (1992)	MEMORY - Digit Scanning (Sternberg)	5M	~13 min	2	TERFENADINE	120		NO

TABLE 10.

Ref#	REFERENCE	TASK	SC#	Duration	Gen	DRUG	Dose: mg	IMPAIRMENT? YES	NO
					1st	**Generation Drugs:**			
132	Yasuda et al. (1998)	DIVIDED ATTENTION (PC)	6	v brief	1	CHLORPHENIRAMINE	2	YES	
132	Yasuda et al. (1998)	DIVIDED ATTENTION (PC)	6	v brief	1	CHLORPHENIRAMINE	4	YES	
131B	Witek, Jr. et al. (1995)	DIVIDED ATTENTION (PC)	6	v. brief	1	CHLORPHENIRAMINE	4		NO
42	Gaillard et al. (1988)	TRACKING + Continuous Memory Task	6	7 min	1	CLEMASTINE	1	YES	
42	Gaillard et al. (1988)	Continuous MEMORY TASK during Tracking	6	7 min	1	CLEMASTINE	1		NO
124	Vuurman et al. (1994)	DIVIDED ATTENTION - ~SCRI	6	12 min	1	CLEMASTINE	2	YES	
16	Burns (1990)	DIVIDED ATTENTION - SCRI	6	12 min	1	DIPHENHYDRAMINE	25		NO
17	Burns & Moskowitz (1980)	DIVIDED ATTENTION - SCRI	6	12 min	1	DIPHENHYDRAMINE	25	YES	
131B	Witek, Jr. et al. (1995)	DIVIDED ATTENTION (PC)	6	v. brief	1	DIPHENHYDRAMINE	25	YES	
18A	Burns & Moskowitz (1993)	DIVIDED ATTENTION - SCRI	6	12 min	1	DIPHENHYDRAMINE	25		NO?
18B	Burns & Moskowitz (1993)	DIVIDED ATTENTION - SCRI	6	12 min	1	DIPHENHYDRAMINE	25	YES	
19	Burns et al. (1994)	DIVIDED ATTENTION - SCRI	6	12 min	1	DIPHENHYDRAMINE	50	YES	
20	Burns et al. (1999 - ms)	DIVIDED ATTENTION - SCRI ('96 ver)	6	12 min	1	DIPHENHYDRAMINE	50		NO
57	Kay et al. (1997)	DIVIDED ATTENTION - CogScreen	6	brief	1	DIPHENHYDRAMINE	50	YES	
73	Moskowitz & Burns (1988)	DIVIDED ATTENTION - SCRI	6	12 min	1	DIPHENHYDRAMINE	50	YES	
102	Roehrs et al. (1993)	DIVIDED ATTENTION - Trk & periph/center targets	6	15 min	1	DIPHENHYDRAMINE	50	YES	
127	Wilkinson & Moskowitz (1990)	DIVIDED ATTENTION - SCRI	6	12 min	1	DIPHENHYDRAMINE	50	YES	
129	Wilkinson et al. (1999 - ms)	DIVIDED ATTENTION - SCRI ('96ver)	6	12 min	1	DIPHENHYDRAMINE	50	YES	
130B	Witek, Jr. et al. (1992)	DIVIDED ATTENTION (PC)	6	v. brief	1	DIPHENHYDRAMINE	50	YES	
131A	Witek, Jr. et al. (1995)	DIVIDED ATTENTION (PC)	6	v. brief	1	DIPHENHYDRAMINE	50	YES	
131B	Witek, Jr. et al. (1995)	DIVIDED ATTENTION (PC)	6	v. brief	1	DIPHENHYDRAMINE	50	YES	
70	Mohs et al. (1978)	DIVIDED ATTENTION (digit transf & ltr detect; not PC)	6	15 min	1	DIPHENHYDRAMINE	100		NO
106	Saarialho-Kere et al. (1989)	TRACKING & CRT test (this is D-A!)	6	?	1	DIPHENHYDRAMINE	100	YES	
111	*Seidel et al. (1987)*	*D-A ("VIG": Trk & periph vs ctr targets)*	*6*	*30 min*	*1*	*HYDROXYZINE*	*25*	YES	
55	Irving & Jones (1992)	DIVIDED ATTENTION - per SCRI	6	12 min	1	TRIPOLIDINE	2.5		NO
55	Irving & Jones (1992)	DIVIDED ATTENTION - per SCRI	6	12 min	1	TRIPOLIDINE	5		NO
121	Valk et al. (1997)	VigTrack - "dual-task" (palmtop PC)	6	5 min	1	TRIPOLIDINE	5	YES	
58	Kerr et al. (1994)	TRACKING with D-A task	6	1 min	1	TRIPOLIDINE	10	YES	
104	Rombaut et al. (1991)	DIVIDED ATTENTION - Trk & peripheral signals	6	1 min	1	TRIPOLIDINE	10		NO
					2nd	**Generation Drugs:**			
51	Hindmarch & Easton (1986)	TRACKING & Peripheral Signals Task	6	1 min	2	ASTEMIZOLE	10		NO
111	Seidel et al. (1987)	D-A ("VIG": Trk & periph vs ctr targets)	6	30 min	2	CETIRIZINE	5		NO
95	Ramaekers et al. (1992)	DIVIDED ATTENTION - per SCRI	6	12 min	2	CETIRIZINE	10	YES	
100	Riedel et al. (1990)	DIVIDED ATTENTION	6		2	CETIRIZINE	10		NO
111	Seidel et al. (1987)	D-A ("VIG": Trk & periph vs ctr targets)	6	30 min	2	CETIRIZINE	10		NO
100	Riedel et al. (1990)	DIVIDED ATTENTION	6		2	CETIRIZINE	20		NO
111	Seidel et al. (1987)	D-A ("VIG": Trk & periph vs ctr targets)	6	30 min	2	CETIRIZINE	20		NO
42	Gaillard et al. (1988)	TRACKING + Continuous Memory Task	6	7 min	2	LORATADINE	10		NO
42	Gaillard et al. (1988)	Continuous MEMORY TASK during Tracking	6	7 min	2	LORATADINE	10	YES	
57	Kay et al. (1997)	DIVIDED ATTENTION - CogScreen	6	brief	2	LORATADINE	10		NO bP
95	Ramaekers et al. (1992)	DIVIDED ATTENTION - per SCRI	6	12 min	2	LORATADINE	10		NO
121	Valk et al. (1997)	VigTrack - "dual-task" (palmtop PC)	6	5 min	2	LORATADINE	10		NO
127	Wilkinson & Moskowitz (1990)	DIVIDED ATTENTION - SCRI	6	12 min	2	LORATADINE	10		NO
133	Comer et al. (1998)	DIVIDED ATTENTION - Miller et al '88	6	10 min	2	LORATADINE	10		NO
133	Comer et al. (1998)	DIVIDED ATTENTION - Miller et al '88	6	10 min	2	LORATADINE	20		NO
42	Gaillard et al. (1988)	Continuous MEMORY TASK during Tracking	6	7 min	2	TERFENADINE	60	YES	
42	Gaillard et al. (1988)	TRACKING + Continuous Memory Task	6	7 min	2	TERFENADINE	60		NO
58	Kerr et al. (1994)	TRACKING with D-A task	6	1 min	2	TERFENADINE	60		NO
73	Moskowitz & Burns (1988)	DIVIDED ATTENTION - SCRI	6	12 min	2	TERFENADINE	60		NO bP
131A	Witek, Jr. et al. (1995)	DIVIDED ATTENTION (PC)	6	v. brief	2	TERFENADINE	60		NO
18A	Burns & Moskowitz (1993)	DIVIDED ATTENTION - SCRI	6	12 min	2	TERFENADINE	60		NO
18B	Burns & Moskowitz (1993)	DIVIDED ATTENTION - SCRI	6	12 min	2	TERFENADINE	60		NO
18B	Burns & Moskowitz (1993)	DIVIDED ATTENTION - SCRI	6	12 min	2	TERFENADINE	120		NO

Note: NO bP = NO significant impairment, and performance was better than Placebo.
PC = Task presented on computerized system

Sheet: VIG TABLE 11 • **VIGILANCE TASKS - Summary of impairment findings as a function of DRUG and Dose - ACUTE DOSING only**

page 2: sorted by Generation, DRUG, Dose, Ref#, SC#

Ref#	REFERENCE	TASK	SC#	Duration	Gen	DRUG	Dose: mg	IMPAIRMENT? YES	NO
					1st	Generation Drugs:			
91	Peck et al. (1975)	VIGILANCE - Auditory (Wilkinson RT; 1hr)	7	1 hr	1	CLEMASTINE	1	YES	
91	Peck et al. (1975)	VIGILANCE - Auditory (Wilkinson RT; 1hr)	7	1 hr	1	CLEMASTINE	2	YES	
124	Vuurman et al. (1994)	VIGILANCE - Sustained Attention, Vis.	7?	11 min	1	CLEMASTINE	2		NO
122	Vermeeren et al. (1998)	VIGILANCE - Sustained Attention - ~`SCRI (45min)	7	45 min	1	CLEMASTINE	3		NO wP
16	Burns (1990)	VIGILANCE - SCRI	7	40 min	1	DIPHENHYDRAMINE	25	YES	
38	Fine et al. (1994)	VIGILANCE - Visual, 2-hr (10min blks x12)	7	2 hr	1	DIPHENHYDRAMINE	25	YES	
18A	Burns & Moskowitz (1993)	VIGILANCE - SCRI	7	40 min	1	DIPHENHYDRAMINE	25	YES	
18B	Burns & Moskowitz (1993)	VIGILANCE - SCRI	7	40 min	1	DIPHENHYDRAMINE	25	YES	
19	Burns et al. (1994)	VIGILANCE - SCRI	7	40 min	1	DIPHENHYDRAMINE	50	YES	
20	Burns et al. (1999 - ms)	VIGILANCE - SCRI	7	40 min	1	DIPHENHYDRAMINE	50	YES	
39	Fink et al. (1979)	Continuous Perf Task (CPT) during EEG	7		1	DIPHENHYDRAMINE	50	YES	
56	Katz et al. (1998)	Continuous Performance Task (vig?)	7	brief	1	DIPHENHYDRAMINE	50	YES	
57	Kay et al. (1997)	Continuous Perf. Task - Kay G	7	5 min	1	DIPHENHYDRAMINE	50	YES	
66	Lines et al. (1997)	VIGILANCE - Sustained Attention, Vis.	7	10 min	1	DIPHENHYDRAMINE	50	YES	
66	Lines et al. (1997)	VIGILANCE - Sustained Attention, Aud.	7	~10min x2	1	DIPHENHYDRAMINE	50		NO
73	Moskowitz & Burns (1988)	VIGILANCE - SCRI	7	40 min	1	DIPHENHYDRAMINE	50	YES	
108	Sands et al. (1997)	Continuous Performance Task (vig?)	7	brief	1	DIPHENHYDRAMINE	50	YES	
110	Schweitzer et al. (1994)	Simulated Assembly Line Task - SALT (PC)	7	1 hr	1	DIPHENHYDRAMINE	50	YES	
126	Walsh et al. (1994)	Simulated Assembly Line Task - SALT (PC)	7	1 hr x4	1	DIPHENHYDRAMINE	50	YES	
127	Wilkinson & Moskowitz (1990)	VIGILANCE - SCRI	7	40 min	1	DIPHENHYDRAMINE	50	YES	
129	Wilkinson et al. (1999 - ms)	VIGILANCE - SCRI	7	40 min	1	DIPHENHYDRAMINE	50	YES	
108	Sands et al. (1997)	Continuous Performance Task (vig?)	7	brief	1	DIPHENHYDRAMINE	75	YES	
68	Mattila et al. (1986)	ATTENTION Test (concentrated attn?)	7?	5 min	1	DIPHENHYDRAMINE	100		NO wB
125	Walsh et al. (1992)	Simulated Assembly Line Task - SALT (PC)	7	50 min x8	1	HYDROXYZINE	25	YES	
21	Bye et al. (1974)	VIGILANCE - Auditory	7	1 hr	1	TRIPOLIDINE	2.5	YES	
91	Peck et al. (1975)	VIGILANCE - Auditory (Wilkinson RT; 1hr)	7	1 hr	1	TRIPOLIDINE	2.5	YES	
21	Bye et al. (1974)	VIGILANCE - Auditory	7	1 hr	1	TRIPOLIDINE	5	YES	
22	Bye et al. (1977)	VIGILANCE - Auditory	7	1 hr	1	TRIPOLIDINE	5	YES	
91	Peck et al. (1975)	VIGILANCE - Auditory (Wilkinson RT; 1hr)	7	1 hr	1	TRIPOLIDINE	5	YES	
					2nd	Generation Drugs:			
84	Nicholson et al. (1998)	VIGILANCE - Visual digits, 15min	7	15 min	2	CETIRIZINE	5		NO
84	Nicholson et al. (1998)	VIGILANCE - Visual digits, 15min	7	15 min	2	CETIRIZINE	10		NO
100	Riedel et al. (1990)	VIGILANCE	7		2	CETIRIZINE	10		NO
110	Schweitzer et al. (1994)	Simulated Assembly Line Task - SALT (PC)	7	1 hr	2	CETIRIZINE	10		NO
125	Walsh et al. (1992)	Simulated Assembly Line Task - SALT (PC)	7	50 min x8	2	CETIRIZINE	10		NO?1x
126	Walsh et al. (1994)	Simulated Assembly Line Task - SALT (PC)	7	1 hr x4	2	CETIRIZINE	10		NO
84	Nicholson et al. (1998)	VIGILANCE - Visual digits, 15min	7	15 min	2	CETIRIZINE	20		NO
100	Riedel et al. (1990)	VIGILANCE	7		2	CETIRIZINE	20		NO
122	Vermeeren et al. (1998)	VIGILANCE - Sustained Attention - ~`SCRI (45min)	7	45 min	2	FEXOFENADINE	120		NO
122	Vermeeren et al. (1998)	VIGILANCE - Sustained Attention - ~`SCRI (45min)	7	45 min	2	FEXOFENADINE	240		NO
57	Kay et al. (1997)	Continuous Perf. Task - Kay G	7	5 min	2	LORATADINE	10		NO
127	Wilkinson & Moskowitz (1990)	VIGILANCE - SCRI	7	40 min	2	LORATADINE	10		NO
39	Fink et al. (1979)	Continuous Perf Task (CPT) during EEG	7		2	TERFENADINE	60		NO
73	Moskowitz & Burns (1988)	VIGILANCE - SCRI	7	40 min	2	TERFENADINE	60		NO bP
18A	Burns & Moskowitz (1993)	VIGILANCE - SCRI	7	40 min	2	TERFENADINE	60		NO
18B	Burns & Moskowitz (1993)	VIGILANCE - SCRI	7	40 min	2	TERFENADINE	60		NO
18B	Burns & Moskowitz (1993)	VIGILANCE - SCRI	7	40 min	2	TERFENADINE	120		NO

Note
NO wP = NO significant impairment, but worse than Placebo.
NO wB = NO significant impairment, but worse than Baseline.
NO bP = NO significant impairment, and better than Placebo.
NO? 1x = only one measure at single time point, of many, was significantly impaired.
PC = Task presented on computerized system.
RT = Reaction Time

TRACKING TASKS - Summary of impairment findings as a function of DRUG and Dose - ACUTE DOSING only

sheet: TRACK
SC# 8, 8Cr

TABLE 12.

Page 2: sorted by Generation, DRUG, Dose, Ref#, SC#.

Ref#	REFERENCE	TASK (or Subjective SEDATION)	SC#	Duration	Gen	DRUG	Dose, mg	IMPAIRMENT? YES	NO
					1st	**Generation Drugs:**			
26	Clarke & Nicholson (1978)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	1	CHLORPHENIRAMINE	4	YES	
61	Kulshrestha et al. (1978)	PURSUIT ROTOR - (Tracking)	8	brief	1	CHLORPHENIRAMINE	4		NO
76	Nicholson (1979)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	1	CHLORPHENIRAMINE	4		NO
26	Clarke & Nicholson (1978)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	1	CLEMASTINE	1	YES	
42	Gaillard et al. (1988)	TRACKING - Pursuit; performed alone	8	7 min	1	CLEMASTINE	1	YES	
93	Pishkin et al. (1983)	PURSUIT ROTOR - (Tracking)	8	v. brief	1	CLEMASTINE	1		NO
112	Seppala et al. (1981)	TRACKING Task (steer black dot on trk)	8	30 sec	1	CLEMASTINE	1		NO
53	Hopes et al. (1992)	TRACKING - Rotor & Pursuit tasks	8	10 min ea?	1	CLEMASTINE	2	YES	
93	Pishkin et al. (1983)	PURSUIT ROTOR - (Tracking)	8	v. brief	1	CLEMASTINE	2		NO
124	Vuurman et al. (1994)	CRITICAL TRACKING (CTT) - ~SCRI (5 trials)	8Cr	5 min	1	CLEMASTINE	2	YES	
64	Levander et al. (1985)	TRACKING, Adaptive (~VMC per Nicholson)	8Cr	8 min	1	CLEMASTINE	3	YES	
122	Vermeeren et al. (1998)	CRITICAL TRACKING (CTT) - ~SCRI (5 trials	8Cr	v. brief	1	CLEMASTINE	3	YES	
16	Burns (1990)	CRITICAL TRACKING (CTT) - SCRI	8Cr	20+ min	1	DIPHENHYDRAMINE	25	YES	
17	Burns & Moskowitz (1980)	COMPENSATORY TRACKING - SCRI	8	6 min	1	DIPHENHYDRAMINE	25		NO
17	Burns & Moskowitz (1980)	CRITICAL TRACKING (CTT) - SCRI	8Cr	20+ min	1	DIPHENHYDRAMINE	25		NO wP
27	Cohen et al. (1984)	TRACKING - Adaptive (VMC)	8Cr	10 min	1	DIPHENHYDRAMINE	25	YES	
67	Linnoila (1973)	TRACKING (Coordination tests I & II)	8	v. brief	1	DIPHENHYDRAMINE	25		NO
18A	Burns & Moskowitz (1993)	CRITICAL TRACKING (CTT) - SCRI	8Cr	20+ min	1	DIPHENHYDRAMINE	25	YES	
18B	Burns & Moskowitz (1993)	CRITICAL TRACKING (CTT) - SCRI	8Cr	20+ min	1	DIPHENHYDRAMINE	25	YES	
20	Burns et al. (1999 - ms)	CRITICAL TRACKING (CTT) - SCRI	8Cr	20+ min	1	DIPHENHYDRAMINE	50		NO wP
27	Cohen et al. (1984)	TRACKING - Adaptive (VMC)	8Cr	10 min	1	DIPHENHYDRAMINE	50	YES	
29	Cohen et al. (1987)	TRACKING - Adaptive (VMC)	8Cr	10 min	1	DIPHENHYDRAMINE	50	YES	
57	Kay et al. (1997)	TRACKING - solo via CogScreen	8	brief	1	DIPHENHYDRAMINE	50	YES	
67	Linnoila (1973)	TRACKING (Coordination tests I & II)	8	v. brief	1	DIPHENHYDRAMINE	50		NO
73	Moskowitz & Burns (1988)	CRITICAL TRACKING (CTT) - SCRI	8Cr	20+ min	1	DIPHENHYDRAMINE	50	YES	
93	Pishkin et al. (1983)	PURSUIT ROTOR - (Tracking)	8	v. brief	1	DIPHENHYDRAMINE	50		NO
98	Rice & Snyder (1993)	TRACKING - WRPAB (Unstable Trking)	8	v. brief	1	DIPHENHYDRAMINE	50	YES	
127	Wilkinson & Moskowitz (1990)	CRITICAL TRACKING (CTT) - SCRI	8Cr	20+ min	1	DIPHENHYDRAMINE	50	YES	
129	Wilkinson et al. (1999 - ms)	CRITICAL TRACKING (CTT) - SCRI	8Cr	20+ min	1	DIPHENHYDRAMINE	50	YES	
130A	Witek, Jr. et al. (1992)	TRACKING	8	v. brief	1	DIPHENHYDRAMINE	50	YES	
27	Cohen et al. (1984)	TRACKING - Adaptive (VMC)	8Cr	10 min	1	DIPHENHYDRAMINE	100	YES	
68	Mattila et al. (1986)	TRACKING Task (Coordination test)	8	30 sec	1	DIPHENHYDRAMINE	100		NO wB
64	Levander et al. (1985)	TRACKING, Adaptive (~VMC per Nicholson)	8Cr	8 min	1	HYDROXYZINE	20	YES	
93	Pishkin et al. (1983)	PURSUIT ROTOR - (Tracking)	8	v. brief	1	HYDROXYZINE	25		NO
28	Cohen et al. (1985)	TRACKING - Adaptive (VMC)	8Cr	10 min	1	TRIPOLIDINE	2.5	YES	
55	Irving & Jones (1992)	Adaptive TRACKING - Pursuit (Critical?)	8	10 min	1	TRIPOLIDINE	2.5		NO
76	Nicholson (1979)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	1	TRIPOLIDINE	2.5	YES	
28	Cohen et al. (1985)	TRACKING - Adaptive (VMC)	8Cr	10 min	1	TRIPOLIDINE	5	YES	
55	Irving & Jones (1992)	Adaptive TRACKING - Pursuit (Critical?)	8	10 min	1	TRIPOLIDINE	5		NO
12	Bradley & Nicholson (1986)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	1	TRIPOLIDINE	10	YES	
14	Bradley & Nicholson (1987)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	1	TRIPOLIDINE	10	YES	
76	Nicholson (1979)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	1	TRIPOLIDINE	10	YES	
77	Nicholson & Stone (1982)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	1	TRIPOLIDINE	10	YES	
79	Nicholson & Stone (1983)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	1	TRIPOLIDINE	10	YES	
80	Nicholson & Stone (1984)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	1	TRIPOLIDINE	10	YES	
82	Nicholson & Stone (1986)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	1	TRIPOLIDINE	10	YES	
13A	Bradley et al. (1987)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	1	TRIPOLIDINE	10	YES	
13B	Bradley et al. (1987)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	1	TRIPOLIDINE	10	YES	

continued...

TRACKING TASKS - Summary of impairment findings as a function of DRUG and Dose - ACUTE DOSING only

continued... Page 2: sorted by Generation, DRUG, Dose, Ref#, SC#.

Ref#	REFERENCE	TASK (or Subjective SEDATION)	SC#	Duration	Gen	DRUG	Dose, mg	IMPAIRMENT? YES	NO
				2nd Generation Drugs:					
77	Nicholson & Stone (1982)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	2	ASTEMIZOLE	20		NO
113	Seppala & Savolainen (1982)	TRACKING - "Coord.Task ("steer black dot on	8	30 sec	2	ASTEMIZOLE	30		NO
84	Nicholson & Turner (1998)	TRACKING Task (compensatory?)	8	3 min	2	CETIRIZINE	5	YES	
84	Nicholson & Turner (1998)	TRACKING Task (compensatory?)	8	3 min	2	CETIRIZINE	10		NO
95	Ramaekers et al. (1992)	CRITICAL TRACKING (CTT) - ~SCRI, but 5tri	8Cr	brief	2	CETIRIZINE	10		NO
100	Riedel et al. (1990)	CRITICAL TRACKING (CTT)	8Cr		2	CETIRIZINE	10	YES	
84	Nicholson & Turner (1998)	TRACKING Task (compensatory?)	8	3 min	2	CETIRIZINE	20	YES	
100	Riedel et al. (1990)	CRITICAL TRACKING (CTT)	8Cr		2	CETIRIZINE	20	YES	
122	Vermeeren et al. (1998)	CRITICAL TRACKING (CTT) - ~SCRI (5 trials	8Cr	v. brief	2	FEXOFENADINE	120	YES	
122	Vermeeren et al. (1998)	CRITICAL TRACKING (CTT) - ~SCRI (5 trials	8Cr	v. brief	2	FEXOFENADINE	240	YES	
14	Bradley & Nicholson (1987)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	2	LORATADINE	10		NO
42	Gaillard et al. (1988)	TRACKING - Pursuit; performed alone	8	7 min	2	LORATADINE	10		NO
57	Kay et al. (1997)	TRACKING - solo via CogScreen	8	brief	2	LORATADINE	10		NO
95	Ramaekers et al. (1992)	CRITICAL TRACKING (CTT) - ~SCRI, but 5tri	8Cr	brief	2	LORATADINE	10		NO
127	Wilkinson & Moskowitz (1990)	CRITICAL TRACKING (CTT) - SCRI	8Cr	20+ min	2	LORATADINE	10		NO
14	Bradley & Nicholson (1987)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	2	LORATADINE	20		NO
14	Bradley & Nicholson (1987)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	2	LORATADINE	40		NO
26	Clarke & Nicholson (1978)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	2	TERFENADINE	60		NO
42	Gaillard et al. (1988)	TRACKING - Pursuit; performed alone	8	7 min	2	TERFENADINE	60		NO
61	Kulshrestha et al. (1978)	PURSUIT ROTOR - (Tracking)	8	brief	2	TERFENADINE	60		NO
73	Moskowitz & Burns (1988)	CRITICAL TRACKING (CTT) - SCRI	8Cr	20+ min	2	TERFENADINE	60		NO bP
77	Nicholson & Stone (1982)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	2	TERFENADINE	60		NO
79	Nicholson & Stone (1983)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	2	TERFENADINE	60		NO
82	Nicholson & Stone (1986)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	2	TERFENADINE	60		NO
130A	Witek, Jr. et al. (1992)	TRACKING	8	v. brief	2	TERFENADINE	60		NO
18A	Burns & Moskowitz (1993)	CRITICAL TRACKING (CTT) - SCRI	8Cr	20+ min	2	TERFENADINE	60		NO
18B	Burns & Moskowitz (1993)	CRITICAL TRACKING (CTT) - SCRI	8Cr	20+ min	2	TERFENADINE	60		NO
82	Nicholson & Stone (1986)	TRACKING (Vis. Motor Coord. = VMC)	8Cr	10 min	2	TERFENADINE	120		NO
18B	Burns & Moskowitz (1993)	CRITICAL TRACKING (CTT) - SCRI	8Cr	20+ min	2	TERFENADINE	120		NO

NOTE: Across all types of TRACKING TASKS, the 1st generation drugs were found to be significantly impairing in 68.8% of the times tested; this is compared to 18.8% for the 2nd generation drugs. However, when CRITICAL TRACKING TASKS specifically were used, impairment was found in 90.3% (28/31) vs 19.0% (4/21) of the cases, for the 1st and 2nd generation drugs, respectively. Moreover, at least 2 of the 3 test findings for the 1st generation drugs which were not significant nonetheless showed performance which was clearly worse than Placebo ("NO wP" in table above) and in fact approached statistical significance ($p < 0.08$).

Sheet: RT Tasks TABLE 13. **REACTION TIME TASKS - Summary of Impairment findings as a function of DRUG and Dose - ACUTE DOSING only**

SC# 9 Page 2: sorted by Generation, DRUG, Dose, Ref#, SC#.

Ref#	REFERENCE	TASK	SC#	Duration	Gen.	DRUG	Dose, mg	IMPAIRMENT? YES	IMPAIRMENT? NO
					1st	**Generation Drugs:**			
8	Biehl (1979)	COMPLEX REACTION TEST	9C	~ 3min	1	CHLORPHENIRAMINE	4		NO
8	Biehl (1979)	REACTION TIME - simple	9S	v. brief	1	CHLORPHENIRAMINE	4		NO
35	Dhorranintra et al. (1990)	REACTION TIME - Choice (red light)	9C	brief	1	CHLORPHENIRAMINE	4	YES	
40	Franks et al. (1978)	REACTION TIME - Complex	9C		1	CHLORPHENIRAMINE	4		NO
40	Franks et al. (1978)	REACTION TIME - Simple, Aud & Vis	9S		1	CHLORPHENIRAMINE	4		NO
61	Kulshrestha et al. (1978)	REACTION TIME - Simple (single light)	9S	brief	1	CHLORPHENIRAMINE	4		NO
131B	Witek, Jr. et al. (1995)	REACTION TIME, Choice (CRT); Vis	9C	v. brief	1	CHLORPHENIRAMINE	4	YES	
63	Lee et al. (1988)	REACTION TIME, SIMPLE - Auditory	9S	v. brief	1	CHLORPHENIRAMINE	12	YES	
41	Franks et al. (1979)	REACTION TIME - Complex	9C		1	CLEMASTINE	1		NO
41	Franks et al. (1979)	REACTION TIME - Simple, Aud & Vis	9S		1	CLEMASTINE	1		NO
42	Gaillard et al. (1988)	REACTION TASK - visual field: digits, degraded	9	24 min	1	CLEMASTINE	1		NO
91	Peck et al. (1975)	REACTION TIME, Simple (SRT); Aud	9S	15 min	1	CLEMASTINE	1	YES	
93	Pishkin et al. (1983)	REACTION TIME, SRT & CRT (Speeded Interference Task);	9	v. brief	1	CLEMASTINE	1		NO
112	Seppala et al. (1981)	Complex CRT; (vis/aud; pedal/button)	9C	~1min	1	CLEMASTINE	1		NO
87	Patat et al. (1994)	REACTION TIME, Choice (CRT); Visual	9C	50 trials	1	CLEMASTINE	2	YES	
91	Peck et al. (1975)	REACTION TIME, Simple (SRT); Aud	9S	15 min	1	CLEMASTINE	2	YES	
93	Pishkin et al. (1983)	REACTION TIME, SRT & CRT (Speeded Interference Task);	9	v. brief	1	CLEMASTINE	2		NO
64	Levander et al. (1985)	REACTION TIME - Choice; visual	9C	v. brief	1	CLEMASTINE	3	YES	
64	Levander et al. (1985)	REACTION TIME - Simple; aud & visual	9S	v. brief	1	CLEMASTINE	3	YES	
122	Vermeeren et al. (1998)	REACTION TIME, Choice (CRT); Vis (L&R w. distractors)	9C	v. brief	1	CLEMASTINE	3		NO
27	Cohen et al. (1984)	REACTION TIME - Simple, Visual	9S	5 min	1	DIPHENHYDRAMINE	25	YES	
67	Linnoila (1973)	REACTION TIME, Choice (CRT)	9C	v. brief	1	DIPHENHYDRAMINE	25		NO
131B	Witek, Jr. et al. (1995)	REACTION TIME, Choice (CRT); Vis	9C	v. brief	1	DIPHENHYDRAMINE	25	YES	
4	Berlinger et al. (1982)	REACTION TIME - Simple	9S	very brief	1	DIPHENHYDRAMINE	50		NO
24	Carruthers et al. (1978)	REACTION TIME - simple, visual	9S	v. brief	1	DIPHENHYDRAMINE	50	YES	
27	Cohen et al. (1984)	REACTION TIME - Simple, Visual	9S	5 min	1	DIPHENHYDRAMINE	50	YES	
29	Cohen et al. (1987)	REACTION TIME - Simple, Visual	9S	5 min	1	DIPHENHYDRAMINE	50	YES	
56	Katz et al. (1998)	REACTION TIME - Simple; visual?	9S	brief	1	DIPHENHYDRAMINE	50	YES	
57	Kay et al. (1997)	REACTION TIME - Simple; CogScreen	9S	brief	1	DIPHENHYDRAMINE	50		NO
66	Lines et al. (1997)	REACTION TIME, Choice; (& CPRT)	9C	brief	1	DIPHENHYDRAMINE	50		NO
67	Linnoila (1973)	REACTION TIME, Choice (CRT)	9C	v. brief	1	DIPHENHYDRAMINE	50		NO bC
93	Pishkin et al. (1983)	REACTION TIME, SRT & CRT (Speeded Interference Task);	9	v. brief	1	DIPHENHYDRAMINE	50		NO
98	Rice & Snyder (1993)	Four Choice REACTION TIME - WRPAB	9C	v. brief	1	DIPHENHYDRAMINE	50		NO
108	Sands et al. (1997)	REACTION TIME - (PC task)	9	brief	1	DIPHENHYDRAMINE	50	YES	
116	Spector et al. (1980)	REACTION TIME, Simple (SRT) - visual	9S	v. brief	1	DIPHENHYDRAMINE	50		NO
130A	Witek, Jr. et al. (1992)	REACTION TIME, Choice (CRT); Vis	9C	v. brief	1	DIPHENHYDRAMINE	50	YES	
130B	Witek, Jr. et al. (1992)	REACTION TIME, Choice (CRT); Vis	9C	v. brief	1	DIPHENHYDRAMINE	50	YES	
131A	Witek, Jr. et al. (1995)	REACTION TIME, Choice (CRT); Vis	9C	v. brief	1	DIPHENHYDRAMINE	50	YES	
131B	Witek, Jr. et al. (1995)	REACTION TIME, Choice (CRT); Vis	9C	v. brief	1	DIPHENHYDRAMINE	50	YES	
108	Sands et al. (1997)	REACTION TIME - (PC task)	9	brief	1	DIPHENHYDRAMINE	75	YES	
27	Cohen et al. (1984)	REACTION TIME - Simple, Visual	9S	5 min	1	DIPHENHYDRAMINE	100	YES	
68	Mattila et al. (1986)	REACTION TIME, Choice (CRT); Vis & Aud	9C	v. brief	1	DIPHENHYDRAMINE	100		NO
94	Preston et al. (1992)	REACTION TIME tests - SRT & CRT	9	v. brief	1	DIPHENHYDRAMINE	100		NO
94	Preston et al. (1992)	REACTION TIME tests - SRT & CRT	9	v. brief	1	DIPHENHYDRAMINE	200		NO
64	Levander et al. (1985)	REACTION TIME - Choice; visual	9C	v. brief	1	HYDROXYZINE	20	YES	
64	Levander et al. (1985)	REACTION TIME - Simple; aud & visual	9S	v. brief	1	HYDROXYZINE	20	YES	
65	Levander et al. (1991)	REACTION TIME - Choice; visual	9C	v. brief	1	HYDROXYZINE	20		NO
65	Levander et al. (1991)	REACTION TIME - Simple; aud & visual	9S	v. brief	1	HYDROXYZINE	20		NO
93	Pishkin et al. (1983)	REACTION TIME, SRT & CRT (Speeded Interference Task);	9	v. brief	1	HYDROXYZINE	25		NO
28	Cohen et al. (1985)	REACTION TIME - Simple, Visual	9S	5 min	1	TRIPOLIDINE	2.5	YES	
48	Hamilton et al. (1982)	REACTION TIME - Simple, Auditory	9S	15 min	1	TRIPOLIDINE	2.5		NO
91	Peck et al. (1975)	REACTION TIME, Simple (SRT); Aud	9S	15 min	1	TRIPOLIDINE	2.5	YES	
22	Bye et al. (1977)	REACTION TIME - Auditory	9	15 min	1	TRIPOLIDINE	5	YES	
28	Cohen et al. (1985)	REACTION TIME - Simple, Visual	9S	5 min	1	TRIPOLIDINE	5	YES	
91	Peck et al. (1975)	REACTION TIME, Simple (SRT); Aud	9S	15 min	1	TRIPOLIDINE	5	YES	
117	Swire et al. (1989)	REACTION TIME, Simple (SRT) - during ERP	9S	8 min	1	TRIPOLIDINE	7.5		NO
12	Bradley & Nicholson (1986)	REACTION TIME - COMPLEX - CRT	9C	~5 min	1	TRIPOLIDINE	10		NO
58	Kerr et al. (1994)	REACTION TIME - Choice (CRT) Leeds	9C	20 trials	1	TRIPOLIDINE	10	YES	
104	Rombaut et al. (1991)	REACTION TIME, Choice (CRT)	9C	v. brief	1	TRIPOLIDINE	10		NO
13A	Bradley et al. (1987)	REACTION TIME - COMPLEX - CRT	9C	~5 min	1	TRIPOLIDINE	10		NO
13B	Bradley et al. (1987)	REACTION TIME - COMPLEX - CRT	9C	~5 min	1	TRIPOLIDINE	10		NO

continued...

Sheet: RT Tasks

REACTION TIME TASKS - Summary of impairment findings as a function of DRUG and Dose - ACUTE DOSING only

continued...

Page 2: sorted by Generation, DRUG, Dose, Ref#, SC#.

Ref#	REFERENCE	TASK	SC#	Duration	Gen	DRUG	Dose, mg	IMPAIRMENT? YES	IMPAIRMENT? NO
					2nd	**Generation Drugs:**			
65	Levander et al. (1991)	REACTION TIME - Choice; visual	9C	v. brief	2	CETIRIZINE	10		NO
65	Levander et al. (1991)	REACTION TIME - Simple; aud & visual	9S	v. brief	2	CETIRIZINE	10		NO
95	Ramaekers et al. (1992)	REACTION TIME, Choice (CRT); Sternberg digits	9C	10 min	2	CETIRIZINE	10	**YES**	
95	Ramaekers et al. (1992)	Response Competition Test (RCT)	9C	15 min	2	CETIRIZINE	10		NO
100	Riedel et al. (1990)	REACTION TIME, Choice (CRT); Sternberg digits	9C		2	CETIRIZINE	10	**YES**	
6	Betts et al. (1989)	REACTION TIME, Choice (CRT)	9C		2	CETIRIZINE	20		NO
6	Betts et al. (1989)	REACTION TIME, Simple (SRT)	9S		2	CETIRIZINE	20	**YES**	
100	Riedel et al. (1990)	REACTION TIME, Choice (CRT); Sternberg digits	9C		2	CETIRIZINE	20	**YES**	
122	Vermeeren et al. (1998)	REACTION TIME, Choice (CRT); Vis (L&R w. distractors)	9C	v. brief	2	FEXOFENADINE	120		NO
122	Vermeeren et al. (1998)	REACTION TIME, Choice (CRT); Vis (L&R w. distractors)	9C	v. brief	2	FEXOFENADINE	240		NO
37	Englisch et al. (1996)	REACTION TIME - Choice; CRT in ODT	9C		2	LORATADINE	10		NO
42	Gaillard et al. (1988)	REACTION TASK - visual field: digits, degraded	9	24 min	2	LORATADINE	10		NO
57	Kay et al. (1997)	REACTION TIME - Simple; CogScreen	9S	brief	2	LORATADINE	10		NO
95	Ramaekers et al. (1992)	REACTION TIME, Choice (CRT); Sternberg digits	9C	10 min	2	LORATADINE	10		NO
95	Ramaekers et al. (1992)	Response Competition Test (RCT)	9C	15 min	2	LORATADINE	10		NO
109	Schaffler et al. (1994)	REACTION TIME, Choice - CRT (during ODT)	9C	dur ODT	2	LORATADINE	10		NO
6	Betts et al. (1989)	REACTION TIME, Choice (CRT)	9C		2	TERFENADINE	60		NO
6	Betts et al. (1989)	REACTION TIME, Simple (SRT)	9S		2	TERFENADINE	60		NO
7	Bhatti & Hindmarch (1989)	CHOICE REACTION TIME (CRT)	9C	very brief	2	TERFENADINE	60		NO
42	Gaillard et al. (1988)	REACTION TASK - visual field: digits, degraded	9	24 min	2	TERFENADINE	60		NO
58	Kerr et al. (1994)	REACTION TIME - Choice (CRT) Leeds	9C	20 trials	2	TERFENADINE	60		NO
61	Kulshrestha et al. (1978)	REACTION TIME - Simple (single light)	9S	brief	2	TERFENADINE	60		NO
117	Swire et al. (1989)	REACTION TIME, Simple (SRT) - during ERP	9S	8 min	2	TERFENADINE	60		NO
130A	Witek, Jr. et al. (1992)	REACTION TIME, Choice (CRT); Vis	9C	v. brief	2	TERFENADINE	60		NO
131A	Witek, Jr. et al. (1995)	REACTION TIME, Choice (CRT); Vis	9C	v. brief	2	TERFENADINE	60		NO
6	Betts et al. (1989)	REACTION TIME, Choice (CRT)	9C		2	TERFENADINE	120		NO
6	Betts et al. (1989)	REACTION TIME, Simple (SRT)	9S		2	TERFENADINE	120		NO
7	Bhatti & Hindmarch (1989)	CHOICE REACTION TIME (CRT)	9C	very brief	2	TERFENADINE	120		NO
74	Murri et al. (1992)	REACTION TIME, Simple (SRT); Vis & Aud	9S	brief	2	TERFENADINE	120		NO
7	Bhatti & Hindmarch (1989)	CHOICE REACTION TIME (CRT)	9C	very brief	2	TERFENADINE	240		NO

TABLE 14. PHYSIOLOGICAL MEASURES - Summary of impairment findings as a function of DRUG and Dose - ACUTE DOSING only

Sheet: PHYSIO.
page 2: sorted by Generation, DRUG, Dose, Ref#, SC#.

Ref#	REFERENCE	TASK	SC#	Duration	Gen	DRUG	Dose: mg	IMPAIRMENT? YES	NO
					1st	**Generation Drugs:**			
47	Goldstein et al. (1968)	EEG	10		1	CHLORPHENIRAMINE	2		NO
47	Goldstein et al. (1968)	EEG	10		1	CHLORPHENIRAMINE	4	YES	
69	Meador et al. (1989)	ERP - tonal oddball vigilance for P3	10		1	CHLORPHENIRAMINE	8	YES	
83	Nicholson et al. (1991)	Multiple Sleep Latency Test - MSLT	10M	20 min	1	CHLORPHENIRAMINE	8	YES	
63	Lee et al. (1988)	EEG - power spectrum analysis	10	?	1	CHLORPHENIRAMINE	12		NO bP
53	Hopes et al. (1992)	EEG - auditory tones for vigilance	10	20 min?	1	CLEMASTINE	2	YES	
30	Curran et al. (1998)	ERP during Oddball task (auditory - tones)	10	~ 20 min?	1	DIPHENHYDRAMINE	25		NO
30	Curran et al. (1998)	ERP during Word Recognition (visual)	10	~ 20 min?	1	DIPHENHYDRAMINE	25		NO
47	Goldstein et al. (1968)	EEG	10		1	DIPHENHYDRAMINE	25	YES	
30	Curran et al. (1998)	ERP during Oddball task (auditory - tones)	10	~ 20 min?	1	DIPHENHYDRAMINE	50	YES	
30	Curran et al. (1998)	ERP during Word Recognition (visual)	10	~ 20 min?	1	DIPHENHYDRAMINE	50	YES	
39	Fink et al. (1979)	EEG	10		1	DIPHENHYDRAMINE	50	YES	
47	Goldstein et al. (1968)	EEG	10		1	DIPHENHYDRAMINE	50	YES	
101	Roehrs et al. (1984)	Multiple Sleep Latency Test - MSLT	10M	1 hr	1	DIPHENHYDRAMINE	50	YES	
102	Roehrs et al. (1993)	Multiple Sleep Latency Test - MSLT	10M	20 min	1	DIPHENHYDRAMINE	50	YES	
110	Schweitzer et al. (1994)	Multiple Sleep Latency Test - MSLT	10M	20 min	1	DIPHENHYDRAMINE	50	YES	
114	Simons FE et al. (1996)	ERP during Oddball task (auditory - tones)	10	20 min (5mir	1	DIPHENHYDRAMINE	50	YES	
119	Tharion et al. (1994)	ERP - visual patterns (PREP)	10		1	DIPHENHYDRAMINE	50	YES	
119	Tharion et al. (1994)	ERP - auditory (BAEP)	10		1	DIPHENHYDRAMINE	50		NO
126	Walsh et al. (1994)	Multiple Sleep Latency Test - MSLT	10M	20 min	1	DIPHENHYDRAMINE	50	YES	
115A	Simons KJ et al. (1994)	ERP during Oddball task (auditory - tones)	10	20 min (5mir	1	DIPHENHYDRAMINE	50	YES	
111	Seidel et al. (1987)	Multiple Sleep Latency Test - MSLT	10M	20 min	1	HYDROXYZINE	25	YES	
9	Blom et al. (1992)	EEG - spectral analysis for 5 bands	10		1	HYDROXYZINE	30	YES	
115A	Simons KJ et al. (1994)	ERP during Oddball task (auditory - tones)	10	20 min (5mir	1	HYDROXYZINE	50	YES	
82	Nicholson & Stone (1986)	Multiple Sleep Latency Test - MSLT	10M	20 min	1	TRIPOLIDINE	2.5	YES	
82	Nicholson & Stone (1986)	Multiple Sleep Latency Test - MSLT	10M	20 min	1	TRIPOLIDINE	5	YES	
83	Nicholson et al. (1991)	Multiple Sleep Latency Test - MSLT	10M	20 min	1	TRIPOLIDINE	5	YES	
117	Swire et al. (1989)	ERP during Oddball task (auditory - tones)	10	8 min	1	TRIPOLIDINE	7.5		NO
					2nd	**Generation Drugs:**			
114	Simons FE et al. (1996)	ERP during Oddball task (auditory - tones)	10	20 min (5mir	2	ASTEMIZOLE	10		NO
115A	Simons KJ et al. (1994)	ERP during Oddball task (auditory - tones)	10	20 min (5mir	2	ASTEMIZOLE	10		NO
84	Nicholson & Turner (1998)	Multiple Sleep Latency Test - MSLT	10M	20 min	2	CETIRIZINE	5		NO
111	Seidel et al. (1987)	Multiple Sleep Latency Test - MSLT	10M	20 min	2	CETIRIZINE	5		NO
84	Nicholson & Turner (1998)	Multiple Sleep Latency Test - MSLT	10M	20 min	2	CETIRIZINE	10	YES	
89	Pechadre et al. (1988)	EEG - quantitative, spectral analysis	10	5 min	2	CETIRIZINE	10		NO
90	Pechadre et al. (1991)	EEG - quantitative, spectral analysis	10	5 min	2	CETIRIZINE	10		NO
95	Ramaekers et al. (1992)	EEG, during Drive	10	1 hr	2	CETIRIZINE	10	YES	
110	Schweitzer et al. (1994)	Multiple Sleep Latency Test - MSLT	10M	20 min	2	CETIRIZINE	10		NO
111	Seidel et al. (1987)	Multiple Sleep Latency Test - MSLT	10M	20 min	2	CETIRIZINE	10		NO
114	Simons FE et al. (1996)	ERP during Oddball task (auditory - tones)	10	20 min (5mir	2	CETIRIZINE	10		NO
126	Walsh et al. (1994)	Multiple Sleep Latency Test - MSLT	10M	20 min	2	CETIRIZINE	10		NO
33	De Roeck et al. (1990)	Multiple Sleep Latency Test - MSLT	10M	20 min	2	CETIRIZINE	20		NO?
84	Nicholson & Turner (1998)	Multiple Sleep Latency Test - MSLT	10M	20 min	2	CETIRIZINE	20		NO
111	Seidel et al. (1987)	Multiple Sleep Latency Test - MSLT	10M	20 min	2	CETIRIZINE	20		NO
90	Pechadre et al. (1991)	EEG - quantitative, spectral analysis	10	5 min	2	LORATADINE	10		NO
95	Ramaekers et al. (1992)	EEG, during Drive	10	1 hr	2	LORATADINE	10		NO
114	Simons FE et al. (1996)	ERP during Oddball task (auditory - tones)	10	20 min (5mir	2	LORATADINE	10		NO
33	De Roeck et al. (1990)	Multiple Sleep Latency Test - MSLT	10M	20 min	2	LORATADINE	20		NO
90	Pechadre et al. (1991)	EEG - quantitative, spectral analysis	10	5 min	2	LORATADINE	40	YES	
39	Fink et al. (1979)	EEG	10		2	TERFENADINE	60		NO
69	Meador et al. (1989)	ERP - tonal oddball vigilance for P3	10		2	TERFENADINE	60		NO?
89	Pechadre et al. (1988)	EEG - quantitative, spectral analysis	10	5 min	2	TERFENADINE	60	YES	
101	Roehrs et al. (1984)	Multiple Sleep Latency Test - MSLT	10M	1 hr	2	TERFENADINE	60		NO
114	Simons FE et al. (1996)	ERP during Oddball task (auditory - tones)	10	20 min (5mir	2	TERFENADINE	60		NO bP
117	Swire et al. (1989)	ERP during Oddball task (auditory - tones)	10	8 min	2	TERFENADINE	60		NO
119	Tharion et al. (1994)	ERP - visual patterns (PREP)	10		2	TERFENADINE	60		NO
119	Tharion et al. (1994)	ERP - auditory (BAEP)	10		2	TERFENADINE	60		NO

Note: 100% of findings for 1st generation drugs (9/9 vs 1/11=9.1% for 2nd gen.) showed significant sedation as measured by MSLT (SC# 10M).
EEG and ERP findings (SC# 10) were more variable, resulting in 68.4% "YES" significant impairment in 1st generation drugs (13/19) vs 17.6% in 2nd generation drugs (3/17).
Overall (SC# 10, 10M), the Physiological measures of sedation demonstrated significant impairment in 78.6% 1st generation drugs vs 14.3% 2nd gen.

Appendix B

EXAMPLE of an Impairment Summary Sheet

YES/NO Counts by Behavioral Category

DRIVING-RELATED SKILLS PERFORMANCE IMPAIRMENT as a function of ANTIHISTAMINE (Drug/Dose), TASK CATEGORY and DOSING (Acute/Repeated)

Results shown for:

TASK CATEGORY: *DRIVING & PILOTING*
SC#: *1 (1R,1C,1S,1?)*
Road, Circuit, Simulators

DOSING: *ACUTE*
..

Total # Tests: *55* **

NOTE: RESULTS shown are from data coded for Total of n=138 separate studies as reported in 130 scientific papers.

TABLE below reflects results from #STUDIES: 17
cited in #REFS: 16
Results of Query: #data lines: 22

** "TEST" = an experimental test of a given drug, dose, and task measure;
"YES" = statistically significant impairment relative to Placebo ($p < 0.05$).

1st generation:

DRUG CODE & Dose (mg):	D1: CHLORPHENIRAMINE					D2: CLEMASTINE				D3: DIPHENHYDRAMINE				D4: HYDROXYZINE				D5: TRIPOLIDINE			
	D1-4	D1-6	D1-8	D1-12	D1-16	D2-1	D2-2	D2-3	D2-4	D3-25	D3-50	D3-75+	D3-150+	D4-10	D4-25	D4-30	D4-50	D5<5	D5-5	D5-7.5	D5-10+
	2.4	6	8	12	16	1	2	3	4	25	50	75,100	150,200+	10	20-25	30	50	1.5,2.5	5	7.5	10,15,20
23 #tests:	1	0	0	0	0	0	1	1	0	1	4	1	0	0	0	0	0	4	6	0	4
12 #NO:	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	4	4	0	1
11 #YES:	1	0	0	0	0	0	1	1	0	0	3	0	0	0	0	0	0	0	2	0	3
47.8% %YES:	100.0%	ERR	ERR	ERR	ERR	ERR	100.0%	100.0%	ERR	0.0%	75.0%	0.0%	ERR	ERR	ERR	ERR	ERR	0.0%	33.3%	ERR	75.0%

CHLORPHENIRAMINE across dose
#tests: 1
#NO: 0
#YES: 1
%YES: 100.0%

CLEMASTINE across dose
#tests: 2
#NO: 0
#YES: 2
%YES: 100.0%

DIPHENHYDRAMINE across dose
#tests: 6
#NO: 3
#YES: 3
%YES: 50.0%

HYDROXYZINE across dose
#tests: 0
#NO: 0
#YES: 0
%YES: ERR

TRIPOLIDINE across dose
#tests: 14
#NO: 9
#YES: 5
%YES: 35.7%

2nd generation:

DRUG CODE & Dose (mg):	N1: ASTEMIZOLE				N2: CETIRIZINE			N3: FEXOFENADINE			N4: LORATADINE			N5: TERFENADINE		
	N1-10	N1-20	N1-30	N1-40	N2-5	N2-10	N2-20	N3-60	N3-120	N3-240	N4-10	N4-20	N4-40	N5-60	N5-120	N5-240
	10	20	30	40	5	10	20	60	120	240	10	20	40	60	120	240
32 #tests:	0	0	0	0	1	4	2	0	1	1	6	1	0	7	6	3
28 #NO:	0	0	0	0	1	3	1	0	1	1	6	1	0	6	6	2
4 #YES:	0	0	0	0	0	1	1	0	0	0	0	0	0	1	0	1
12.5% %YES:	ERR	ERR	ERR	ERR	0.0%	25.0%	50.0%	ERR	0.0%	0.0%	0.0%	0.0%	ERR	14.3%	0.0%	33.3%

ASTEMIZOLE across dose
#tests: 0
#NO: 0
#YES: 0
%YES: ERR

CETIRIZINE across dose
#tests: 7
#NO: 5
#YES: 2
%YES: 28.6%

FEXOFENADINE across dose
#tests: 2
#NO: 2
#YES: 0
%YES: 0.0%

LORATADINE across dose
#tests: 7
#NO: 7
#YES: 0
%YES: 0.0%

TERFENADINE across dose
#tests: 16
#NO: 14
#YES: 2
%YES: 12.5%

RESULTS in above table are from the following studies; REFERENCE numbers of research articles are shown:

Ref#: see master list for SC#: 1 (1R,1C,1S,1?)

Appendix C

EXAMPLE of a Study Summary Sheet

(Note: A Study Summary Sheet was generated for each of n=138 studies from the 130 references. Copies are available from the authors upon request.)

STUDY SUMMARY SHEET

CITATION

REF# 122
YEAR 1998
AUTHORS Vermeeren A, O'Hanlon JF.
TITLE Fexofenadine's effects, alone and with alcohol, on actual driving and psychomotor performance.
SOURCE J Allergy Clin Immunol
VOL:PP 101: 306-311
ALCOHOL? Y [N=No, Y=Yes] IF study also included ALCOHOL treatment, coded results below reflect No Alcohol (or Placebo drink) conditions for test of drug alone effects

METHOD

Blind	PC+	DESIGN	Ss (n)	Males (n)	AGES	AGE (M)	Population	PostDose	TEST duration	Acute	Repeat	Residual	Alerting effects?
DB	D2	Cross x6	24	12	21 - 45	31.5 +-8.5	Healthy volunteers	1.5h perf,+3drive	1hr perf, 1hr drive	Day 1	Day4, 5+alc		Fex 240mg improve drive & attenuate alc impair.

COMMENTS: Train: sep day; clemastine 2mg bid (h.s., AM day1) coded as 3mg Acute & 4mg R; F120,240AM, so A; F120bid, F60bid, so R: 240, 120mg; fexo improved drive & attenuated alc impair; but sig impair CTT!

RESULTS: DID STUDY SHOW STATISTICALLY SIGNIFICANT IMPAIRMENT (relative to Placebo) as function of DRUG (and DOSE) SHOWN BELOW?

RESULTS	TASK (or Subjective SEDATION)	SC#	TaskDUR	A	R	Resid.	D1: CHLORPHENIRAMINE 2.4mg 6mg 8,10 12mg 18mg	D2: CLEMASTINE 1mg 2mg 3mg 4mg	D3: DIPHENHYDRAMINE 25mg 50mg 75,100 150mg 200+mg	D4: HYDROXYZINE 10mg 20,25mg 30mg 50mg	D5: TRIPOLIDINE <5mg 5mg 7.5mg 10mg 20mg
1	CRITICAL TRACKING (CTT) - ~SCRI (5 trials)	8Cr	v. brief	X				YES			
2	CRITICAL TRACKING (CTT) - ~SCRI (5 trials)	8Cr	v. brief		X			NO			
3	REACTION TIME, Choice (CRT); Vis (L&R w. di	9C	v. brief	X				NO			
4	REACTION TIME, Choice (CRT); Vis (L&R w. di	9C	v. brief		X			NO			
5	VIGILANCE - Sustained Attention - ~`SCRI (45m	7	45 min	X				NOwP			
6	VIGILANCE - Sustained Attention - ~`SCRI (45m	7	45 min		X			NO			
7	DRIVING - Actual, Highway circuit	1R	~ 1hr	X				YES			
8	DRIVING - Actual, Highway circuit	1R	~ 1 hr		X			YES			
9											
10											
11											
12											
13											
14											
15											
16											
17											
18											

	TASK (or Subjective SEDATION)	SC#	TaskDUR	A	R	Resid.	N1: ASTEMIZOLE 10mg 20mg 30mg 40mg	N2: CETIRIZINE 5mg 10mg 20mg	N3: FEXOFENADINE 60mg 120mg 240mg	N4: LORATADINE 10mg 20mg 40mg	N5: TERFENADINE 60mg 120mg 240mg
1	CRITICAL TRACKING (CTT) - ~SCRI (5 trials)	8Cr	v. brief	X					YES YES		
2	CRITICAL TRACKING (CTT) - ~SCRI (5 trials)	8Cr	v. brief		X				NO NO		
3	REACTION TIME, Choice (CRT); Vis (L&R w. di	9C	v. brief	X					NO NO		
4	REACTION TIME, Choice (CRT); Vis (L&R w. di	9C	v. brief		X				NO NO		
5	VIGILANCE - Sustained Attention - ~`SCRI (45m	7	45 min	X					NO NO		
6	VIGILANCE - Sustained Attention - ~`SCRI (45m	7	45 min		X				NO NO		
7	DRIVING - Actual, Highway circuit	1R	~ 1hr	X					NO NO		
8	DRIVING - Actual, Highway circuit	1R	~ 1 hr		X				NO NO bP		
9											
10											
11											
12											
13											
14											
15											
16											
17											
18											

CODES: Blind: DB=Double-blind, SB=Single-blind PC+: Positive control; Coded for 10 key drugs or other 1st (D) or 2nd (N) generation H1-antagonists or Misc. drugs (M) Dosing: A=Acute, R=Repeated, Resid=Residual effects

SC#: Skill Category: #1=Driving & Flying; 2=Psychomotor; 3=Perception; 4=Visual functions; 5=Cognitive Skills; 6=Divided Attention; 7=Vigilance; 8=Tracking; 9=Reaction Time; 10=Physiological (MSLT, EEG, ERP); 99=Subjective Sedation

YEAR 1998

AUTHORS Vermeeren A, O'Hanlon JF.

COMMENTS: n=24;driving & psychomotor perf; day1,4 &alc day5; O'Hanlon; issue: Fex impair CTT acute dose; improve drive & attenuate alc impair; alerting effect?

RESULTS - Continued... COMMENTS for each line of study results:

RESULTS	TASK (or Subjective SEDATION)	SC#	A	R	Resid.	COMMENTS:
1	CRITICAL TRACKING (CTT) - ~SCRI (5 trials)	8Cr	X			CTT: C3 ~acute sig (Day 1 AM dose,and h.s. dose: C2mg bid); F120,240 as AM doses both sig impair!!
2	CRITICAL TRACKING (CTT) - ~SCRI (5 trials)	8Cr		X		CTT: n.s. Day4; but alc sig impaired, and C and F240 (AM dose) +alc sig > alc alone
3	REACTION TIME, Choice (CRT); Vis (L&R w. distractor	9C	X			CRT: n.s any time or drug dose; but alc sig impaired
4	REACTION TIME, Choice (CRT); Vis (L&R w. distractor	9C		X		CRT: n.s any time or drug dose; but alc sig impaired
5	VIGILANCE - Sustained Attention - ~`SCRI (45min)	7	X			VIG: n.s. any time or drug dose, but C trend impair Day1(p=.075); alc sig impaired
6	VIGILANCE - Sustained Attention - ~`SCRI (45min)	7		X		VIG: n.s. any time or drug dose, but C trend impair Day1(p=.075); alc sig impaired
7	DRIVING - Actual, Highway circuit	1R	X			DRIVE: C sig impaired Day 1&4; n.s. T effect on Day1
8	DRIVING - Actual, Highway circuit	1R		X		DRIVE: C sig impaired Day 1&4; T240mg (h.s/AM) sig improved driving Day4 & F240 (both dose regs) sig atten alc impair!!
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						

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