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WRITER'S DIRECT DIAL

April 17, 1998

The Dockets Management Branch
(HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Room 1-23
Rockville, Maryland 20857

Re: Docket No. 98N-0148
March 18, 1998 Federal Register Notice

TO WHOM THIS TOPIC IS OF CONCERN:

I. INTRODUCTION

This information is being provided as a response to the March 18, 1998, Notice which was published by the FDA in the Federal Register. 63 Fed. Reg. 13258-59. We understand that this document will be forwarded, along with information from the Food and Drug Administration ("FDA"), and the Drug Enforcement Administration ("DEA"), to the World Health Organization ("WHO") which will, in turn, prepare a Critical Review document for use of the Expert Committee on Drug Dependence. These comments deal with only one of the substances identified in the Notice -- ephedrine.

These comments are sponsored by and made on behalf of the Dietary Supplement Safety and Science Coalition ("the Coalition"). The Coalition is comprised of several businesses in the United States which either manufacture or distribute ephedrine alkaloid containing dietary supplement products in the United States and in many other countries. The members of the Coalition are The Chemins Company, Inc., Enrich International, Inc., Market America, Inc., Metabolife International, Inc., Natural Balance, Inc. d/b/a Pep Products, Inc., Omnitrition International, Inc., and Starlight International, Ltd. The address of the Coalition is 1660 Lincoln Street, Suite 1975, Denver, Colorado 80264. The Coalition's mission includes a strong commitment to the use of science when addressing an issue such as this one which involves ephedra.

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II. THE COALITION'S POSITION

The Coalition's position is that ephedrine should not be added to any of the Schedules of the Convention on Psychotropic Substances. The Coalition urges the WHO, the Expert Committee on Drug Dependence and the Commission on Narcotic Drugs, a part of the United Nations' Economic and Social Council, not to add ephedrine to any of those Schedules.

The Coalition urges this position (1) because the weight of available information demonstrates that (A) ephedrine has traditionally and safely been used for medicinal purposes, and currently is being used safely for both medicinal and food purposes, (B) no widespread pattern of abuse of ephedrine exists in the United States or worldwide, (C) ephedrine is not a psychotropic substance when used at dosage levels normally suggested on the labels of products which contain ephedrine, (D) ephedrine is not a substance which meets the criteria of paragraph 4 of Article 2 of the Convention, and (2) because ephedrine is not a controlled substance in the United States and there is no reason to believe that it will be in the reasonably foreseeable future.

The Coalition is furnishing three new items of scientific interest as a part of these comments. They are:

[1] April 17, 1998 letter report from Tim Meredith, M.D., of Vanderbilt University. Exhibit 1. See page 11 of this document for a discussion of this report.

[2] April 8, 1998 report from Hauser Laboratories Services. Exhibit 2. See page 14 of this document for a discussion of this report.

[3] April 17, 1998 letter report from Science, Toxicology and Technology Consultants. Exhibit 3. See page 13 of this document for a discussion of this report.

III. SPECIFIC RESPONSES TO THE DATA COLLECTION QUESTIONNAIRE OF THE WHO

The Coalition does not have any significant amount of reliable information to furnish in response to Topics 4, 5 and 6 of the Questionnaire. Furthermore, we understand from the FDA

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that the Expert Committee's primary focus will not be on illegal trafficking in ephedrine, but on the potential for and actual abuse of ephedrine by overuse. Therefore, the Coalition is responding to Topics 1-3 only, except as specifically noted.

WHO Question #1. Availability of the substance (registered, marketed, dispensed, etc.).

(A) Traditional Availability.

Dennis Jones, Ph.D.'s historical data on the historical use of ma huang or ephedra was well-described by him in an October 9, 1995 submission to the FDA Committee on Food Products; his curriculum vitae is attached as Exhibit 4:

"The oldest current record of man's interest in Ephedra dates back approximately 20,000 years, to the burial of a Neanderthal individual in what is now Iraq (Lietava, 1992), who was buried with a number of plants, including Ephedra altissima.

Under the name Ma huang [CHINESE LETTERS], Ephedra has traditionally been used as an invigorating tea or infusion with beneficial effects on respiration in China for more than 5000 years (Stuart, 1979), and the earliest written reference to its use and properties is attributed by some experts to the Emperor, Shen Nung (circa 3100 B.C.) in what may have been the first ever Pharmacopoeia, the *Ben Cao Chien* (others claim that the Shen Nung Ben Cao Chien did not appear until about 100 B.C.). This work was substantially revised and enlarged by Li Shih-Chen (1596).

The Indo-Aryans knew Ephedra as an edible plant that gave strength and happiness, and combated exhaustion (Mahdihassan, 1981). Though Indo-Aryans traditionally believed that substances conferring longevity were mainly inorganic, Ephedra was considered as a food with similar beneficial properties (Mahdihassan, 1984), and there is strong evidence that the Rigveda references to *soma* actually describe Ephedra juice (Mahdihassan and Mehdi, 1989). Soma, according to the Rigveda, was the drink of longevity which was even given to newborn infants; this Aryan custom was later to be followed by the Romans, and is still practiced among the Parsee of

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Bombay and in parts of Iran. Lewis and Elvin-Lewis (1977) also report a long history of use of the dried stems of *Ephedra gerardiana* in Northern India and Pakistan.

Ephedra was wellknown to the Romans, and was clearly described by Gaius Plinius Secundus in 77 A.D. (see Rackham et al., 1956-1966) in his *Natural History*, a work that encompassed 37 volumes, of which 12 dealt solely with the healing properties of plants! The herb was apparently not widely used in Europe after the times of the Romans (Moritz, 1953), though sporadic references do occur in medieval European literature; Gerard (1597), for example, refers to *Herba Ephedrae* (presumed to be *Ephedra fragilis*) as the 'Great shrubbe sea Grape'.

In North America, historical use of *Ephedra* species is well-documented (Kowalchik and Hylton, 1987; Moerman, 1986; Rose, 1972; Saunders, 1920; Tyler, 1982).[...]

Traditional users of *Ephedra* herb recommend dosages that are in excess of those given for ephedrine or pseudoephedrine in pharmaceutical forms, and are also very much higher than those recommended for Dietary Supplements containing Ma huang in the United States. For example, according to Chinese reference works (such as Ou Ming, 1989), Ma huang proper is generally given 3 times daily as a decoction of 3-10 grams of the stems, corresponding to a daily range of 112-180 mg alkaloids at the low end to 375-600 mg alkaloids at the high end, assuming that the Ma huang will contain 1.25% - 2% total alkaloids.

The British Herbal Pharmacopoeia (1983) is somewhat more conservative, but still recommends a dose of 1-4 grams 3 times daily (thus 125-500 mg alkaloids per day), for a herb with a minimum alkaloid content of 1.25%.

These relatively high dosages may be explained by the fact that the herb does not behave like pure ephedrine alkaloids; for example, according to the British Herbal Pharmacopoeia (1983), *Ephedra herb does not have the marked pressor effect of ephedrine*. This appears to be due to slower absorption of the

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alkaloids from the herb than from pharmaceutical formulations (Harada and Nishimura, 1981; Reid, 1986), so there is no sudden rush of ephedrine into the body. The differences between pure ephedrine and Ma huang also show up in formal animal safety studies; Minamatsu et al. (1991) compared pure ephedrine with an extract of Ma huang, and concluded that the extract was less lethal. They also noted that while animals which died after ephedrine administration showed histological changes in some organs, these changes were not found in animals which died after large doses of extract, suggestive of lower classical toxicity.

While most attention has been focused on medicinal use of Ephedra herb, Tanaka (1976) describes Ephedra as a food plant, and Katiyar et al. (1990) report use of parts of the plant as food in some Himalayan tribes. The USDA (1937) classified Ephedra as a highly beneficial forage crop, and allowing meat and milk animals to graze on Ephedra apparently improves meat and milk quality and quantity as well as overall health of the animals (Kovacevic et al., 1974)."

Ephedrine has been available in Germany since 1896 and in the U.S. since 1926. Chen, K.K., Schmidt, C.F. Ephedrine and Related Substances (Baltimore 1930). In 1926, ephedrine was approved for sale in the U.S. by the American Medical Association. The ephedrine-containing herb, Ma Huang (ephedra) has been used in Chinese medicine for 5,200 years. Larry S. Hobbs, "Ephedrine + Caffeine = The Ideal Diet Pill," Townsend Letter for Doctors & Patients, at 62 (June 1996).

(B) Availability in the United States Today

Today, in the United States, ephedrine is legally used as an ingredient in prescription and OTC drug products for therapeutic purposes and in a class of foods, called dietary supplements, for several dietary purposes.

(1) Food Products.

The food products in which ephedrine is primarily used are a special type of food called dietary supplements. "Dietary Supplement" is a term defined by Sec. 201(ff) of the Federal Food Drug and Cosmetic Act ["FFDCA"] of the United States. Sec.

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201(ff) was established by the United States Congress when it enacted Section 3 of the Dietary Supplement Health and Education Act of 1994 ["DSHEA"] which became effective on October 25, 1994. Ephedrine, when used in foods, is normally a constituent of ma huang, an herb, which is also known as ephedra; ephedra can be sold as a dietary supplement product or as an ingredient in a dietary supplement product as long as it is not promoted to prevent, treat, cure, diagnose or mitigate a disease condition. Each day in the United States, millions of dietary supplements - tablets and capsules - are sold and ingested which contain ephedra and, consequently, ephedrine. No prior approval or notice to the FDA, the DEA or any other governmental entity or agency need be acquired or given before these dietary products are manufactured, distributed, purchased and used.

Ephedrine alkaloid-containing dietary supplements are made available to consumers via several marketing channels. They are sold in:

- ♦ health food stores
- ♦ drug stores
- ♦ mass merchandise retail stores
- ♦ in kiosks in shopping malls
- ♦ in mail-order catalogs

Also, a large volume of these products are sold directly to consumers in their homes by multi-level marketing organizations, also known as direct selling organizations. The volume of ephedrine-containing dietary supplements sold is significant. At least 50 companies in the U.S. manufacture or distribute dietary supplements which contain ephedrine alkaloids. One company alone, Metabolife International, Inc. of San Diego, California, sells 60 million tablets per month of Metabolife 356 -- a product which contains ma huang. This product has an excellent safety record; no serious adverse health claims or events from abuse, overuse, or any other reason have been reported about this product. There is no "black market" for ephedrine alkaloid-containing dietary supplement products because there is no need for clandestine sales.

The dietary benefits which people experience from consuming ephedrine-containing dietary supplements are weight management, which includes weight loss, and a "sense of well-being"; this latter benefit is sometimes characterized by consumers with statements such as "I feel more energetic" even though the effect of the ephedrine alkaloids doesn't arise from calories. The two health benefits described above are consistent with the

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definitions of "food" and "dietary supplement" in the Federal Food, Drug and Cosmetic Act.

(2) Drug Products.

Ephedrine is available in prescription and over-the-counter ["OTC"] drug products in the United States. Ephedrine is present in OTC drug products which are sold in the United States as bronchodilators to treat asthma and as decongestants to treat colds. Part 341 of Title 21 of the Code of Federal Regulations of the United States contains detailed regulations with respect to those products. Those regulations contain provisions which address the Indications, Warnings and Directions which must be on the label of each OTC drug product. For example, 21 C.F.R. (Code of Federal Regulations) §341.16 and §341.76(d)(1) address bronchodilator drug products; the latter regulation provides that the Directions, to a consumer, on the label should contain this language:

"Adult and children 12 years of age and over: Oral dosage is 12.5 to 25 milligrams in 24 hours, not to exceed 150 milligrams in 24 hours or as directed by a doctor. Do not exceed recommended dosage unless directed by a doctor. Children under 12 years of age: Consult a doctor."

By complying with these regulations, no pre-market approval from the FDA is required for these OTC drug products. The daily amount of ephedrine permitted in an OTC bronchodilator drug product far exceeds the amount of ephedrine alkaloids which would be ingested if the suggested or recommended usage language on a typical dietary supplement container was followed. See Exhibit 5 which is a label from Metabolife 356, a typical dietary supplement.

(C) Legal Status of Ephedrine in the United States

(1) Controlled Substances.

Ephedrine is not a controlled substance in the United States; furthermore it is not regarded by the DEA as an immediate precursor of methamphetamine which is a controlled substance, or of any other controlled substance. The statutes of the United States define "controlled substance" at 21 U.S.C. §802(6). That statute reads:

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The term "controlled substance" means a drug or other substance, or immediate precursor, included in schedule I, II, III, IV, or V of part B of this subchapter.

These five schedules of controlled substances are a part of 21 U.S.C. §812. In the United States, there are three criteria which must be considered when determining whether to place a substance on one of the five schedules. In general, a substance should and can be placed on an appropriate controlled substance schedule if it has a potential for abuse and the abuse of it or another substance may lead to at least a limited physical or psychological dependence relative to other scheduled substances. The placement of a particular substance depends on the level of potential for abuse, the level of potential dependence caused by the substance and the extent of its medical use in treatment in the United States.

These U.S. laws which govern the manufacture, distribution and use of controlled substances and listed chemicals had their origin with Congress' enactment of the Comprehensive Drug Abuse Prevention and Control Act of 1970. Many additions to that law have occurred since 1970. A comprehensive set of federal administrative regulations have been issued which implement those statutes. Those regulations are contained at Title 21, Parts 1301-1316 of The Code of Federal Regulations.

In the United States, one of the federal appellate courts, when interpreting the U.S. laws on controlled substances, clearly described the core analysis which should be engaged in when trying to decide whether a substance should be scheduled as a controlled substance:

"The applicable law is cogently set out by Judge Butzner in Carter-Wallace, Inc. v. Gardner, 417 F.2d 1086 (4th Cir. 1969), in which Carter-Wallace, Inc. attacked a Food and Drug Administration order subjecting meprobamate to control as a depressant drug. The court stated: "in selecting 'potential for abuse' as one of the criteria for subjecting a drug to special control, the House Committee did not intend this to be determined on the basis of the drug's having a potential for isolated or occasional nontherapeutic purposes. Instead, the committee recommended that a drug's potential for abuse should be determined 'on the basis of its having been demonstrated to have such depressant or stimulant

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effect on the central nervous system as to make it reasonable to assume that there is a substantial potential for the occurrence of significant diversions from legitimate drug channels, significant use by individuals contrary to professional advice, or substantial capability of creating hazards to the health of the user or the safety of the community.'"

(2) Ephedrine is a listed chemical only.

Ephedrine is a "listed chemical" only. 21 C.F.R. §1310.02(a)(3) lists "ephedrine, its salts, optical isomers, and salts of optical isomers" as List I chemicals. Ephedrine has been assigned 8113 as its DEA Chemical Code Number.

A List I chemical is defined at 21 U.S.C. §802 (34) as being "a chemical specified by regulation of the Attorney General as a chemical that is used in manufacturing a controlled substance in violation of this subchapter and is important to the manufacture of the controlled substances..." Because ephedrine is a List I chemical, its manufacture and distribution is regulated by the DEA. 21 U.S.C. §§822-827 require most persons who manufacture or distribute a controlled substance or a List I chemical to register annually with the United States Attorney General. Also, each regulated person, as defined by 21 U.S.C. §802(38) who engages in a regulated transaction involving a listed chemical must keep a record of the transaction for two years after the date of the transaction. 21 U.S.C. §830(a). Violations of the United States laws with respect to listed chemicals are set out at 21 U.S.C. §841(d), (f) and (g).

(3) Proposed FDA Regulation.

The FDA, in June of 1997, proposed a regulation which would impact the availability to consumers of dietary supplements which contain ephedrine alkaloids. 62 Fed. Reg. 30678. Most importantly, for the purpose of the issues being addressed in these comments, the regulation would permit the continued manufacturing, distribution and sale of dietary supplements which contain ephedrine alkaloids. The proposed regulation, however, would: (1) limit the amount of ephedrine in a single serving to less than 8 mg; (2) limit the daily intake of ephedrine to less than 24 mg; (3) prohibit the combination of ephedrine and substances that have a known stimulant effect, such as caffeine; (4) prohibit the use of dietary supplements containing ephedrine for long-term use; and (5) require certain warnings and statements on the package label or labeling. This

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Coalition and hundreds of other persons filed objections to that proposed rule. The Coalition's comprehensive written response focused on the lack of valid scientific data for many provisions of this proposed regulation.

The period for filing comments about that proposed regulation closed in early December of 1997. The FDA has not yet indicated whether it intends to issue that regulation or a modified one, to pursue some other administrative course of action, or to withdraw the regulation entirely.

WHO Question #2. Extent of abuse of the substance [ephedrine]

There is some abuse by overuse of ephedrine by persons in the United States. By "overuse," we mean the act of a consumer which results in his or her ingesting more than the quantity recommended or suggested on the product label in an effort to obtain some perceived benefit. We believe that the amount of that abuse is very small when compared with the volume of ephedrine-containing prescription and OTC drug products and dietary supplements which are consumed without abuse in the United States. The Coalition strongly believes that there is no compelling evidence or other satisfactory basis for the Expert Committee or the WHO to make either of the findings required by Paragraph 4 of Article 2 of the Convention or to make any recommendation about ephedrine being a controlled substance to the Commission. Paragraph 4 states:

"4. If the World Health Organization finds:

- (a) That the substance has the capacity to produce
 - (i) (1) a state of dependence, and
 - (2) central nervous system stimulation or depression, resulting in hallucinations or disturbances in motor function or thinking or behaviour or perception or mood, or
 - (ii) similar abuse and similar ill effects as a substance in Schedule I, II, III or IV, and
- (b) that there is sufficient evidence that the substance is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control,

the World Health Organization shall communicate to the Commission an assessment of the substance, including

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the extent or likelihood of abuse, the degree of seriousness of the public health and social problem and the degree of usefulness of the substance in medical therapy, together with recommendations on control measures, if any, that would be appropriate in the light of this assessment."

(A) REASONS FOR COALITION'S POSITION

(1) If ephedrine abuse from intentional overuse was or is a significant problem in the United States, both the FDA and DEA would have taken swift regulatory measures to attempt to prevent or curtail this abuse and would seek Congress' help in classifying ephedrine as a controlled substance. Neither federal agency has done so.

This same concept of abuse is an integral part of the controlled substance statutes of the United States. See previous Sec. (C) of Part III [in response to Question #1] of this document. As previously pointed out, ephedrine is not a controlled substance in the United States, but is a listed chemical. When Congress made that determination, it decided that ephedrine is important to the manufacture of a controlled substance, but it did not decide that ephedrine had a potential for abuse or that it had the capacity to produce a state of dependence.

(2) The Scientific Perspective.

According to Dr. Tim Meredith, Director of the Center for Clinical Toxicology at Vanderbilt University Medical Center, ephedrine is not a psychotropic substance except in extreme circumstances and, in light of the requirements of paragraph 4, Article 2 of the Convention, should not be recommended for inclusion on one of the Convention's schedules of controlled substances. He states:

"In my view, ephedrine is not a psychotropic substance as defined in paragraph (e) of Article 1 of the Convention, nor do I believe that it should be categorized as such. Ephedrine does not, in my view, meet the requirements of paragraph 4(a) of Article 2 of the Convention.

Ephedrine is a mild central nervous system stimulant with a potency, at normal therapeutic doses, similar to that of caffeine. My review of the

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scientific literature has not revealed a pattern of systematic overuse or abuse of ephedrine, or a tendency to produce a state of dependence. Rarely, ephedrine may cause psychosis, but usually in the context of chronic, excessive (non-therapeutic) dosage. The pharmacological properties of ephedrine, and the potential for abuse, are either very different or of a different order of magnitude from those of each of the substances currently listed in the Schedules of the Convention."

See the attached letter dated April 17, 1998 from Tim Meredith, M.D., Exhibit 1.

Except in people who already have a history of drug abuse, ephedrine appears to have a quite low potential for abuse. Larry S. Hobbs, Ephedrine & Caffeine: The Ideal Diet Pill? (3rd ed. June, 1996) at 18. L.D. Chait found that ephedrine did not affect ratings of drug liking in a group of patients without a history of drug abuse, and noted that there is little epidemiological or anecdotal evidence of [ephedrine] abuse, despite the fact that the substance is widely available over the counter a [and by mail] and even sometimes advertised as a "legal" stimulant. Chait, L.D. "Factors influencing the reinforcing and subjective effects of ephedrine in humans." Psychopharmacology 113(3-4): 381-387, 1994. Chait goes on to observe that the profile of ephedrine's subjective effects are similar to that of other mild stimulants, such as caffeine. In particular, repeated doses and prolonged administration of ephedrine show no cumulative effects. Hobbs 2 at 14, citing Reynolds, J.E.F., ed. Martindale: The Extra Pharmacopoeia (30th ed. 1993).

Ephedrine is 5 to 10 times less potent than amphetamines. Although ephedrine's chemical structure is amphetamine-like, its effects are much less potent than amphetamines. Ephedrine is about 5 times less potent than amphetamines in raising systolic blood pressure, 10 times less potent in raising diastolic blood pressure, and 10 times less potent in disturbing sleep. Martin, W.R., Sloan, J.W. et al. "Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methyphenidate in man." Clinical Pharmacology and Therapeutics 12(2): 245-258, 1971. One study even found relaxation to be a more prominent symptom than nervousness in subjects taking ephedrine.

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WHO Question #3. Degree of seriousness of the public health and social problems associated with abuse of the substance.

We have found no information that suggests that there is any public health or social problem associated with abuse of the product by overuse.

We recognize that substantial public safety and public health problems arise from the use and trafficking of methamphetamine, also called "crank". Television "specials" and valid law enforcement reports detail the depth of the social problems involved in and arising from the "cooking" and use of "crank." We also acknowledge that these desperate people use ephedrine to manufacture this illegal drug and that the source of ephedrine is pure ephedrine either stolen or obtained by purchasing, in large volume, products masquerading as legitimate OTC drugs or as legitimate dietary supplements. The right way to deal with this supply problem is to do exactly what U.S. law enforcement authorities are doing. They are taking enforcement action against unscrupulous vendors and imposing regulations which will make it virtually impossible for illicit drug products to acquire large volumes of pure ephedrine products.

(A) Ephedrine alkaloids in dietary supplements are not a precursor to amphetamines. Only pure USP grade ephedrine is used in the manufacturing of amphetamines and similar controlled substances. Dietary supplements are very rarely used, if ever, to make amphetamines or other controlled substances because (1) it is apparently chemically impossible or at least, extremely difficult to do so and (2) because it would cost too much to do so even if it could be done. A recent attempt by a well-respected scientific lab trying to make amphetamines from dietary supplements containing ephedrine did not succeed in that effort. Metabolife International, Inc. hired Hauser Laboratory Services to "attempt to produce methamphetamines from the Metabolife 356 using the 'street' method published in The Journal of Forensic Sciences, Vol. 40, No. 4, July 1995." Each tablet contained an average of 13.1 mg. of ephedra alkaloids, with the contents of the 12 bottles of #356 resulting in approximately 1.3 kg of starting material. The report from Hauser states:

The material was extracted into methanol and the extract was reacted with red phosphorus and hydriodic acid for five hours. The resulting mixture was basified and extracted into freon. The freon was then

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acidified using hydrogen chloride gas. This should have resulted in the production of methamphetamine crystals; however it formed a black tar like material. The material was tested by Gas Chromatography/Mass Spectroscopy (GC/MS) and found to contain mostly ephedra alkaloids and caffeine; the presence of methamphetamine was not detected.

A copy of the Hauser test report is attached as Exhibit 2.

(B) To the best of our knowledge, no legal authority has ever found and seized an illegal lab that was using ephedrine alkaloid-containing dietary supplements to produce methamphetamine or another illegal controlled substance. As demonstrated by the Hauser report, the complex matrix of herbs in such products does not permit conversion to produce pure ephedrine, which in turn would have to be converted into methamphetamine. See the letter from Simone Derayeh of Science, Toxicology and Technology Consultants which is attached as Exhibit 3.

(C) Dietary supplements which contain ephedrine alkaloids are not likely to be purchased by drug dealers for their ephedrine content because (1) the relative high cost of these products even if they were purchased on a volume discount basis and (2) the relatively low amount of ephedrine alkaloids in each bottle of supplements. In a typical bottle of 60 tablets, at 12.5 mg. of ephedrine alkaloids per tablet, only .75 gram of ephedrine alkaloids are present. Since the retail price of a typical bottle of 60 tablets is in the \$20.00 to \$40.00 range, other sources of ephedrine are sought and used by those who engage in drug manufacturing.

(D) The few ephedrine-related deaths per year in the U.S. are not evidence that ephedrine is, itself, a "dangerous drug." Overall, these ephedrine - related deaths need to be put in a larger perspective. For example, in the United States, there were 15 such deaths between 1993 to mid-1996. Yet every year 400 children die in bike accidents, 500 people die from contaminated hamburgers, and 400,000 people die from smoking-related causes. Larry S. Hobbs, Ephedrine & Caffeine: The Ideal Diet Pill? at 14 (3rd ed. June, 1996). "This means that more people die every year from eating hamburgers than have died in the last 100 years from taking ephedrine. . . ."

Another significant contrast arises from medical statistics published on April 15, 1998 in a leading scientific

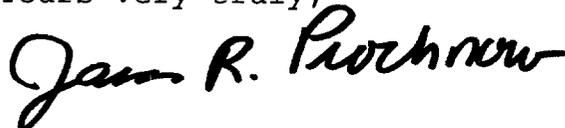
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journal. A new study concluded that "more than 2 million Americans become seriously ill every year because of toxic reactions to correctly prescribed medicines taken properly, and 106,000 die from those reactions." Rick Weiss, "Drug Side Effects Take Deadly Toll," The Denver Post, at 2A (April 15, 1998) (reprinted from The Washington Post). That number makes drug side effects at least the sixth most common cause of death in the U.S., and perhaps even the fourth. The comprehensive study, appearing in the April issue of the Journal of the American Medical Association, suggests that 1 in 15 hospital patients in the U.S. "can expect to suffer from a serious reaction to prescription or over-the-counter medication, and about 5 percent of these will die from it." This study "is stronger than previous ones because it looks only at cases in which drugs were taken correctly. Previous hints of similarly high side-effect rates had been attributed in large part to people getting the wrong medicines or taking them in the wrong doses." (emphasis added). That is, readily available drugs, not dietary supplements, taken in correct doses (not overused or in overdoses) cause a staggering 106,000 deaths per year. See David Bates, M.D. "Drugs and Adverse Drug Reactions: How Worried Should We Be?" JAMA (April 15, 1998), Vol. 279, No. 15, page 1216; Lazarou et al., "Incidence of Adverse Drug Reactions in Hospitalized Patients," JAMA (April 15, 1998), Vol. 279, No. 15, page 1200. Articles attached as Exhibit 6.

CONCLUSION

In conclusion, ephedrine is not a controlled substance in the U.S. today, nor should it be internationally. Ephedrine-containing products (both OTC drugs and dietary supplements) are readily available on the open market. The few cases of overuse of an ephedrine-containing product are isolated incidents, and do not demonstrate any significant or real potential for widespread abuse. In short, there is no medical, psychological, chemical, or legal reason for ephedrine to be recommended as a controlled substance, either nationally or internationally.

Yours very truly,



By: James R. Prochnow
Legal Counsel for the Coalition

JRP/sjm

Exhibit 1

TIM MEREDITH, M.D.
VANDERBILT UNIVERSITY MEDICAL CENTER
Director, Center for Clinical Toxicology
Professor of Medicine and Pathology
Center for Clinical Toxicology
501 Oxford House
1161 21st Avenue South
Nashville, Tennessee 37232-4632
Phone: (615) 936-0760
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E-mail: tim.meredith@mcm.vanderbilt.edu

April 17, 1998

Re: FDA Docket No. 98N-0148
Int'l. Drug Scheduling Notice

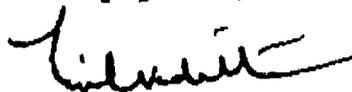
To Whom It May Concern:

I have read the above-referenced Notice and pertinent sections of the Convention on Psychotropic Substances (1971). I have been asked by the Dietary Supplement Safety and Science Coalition ("the Coalition") to respond to the Food and Drug Administration's notice of opportunity to provide data, comments and other information on whether ephedrine, among others, should be included in the Convention's Schedules of psychotropic substances.

In my view, ephedrine is not a psychotropic substance as defined in paragraph (e) of Article 1 of the Convention, nor do I believe that it should be categorized as such. Ephedrine does not, in my view, meet the requirements of paragraph 4(a) of Article 2 of the Convention.

Ephedrine is a mild central nervous system stimulant with a potency, at normal therapeutic doses, similar to that of caffeine. My review of the scientific literature has not revealed a pattern of systematic overuse or abuse of ephedrine, or a tendency to produce a state of dependence. Rarely, ephedrine may cause psychosis, but usually in the context of chronic, excessive (non-therapeutic) dosage. The pharmacological properties of ephedrine, and the potential for abuse, are either very different or of a different order of magnitude from those of each of the substances currently listed in the Schedules of the Convention.

Very truly yours,



Tim Meredith, M.D.

Exhibit 2

HAUSER®

April 8, 1998
Test Report No. C8-0730
Page 1 of 1

CLIENT: Metabolife International Inc.
5070 Santa Fe Street
San Diego, CA 92109

Attn: Mike Ellis

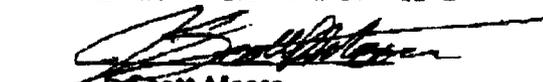
SAMPLES: One case of Metabolife Dietary Supplement 356 was received March 23, 1998. The label listing the ingredients in this product is attached.

TESTS: It was requested that we attempt to produce methamphetamines from the Metabolife Dietary Supplement using the "street" method published in The Journal of Forensic Sciences, Vol. 40, No. 4, July 1995.

RESULTS: The tablets were initially analyzed for ephedra content by High Performance Liquid Chromatography (HPLC). Each tablet was found to contain 13.1 mg/tablet on average of ephedra alkaloids. The contents of the 12 bottles of Metabolife Dietary Supplement 356 were ground resulting in approximately 1.3 kg of starting material (13.7 g ephedra alkaloids). The material was extracted into methanol and the extract was reacted with red phosphorus and hydriodic acid for five hours. The resulting mixture was basified and extracted into freon. The freon was then acidified using hydrogen chloride gas. This should have resulted in the production of methamphetamine crystals, however it formed a black tar like material. The material was tested by Gas Chromatography/Mass Spectroscopy (GC/MS) and found to contain mostly ephedra alkaloids and caffeine, the presence of methamphetamine was not detected.

CONCLUSION: The procedure described above was performed according to the method published in The Journal of Forensic Sciences, Vol. 40, No 4, July 1995, titled "Ephedra's Role As a Precursor in the Clandestine Manufacture of Methamphetamine" by K.M. Andrews. Based on our analysis, it does not appear that this published method can be used to make methamphetamine from Metabolife's Dietary Supplement 356.

**REPORT WRITTEN
& ANALYSIS PERFORMED BY:**


J. Scott Moore
Technician III

REPORT REVIEWED BY:


Nicole M. Enderle
Chemist

This report applies only to the sample, or samples, investigated and is not necessarily indicative of the quality or condition of apparently identical or similar products. As a mutual protection to clients, the public and these Laboratories, this report is submitted and accepted for the exclusive use of the client to whom it is addressed and upon the condition that it is not to be used, in whole or in part, in any advertising or publicity matter without prior written authorization from Hauser Laboratories. This report may be copied only in its entirety.



ST&T DEPARTMENTS:

DOCUMENTS & INFORMATION RESEARCH:

□ MR. MILLER 800.738-4636

PHARMACOLOGY/TOXICOLOGY:

□ DR. ALDRICH □ DR. SNODGRASS

GENERAL MEDICINE, MEDICAL CONSULTATION:

□ DR. STRAUSS: 310.454-6004 FAX:310.454-9768

GENERAL INFORMATION & CONSULTING:

□ MICHAEL SCOTT: 415.441-2163 800.869-4636

**Exhibit 3**

April 17, 1998

Via Facsimile (303) 894-9239

Mr. James Prochnow
 Patton Boggs
 1660 Lincoln Street, Suite 1975
 Denver, CO 80264

Subject: Ephedrine as a Precursor to Methamphetamine

Dear Mr. Prochnow,

Per your request, I have done some research in scientific literature for any references to the synthesis of Methamphetamine using ephedrine, specifically the ephedrine alkaloids present in dietary supplements that contain Ma Huang.

Ma Huang plant is the natural source of Ephedrine in herbal supplements and the Merck Index states that the plant contains 0.75% to 1% ephedrine alkaloids.

Ephedrine can be reduced to yield Methamphetamines in the presence of Hydriodic acid and red phosphorus (Skinner, H.F. 1990. Forensic Science International and Andrews, K.M. 1995. Journal of Forensic Sciences). The reduction reaction also requires other chemicals such as freon gas, several acids and bases, and some form of alcohol for extraction. Nevertheless, I was unable to find any scientific reference to such production using an herbal dietary supplement as the substrate (conversely I have information from Hauser labs to the contrary).

If possible (which has not yet been proven to our lab specialists), the process of isolating Ephedrine from these dietary supplements would need additional steps, reactions, compounds and equipment. The complex matrix of these supplements, presence of various other compounds and the small amount of Ephedrine alkaloids (approximately 12 mg on average/tablet) in each tablet makes the synthesis extremely labor intensive for even the best of the professionally equipped labs. Additionally, the high cost of these supplements and the other compounds required in the reaction makes the method highly improbable and/or uneconomical.

We were also unable to find any record or reference to any lab(s) having been busted in the past for such methods of Methamphetamine synthesis.

Please contact me if you require further search for information in this matter

Kind Regards,

A handwritten signature in cursive script that reads 'Simone Derayeh'.

Simone Derayeh
 Research Associate

SCIENCE, TOXICOLOGY & TECHNOLOGY

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 □ SAN FRANCISCO ADDRESS • P.O. BOX 470116 • SAN FRANCISCO, CALIFORNIA 94147 • (415) 441-2163 • (800) 869-4636

EXECUTIVE SUMMARY OF RESUME:

Dr. Dennis Jones

NAME: Dennis Jones

BORN: 20 July, 1941

NATIONALITIES: Canadian, British

ADDRESSES, PRIVATE:

1411 rue du Fort, #2311
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ADDRESSES, BUSINESS:

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1600 46th Avenue
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19 Donegani Avenue
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QUALIFICATIONS:

M.A. (Cantab.), Ph.D. (Cantab.),
C.Chem, FRSC(UK), MCIC,
C.Biol, M.I.Biol, MBIM

LANGUAGES:

English, Dutch, German, French;
basic knowledge of other
Germanic and Romance languages.

EDUCATION, SCHOOL (PRIMARY/GRAMMAR):

1947 - 1951 Heygarth Road
Primary School, Eastham,
Cheshire (GB).

[Passed the 11+ examination
at the age of 9 years]

1951 - 1960 Wirral Grammar
School for Boys, Bebington,
Cheshire (GB).

[General Certificate of
Education (N.U.J.M.B)]

'O' levels, 1957,
8 subjects:- Mathematics,
Physics, Chemistry, English
Language, English Literature,
German, Latin, Geography.

'A'/'S' levels, 1959/1960,
5 subjects:- Mathematics,
Physics*, Chemistry*,
Biology, General Studies
with Spoken English.
(* = distinction)

State Scholarship awarded in 1959; Open Exhibition to Downing
College, Cambridge, awarded in 1959.

EXECUTIVE SUMMARY OF RESUME:

Dr. Dennis Jones

page: 2.

EDUCATION, UNIVERSITY:

1960 - 1963 University of
Cambridge, Downing College
(as undergraduate).

Pathology, Physiology, Chemistry.

B.A. (Cantab), 1963

1963 - 1966 University of
Cambridge, Downing College
(as Research Student).

H.E. Durham Scholar; British Egg
Marketing Board Scholar.

M.A. (Cantab), 1967; Ph.D., 1971.

CAREER:

- 1960 - 1962 Part-time Assistant, Margarine and Edible Oils Section,
Unilever Research Ltd.
- 1963 - 1966 British Egg Marketing Board Scholar, Department of
Pathology, University of Cambridge.
- 1966 - 1971 University Demonstrator in Nutrition and Food
Chemistry, Department of Applied Biology (formerly
School of Agriculture), University of Cambridge.
- 1971 - 1975 Head of the Anti-atherosclerosis Programme,
Organon International B.V., Oss, Holland.
- 1975 - 1977 Head of Miscellaneous Projects,
Organon International B.V., Oss, Holland.
- 1978 - 1979 Head of Miscellaneous and Exploratory Objectives,
Organon International B.V., Oss, Holland.
- 1979 - 1980 Director of Research, Laboratoires UPSA,
Rueil-Malmaison, France.
- 1980 - 1984 Executive Director, POS Pilot Plant Corporation,
Saskatoon, Saskatchewan.
- 1984 - 1986 Director of Research, Development and Quality
Control, Frank W. Horner Inc., Montreal, Quebec.
- 1986 to
present President, Spencer-Jones Inc., Pointe Claire, Quebec.
- 1991 to
present Vice President Scientific and Commercial Development,
Bariatric International Inc., Lachine, Quebec.
- 1992 to
present President, Fytoresearch Inc., Lachine, Quebec.
- 1993 to
present President, Weight Exchange Inc., Shelburne, Vermont.

EXECUTIVE SUMMARY OF RESUME:

Dr. Dennis Jones

page: 3.

TEACHING EXPERIENCE:

University: Organic Chemistry, Supervision of Practical Classes (1963 - 1964); Organic Chemistry, College Lecturer, Emmanuel College (1964 - 1970); Supervisor, Chemistry, Fitzwilliam College (1967 - 1970); Morbid Histology, demonstrations in practical classes (1963 - 1966); Bacteriology, demonstrations in practical classes (1963 - 1966); Nutrition and Food Chemistry, lecturing and demonstrating in Tripos courses (1966 - 1971).

Technical College: Chemistry for Bakers and Confectioners (1964 - 1966); Microbiology for Bakers and Confectioners (1965 - 1966); Biology for Laboratory Assistants (1965 - 1966); Chemistry for Printers (1964 - 1966); Science for Hairdressers (1965 - 1966); Biochemistry for Medical Technicians (1968 - 1970).

OTHER EXPERIENCE:

Examiner and sometime awarder for Cambridge Local Examinations Syndicate in 'A' level Chemistry (1964 - 1970), 'A' level Biology for Oxford and Cambridge Joint Board (1967 - 1970), and Nuffield Physical Science for College Entrance and Awards (1968). Sometime abstractor for Nutrition Abstracts, Abstracts of World Medicine, Chemical Abstracts, Derwent Publications Ltd. Free-lance translator. UNESCO collaborator.

Consultant (past & present) to various companies, Governmental agencies and Governments in matters relating to technology transfer, management of technology, innovation and new product development. Developed software for nutritional evaluation, CAD software for food and nutritional product development, and interactive software for project evaluation.

COMMITTEES:

Past Chairperson, Expert Committee on Plant Products;
Member, Expert Committee on Plant Products;
Past Member, Canada Committee on Food;
Member, Expert Committee on Human Nutrition;
Past Member, Saskatchewan Council for Biotechnology;
Past Member, Saskatchewan New Technology Council;
Past Member, Research and Technical Committee of the
Canola Council of Canada;
Past Member-at-large, AOCS Protein and Co-Products
Section Committee;
Past President, Saskatoon Opera Association;
Past Member, Board of Directors, Saskatoon Symphony Society.

EXECUTIVE SUMMARY OF RESUME:

Dr. Dennis Jones

page: 4.

PROFESSIONAL AND LEARNED SOCIETIES:

Fellow of the Royal Society of Chemistry;
Member, Chemical Institute of Canada;
Member, American Oil Chemists Society;
Member, Institute of Biology;
Member, British Institute of Management;
Member, Canadian Institute of Food Science and Technology;
Member, Canadian Pharmaceutical Association
Member, American Society of Pharmacognosy.

PUBLICATIONS:

67 scientific or technical,
numerous popular articles
and radio/TV shows.

HOBBIES:

Music (singing opera), wine
making, brewing, shooting,
fishing, countryside, cars,
conservation, reading.

SYNOPSIS:

Formal training in Medical and Life Sciences, Chemistry and Management. Considerable training, experience and interest in Nutrition, Nutritional Pathology, Pharmacology, Food Science and the Management of Technology, in particular in relation to the Agriculture, Food, Pharmaceutical and Chemical Industries.

Significant experience in Systems Analysis and competent in Assembly Language programming of PC-compatible computers based on CPUs from the 8086 family (8088 up to 80486). Designed and developed commercial software packages and utilities.

Some experience in Patents and Licencing. Wide range of scientific interests, not confined to the bounds of the formal training. Aptitude for linguistics and for commercial aspects of technologically-based industries.

EXECUTIVE SUMMARY OF RESUME:

Dr. Dennis Jones

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ADDENDUM: INFORMATION ON SPENCER-JONES INC.

SPENCER-JONES INC.
19 Donegani Avenue
POINTE CLAIRE, Quebec
CANADA H9R 2V6

Spencer-Jones has provided services to the food, agriculture and pharmaceutical industries and to various Government agencies and departments in the areas of technology transfer, scientific public relations, product development, strategic long range planning, management of R & D, project evaluation and appraisal.

In addition, the company has developed proprietary and novel procedures for the computerization of project evaluation in R and/or D based industries, software for nutritional evaluation of diets, and supplies customized software packages, adapted specifically to clients' needs, on request.

Achievements of the company cannot be described in detail, due to clients' requirements of confidentiality, but have included:

- A] Development of a range of dietary health care products on behalf of clients, now successfully marketed;
- B] Development of novel pharmaceutical formulations;
- C] Development of new technology for the manufacture of novel food substances;
- D] Liaison with Regulatory Agencies, resulting in a number of approvals for new food and pharmaceutical products;
- E] Implementation of in- and out-licencing procedures for food and pharmaceutical companies, including product acquisitions;
- F] Planning and implementation of "scientific PR" activities for clients, resulting in wide-spread media attention for their products and services;
- G] Appearance as an expert witness in litigation proceedings and intellectual property disputes on behalf of clients.

Under the terms of the agreement with Bariatrix, all activities in the Food and Nutrition area are now handled exclusively through Bariatrix.

SUGGESTED USE: As a Dietary supplement, orally, adults, ONE to TWO caplets two to three times per day, or every four hours, on an empty stomach one hour before meals. **DO NOT EXCEED EIGHT CAPLETS PER DAY.**

CAUTION: AS WITH ANY DIETARY SUPPLEMENT, SEEK ADVICE FROM A HEALTH CARE PRACTITIONER PRIOR TO USE IF YOU ARE PREGNANT OR NURSING, OR IF YOU HAVE HIGH BLOOD PRESSURE, HEART OR THYROID DISEASE, DIABETES, DIFFICULTY IN URINATION DUE TO PROSTATE ENLARGEMENT, OR IF TAKING A MAO INHIBITOR OR ANY OTHER PRESCRIPTION DRUG, OR INTEND ON TAKING TO REDUCE WEIGHT. REDUCE IF NERVOUSNESS, TREMOR OR NAUSEA OCCUR. NOT INTENDED FOR USE BY PERSONS UNDER THE AGE OF 18. KEEP OUT OF THE REACH OF CHILDREN.

*Based on multi-species clinical laboratory testing.

Natural Herbs
Metabolife™
Dietary Supplement **356**

Herbal formula to enhance your

DIET

and provide
Energy

90 Caplets



**INDEPENDENTLY
LABORATORY
TESTED FOR
*SAFETY***

| Supplement Facts | |
|---|---------------|
| Serving Size 1 Caplet | |
| Amount Per Serving | % Daily Value |
| Vitamin E..... 8 I.U. | 20% |
| Magnesium (as Magnesium Chelate)..... 75 mg | 18% |
| Zinc (as Zinc Chelate)..... 5 mg | 33% |
| Chromium (as Chromium Picolinate)..... 75 mcg | 62% |
| Proprietary Blend..... 720 mg | |
| Guarana Concentrate (seed)..... | |
| (40 mg naturally occurring caffeine) | |
| Ma Huang Concentrate (aerial part)..... | |
| (12 mg naturally occurring ephedrine) | |
| Bee Pollen..... | |
| Ginseng (root)..... | |
| Ginger (root)..... | |
| Lecithin..... | |
| Bovine Complex..... | |
| Damiana (leaf)..... | |
| Sarsaparilla (root)..... | |
| Golden Seal (aerial part)..... | |
| Nettles (leaf)..... | |
| Gotu Kola (aerial part)..... | |
| Spirulina Algae..... | |
| Royal Jelly..... | |

Other Ingredients: Methylcell, silica, croscarmellose sodium, magnesium stearate.

Metabolife International, Inc.
5070 Santa Fe Street San Diego, CA 92109
(619) 490-5222

Natural Herbs

Metabolife™

Dietary Supplement **356**

Herbal formula to enhance your

DIET

and provide
Energy

90 Caplets

**INDEPENDENTLY
LABORATORY
TESTED FOR
*SAFETY***



| Supplement Facts | |
|---|--|
| Serving Size 1 Caplet | |
| Amount Per Serving | % Daily Value |
| Vitamin E..... | 6 I.U. 20% |
| Magnesium (as Magnesium Chelate)..... | 75 mg 18% |
| Zinc (as Zinc Chelate)..... | 5 mg 33% |
| Chromium (as Chromium Picolinate)..... | 75 mcg 62% |
| Proprietary Blend..... | 728 mg |
| Guarana Concentrate (seed)..... | (40 mg naturally-occurring caffeine) |
| Ma Huang Concentrate (aerial part)..... | (12 mg naturally-occurring ephedrines) |
| Bee Pollen..... | |
| Ginseng (root)..... | |
| Ginger (root)..... | |
| Lecithin..... | |
| Bovine Complex..... | |
| Damiana (leaf)..... | |
| Sarsaparilla (root)..... | |
| Golden Seal (aerial part)..... | |
| Nettle (leaf)..... | |
| Gotu Kola (aerial part)..... | |
| Spirulina Algae..... | |
| Royal Jelly..... | |

* Daily Value not established

Other Ingredients: Maltodextrin, silica, croscarmellose sodium, magnesium stearate.

Metabolife International, Inc.
5070 Santa Fe Street San Diego, CA 92109
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veillance. Children are overrepresented as victims of incidents involving DEG-adulterated medication. Parents were only treating the minor fevers and illnesses that children commonly get with a known, "safe," over-the-counter medicine. It never occurred to them that such a routine act could be accompanied by a lethal outcome. This disaster portrays a betrayal of the basic trust between caregiver and care provider—a trust that is within the scope of the right to health care of every child and every citizen, a right that every manufacturer of pharmaceuticals and every government must strive to ensure and protect.

It is significant that the outbreak of DEG poisoning reported by O'Brien et al² occurred in an impoverished developing country. In the global accounting of richer developed vs poorer developing countries, inadequate regulation and surveillance of the safety of medications seem an extraordinarily regressive tax. The glycerin vehicle of the medicine seemed to be the "smoking gun" causing this epidemic, but the authors provide no information about the root cause. How or why did the glycerin get contaminated? Was the cause ignorance, negligence, cost savings, or some other error? Further investigation into the root cause of why this contamination occurred may reveal additional insights into prevention. The authors imply that such incidents will continue to occur until the resources are appropriated to stop them. We can ill afford this purgatory.

O'Brien et al suggest ways to end these calamities. Strict quality control measures in the formulation and dispensing of medications and the passage and enforcement of governmental regulations that ensure the safety of pharmaceuticals are mandatory. The new initiatives that the Haitian government will surely undertake to safeguard their most vulnerable populations against such a mishap in the future must be implemented everywhere; global action is necessary to prevent repeat occurrences. Improved surveillance and early detection of DEG in adulterated medications using inexpensive methods applicable in the field, as suggested by O'Brien et al,² may be additional strategies implemented in a successful global approach.

The Haitian epidemic replays all the past folly involved with DEG contamination. There are no new public health lessons from the Haitian tragedy. Rather we simply must be better students of the old lessons to avoid returning in the future to this particular dark and dangerous wood.

AJan D. Woolf, MD, MPH

1. Alighieri D. *The Divine Comedy*. Norton CE, trans. Chicago, Ill: Encyclopedia Britannica Inc; 1952.
2. O'Brien KL, Selanikic JD, Hechtvert C, et al, for the Acute Renal Failure Investigation Team. Epidemic of podiatric deaths from acute renal failure caused by diethylene glycol poisoning. *JAMA*. 1998;279:1175-1180.
3. Bowic MD, McKenzie D. Diethylene glycol poisoning in children. *S Afr Med J*. 1972;69:931-934.
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6. Okunghae HO, Ighogboja IS, Lawson JO, Nwana JC. Diethylene glycol poisoning in Nigerian children. *Ann Trop Paediatr*. 1992;12:235-238.
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21. Baud FJ, Gallot M, Astier A, et al. Treatment of ethylene glycol poisoning with intravenous 4-methylpyrazole. *N Engl J Med*. 1988;319:97-100.
22. Wiener HL, Richardson KE. Metabolism of diethylene glycol in male rats. *Biochem Pharmacol*. 1989;38:539-541.
23. Scalzo AJ. Diethylene glycol toxicity revisited: the 1996 Haitian epidemic. *J Toxicol Clin Toxicol*. 1996;34:513-516.
24. Wax P. It's happening again: another diethylene glycol mass poisoning. *J Toxicol Clin Toxicol*. 1996;34:517-520.

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Drugs and Adverse Drug Reactions

How Worried Should We Be?

Physicians can hardly pick up a medical journal or a newspaper today without reading about some new medication, and how it promises to completely change the course of a disease or relieve some troublesome symptom. Indeed, the wonders of pharmacology are numerous. It is clear, for example, that after a myocardial infarction patients will live longer if they take β -blockers¹ and that patients with congestive heart failure live

longer and feel better when they take angiotensin-converting enzyme inhibitors.² However, medications are a double-edged sword.

See also p 1200.

Much of the recent work on problems with medications has focused primarily on errors in medication use, which are important.³ But, adverse drug reactions (ADRs) that are not preventable given our current state of knowledge are a more common problem, with a greater human burden. In this issue of *JAMA*, Lazarou and colleagues⁴ attempt to assess the

From the Department of Clinical and Quality Analysis, Partners Healthcare Systems, Boston, Mass.

Reprints: David W. Bates, MD, MSc, Division of General Medicine & Primary Care, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115 (e-mail: dwbates@rics.harvard.edu).

extent of this problem. They performed a meta-analysis of the prospective studies evaluating the incidence of ADRs in hospitalized patients. Even after excluding errors in drug administration, the authors found that ADRs may be the fourth to sixth leading cause of death, and that drug-related injuries occur in 6.7% of hospitalized patients. These data suggest that health care practitioners may miss or pass over many ADRs that occur, even among fatal events.

Can these data be correct? There are a number of concerns about the way the study was done, although the authors adhered to the generally accepted criteria for meta-analyses.⁵ First, an inherent limitation of meta-analysis is that combining the results of small, heterogeneous studies does not necessarily bring one closer to truth, particularly if the processes used to identify and to validate the presence of the events were heterogeneous.⁶ Second, the hospitals studied are probably not representative of hospitals at large. Such studies are more likely to be conducted in academic, tertiary care hospitals; these hospitals have sicker patients, and these patients have more ADRs. Another issue is whether the sites of care sampled within the institutions were representative of the institutions. All these factors could inflate the incidence estimate. It is also surprising that the ADR rate remained constant over time, despite increasing patient acuity and use of larger numbers of medications. Some other data⁷ suggest that the frequency of problems with medications actually may be increasing.

Nonetheless, these data are important, and even if the true incidence of ADRs is somewhat lower than that reported by Lazarou et al,⁴ it is still high, and much higher than generally recognized. Why is this the case? One reason is that hospitals have had strong incentives not to identify too many of these events. Reporting large numbers of adverse events and any serious preventable event brings intense scrutiny from regulators and the public. Thus, most hospitals have relied on spontaneous reporting, which only identifies about 1 in 20 adverse reactions and leads to the perception that injuries from ADRs are less common than they really are.⁸ Also, less research has been done in this area compared with other major causes of death, such as heart disease or cancer. No single specialty or organ system is involved, the Food and Drug Administration is not a funding agency, and research funding for this important area has been scarce.

Another issue is whether tracking nonpreventable drug-related injuries is important, especially after it is known that a specific drug can cause a specific reaction. It is, for several reasons: First, avoiding administration of the same medication to the patient in the future requires knowing and documenting that the patient had a previous allergy or sensitivity. When a patient develops an allergy or sensitivity, it is often not recorded, and patients receive drugs to which they have known allergies or sensitivities with disturbing frequency.⁹ Second, many events not preventable today will likely be preventable in the future, by one of a variety of mechanisms. For instance, design of new and safer drugs is spurred by such data. A good example is development of fexofenidine to replace terfenadine. Terfenadine was associated with cardiac arrhythmias including torsades de pointes, particularly when used in combination with several other commonly used medi-

cations, including erythromycin.⁹ Substitution of the new agent—a terfenadine metabolite that has the therapeutic properties but not the adverse consequences of terfenadine—seems likely to dramatically reduce this risk. Moreover, it is likely that clinicians will improve their ability to predict which patients will experience adverse consequences from specific drugs.

If hospitals are to monitor for ADRs, what approach should they use? Chart review is too expensive to be practical on a routine basis.³ Fortunately, computer surveillance can be used to assist in finding adverse drug events, and this approach is much more efficient than chart review.^{10,11} Today, most hospitals could not immediately implement such a system given the present state of their information systems, but they should be able to do so soon.

But why should hospitals invest in comprehensive monitoring for ADRs, given today's multiple competing priorities? One reason is new regulations, which are being developed by the Health Care Financing Administration.¹² These regulations, released with a request for comment in the *Federal Register*¹² in November, would require hospitals to routinely monitor for adverse drug events and would impose sanctions if they fail to do so. However, as currently written, the regulations seem untenable for a number of reasons, including the requirement for hospitals to perform expensive routine chart review. If rewritten, these regulations could provide a major impetus for quality. For example, hospitals could be required to demonstrate that they routinely measure adverse drug events and medication error rates.

For all medications, a key issue is whether the benefits outweigh the risks. The answer, as demonstrated by large numbers of randomized controlled trials, is yes, but that there must be more attention given to the risk side of the equation. Only after drugs leave the trial setting and are used in sicker patients do their true risks become apparent. Although some risks are inevitable, they can be significantly reduced, and learning more about these risks will make this possible.

David W. Bates, MD, MSc

1. Furberg CD, May GS. Effect of long-term prophylactic treatment on survival after myocardial infarction. *Am J Med*. 1984;76:76-83.
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Incidence of Adverse Drug Reactions in Hospitalized Patients

A Meta-analysis of Prospective Studies

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Objective.—To estimate the incidence of serious and fatal adverse drug reactions (ADR) in hospital patients.

Data Sources.—Four electronic databases were searched from 1966 to 1996.

Study Selection.—Of 153, we selected 39 prospective studies from US hospitals.

Data Extraction.—Data extracted independently by 2 investigators were analyzed by a random-effects model. To obtain the overall incidence of ADRs in hospitalized patients, we combined the incidence of ADRs occurring while in the hospital plus the incidence of ADRs causing admission to hospital. We excluded errors in drug administration, noncompliance, overdose, drug abuse, therapeutic failures, and possible ADRs. Serious ADRs were defined as those that required hospitalization, were permanently disabling, or resulted in death.

Data Synthesis.—The overall incidence of serious ADRs was 6.7% (95% confidence interval [CI], 5.2%-8.2%) and of fatal ADRs was 0.32% (95% CI, 0.23%-0.41%) of hospitalized patients. We estimated that in 1994 overall 2 216 000 (1 721 000-2 711 000) hospitalized patients had serious ADRs and 106 000 (76 000-137 000) had fatal ADRs, making these reactions between the fourth and sixth leading cause of death.

Conclusions.—The incidence of serious and fatal ADRs in US hospitals was found to be extremely high. While our results must be viewed with circumspection because of heterogeneity among studies and small biases in the samples, these data nevertheless suggest that ADRs represent an important clinical issue.

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PUBLIC ATTENTION is currently focused on adverse drug reactions (ADR) as evidenced by a recent bill passed by the US Senate requiring pharmaceutical companies to provide ADR information to consumers.¹ Heightened interest in ADRs was stimulated by the thalidomide tragedy in the 1960s.² To obtain an accurate estimate of ADR incidence in hospital patients, prospective studies were done, beginning in the 1960s, in which a defined population could be kept

under close observation by monitors who recorded all ADR occurrences.^{3,4} These prospective studies have been done on 2 separate populations of patients; those admitted to the hospital due to an ADR (ADRAd),⁵ and those experiencing an ADR while in the hospital (ADRIn).⁷ We report here a meta-analysis of 39 of these prospective studies done in the United States over a period of 32 years from which we obtained ADR incidences for ADRIn and for ADRAd and an overall ADR incidence that combines these 2 groups. We focused mainly on serious and fatal ADRs since they represent the greatest impact of drug therapy. While recognizing the benefits of drug therapy, we chose not to compare benefits of drugs to the side effects of drugs.

METHODS

Definitions

One step we took to reduce heterogeneity was to exclude any data that did not use the following specific definitions:

Adverse Drug Reaction (ADR).—According to the World Health Organization definition,⁸ this is any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy. This definition excludes therapeutic failures, intentional and accidental poisoning (ie, overdose), and drug abuse.⁸ Also, this does not include adverse events due to errors in drug administration or non-compliance (taking more or less of a drug than the prescribed amount).⁸ Using this conservative definition avoids overestimating the ADR incidence.

For editorial comment see p 1216.

Recently, some authors prefer the term *adverse drug event* (ADE), which is an injury resulting from administration of a drug. In contrast to the World Health Organization definition of ADR, the definition of ADE includes errors in administration.⁹ However, we have chosen the World Health Organization definition for ADR because of its frequent use in the studies that we analyzed, and because of our goal to estimate injuries incurred by drugs that were properly prescribed and administered. In those articles that did not use the World Health Organization definition (eg, ADE was used), we examined the raw data and removed adverse events due to errors in administration. However, this was not always feasible since a few articles may have included errors in administration but did not report them separately. Therefore, unfortunately, these latter articles added to the heterogeneity of our data.

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Possible ADR.—This is an ADR that follows a reasonable temporal sequence and for which the ADR is a known response to the drug, although the response may also be explained by the patient's clinical state.¹⁰ Possible ADRs were excluded from our study.

Serious ADR.—This is an ADR that requires hospitalization, prolongs hospitalization, is permanently disabling, or results in death. Serious ADRs include fatal ADRs, which were also analyzed separately.

Prospective Studies.—Patients were present during the study, and monitors were able to interview physicians, nurses, or patients at least once per week. All ADRs were confirmed prior to patient's discharge from the hospital.

Retrospective Studies.—Chart reviews were performed after the patient had left the hospital. These studies were excluded from our analysis.

Literature Search

Electronic databases were searched using the following key word strategy: *adverse drug or adverse reaction or drug-related or drug-induced and hospital*. Three MeSH (Medical Subject Headings) terms were also used where appropriate (ie, *hospitalization, drugs, drug therapy/adverse effects*) in combination with key words. Databases that we used were MEDLINE (1966-1996), Excerpta Medica (1980-1996), International Pharmaceutical Abstracts (1970-1996), and Science Citation Index (1989-1996). The reference sections of all retrieved articles were manually searched for additional studies. In addition, we sent letters to researchers in the field to request unpublished data in order to reduce publication bias.

Selection Criteria

The following criteria were used:

1. The patients studied were not selected for particular conditions or specific drug exposures.
2. Sufficient information was reported in the published study to calculate the incidence of ADRs.
3. English translations of the papers were available.
4. Prospective monitoring was used to identify ADRs.
5. Definitions used in the studies coincided with ours (see "Definitions" subsection for our definitions).

Quality of the Data

Rather than merely assessing the quality of each study,¹¹ we chose instead to improve the quality of our database. First, we used prospective monitoring as an inclusion criterion to exclude the lowest-quality studies (ie, the retrospective stud-

ies). Second, ADRs classified as "possible" were excluded. Attributing causality is always a problem with ADR detection¹² and, by excluding possible ADRs, we reduced the number of false positives in the data.

Heterogeneity

We dealt with heterogeneity among the studies in numerous ways: (1) we placed considerable emphasis on the 95% confidence intervals (CIs) to draw attention to the heterogeneity,¹³ (2) we used a random-effects model to do the analysis because it takes into account the heterogeneity of the various studies,^{13,14} (3) to reduce heterogeneity, we excluded ADRs caused by errors in administration, noncompliance, overdose, drug abuse, or therapeutic failures, (4) for additional ways to reduce heterogeneity, we excluded ADRs not fitting our strict definitions, possible ADRs, and retrospective data.

Data Extraction

We determined the incidence of ADRs in the hospital by extracting the total number of hospital patients in each study experiencing at least 1 ADR and dividing this value by the total number of hospital patients in each study. The ADR incidence was expressed as the percent of patients with an ADR. A data collection form was developed prior to the study for this purpose. Information on nonserious, serious, and fatal reactions was extracted. Other data extracted included the year of the study, ward and hospital type in which the study was performed, mean age, average length of hospital stay, average number of drug exposures for the patients included in the study, and the number of men and women in each study. To test for reliability of our extraction procedures a randomly selected subset of the data was extracted independently by 2 of us (J.L. and B.H.P.) and was found to be very consistent for the published ADR incidence for serious, fatal, and all severities (intraclass correlation coefficient ranging from 0.89 to 0.92).

Analysis of ADR Incidence

We separately analyzed the incidence of ADRin and the incidence of ADRAd and then combined the 2 groups to obtain an overall ADR incidence. We analyzed ADRs of all severities (which included nonserious and serious), ADRs that were serious (which included fatal), and ADRs that were fatal; however, we focused mainly on the serious and fatal ADRs. For each category, we analyzed the ADR incidences obtained from the different studies to determine the mean incidence and the 95% CIs. For this purpose we used a random-effects model for

meta-analysis¹⁵ similar to the method used in the only previous meta-analysis of ADRAd.¹⁶ This is the method of choice because it takes into account the heterogeneity of the various studies.¹⁴

When combining the incidence of ADRin and ADRAd to obtain the overall incidence of ADRs, we avoided double counting patients who were admitted for an ADR and who then also experienced an ADR while in the hospital by assuming the 2 types of events to be independent and deriving an adjusted estimate using the following formula:

$$\begin{aligned} \text{Adjusted Overall Incidence} &= (\text{Incidence of ADRin} \\ &+ \text{Incidence of ADRAd}) \\ &- (\text{Incidence of ADRin} \\ &\times \text{Incidence of ADRAd}). \end{aligned}$$

This provided a slightly smaller estimate of the ADR incidence. For example, the mean estimate for the overall number of serious ADRs per year (see "Results" section) would change by 32 000 patients, dropping from 2 249 000 (no adjustment) to 2 216 000 (our estimate using the adjustment).

When comparing groups, we used both parametric and nonparametric methods. The results were always the same for the 2 methods. Hence, for group comparisons, whenever possible, we reported the results of the more robust nonparametric Wilcoxon rank sum test.¹⁷ All statistical analyses were performed using the SAS statistical software package, version 6.11 (Statistical Analysis System, Cary, NC).

Number of Patients With ADRs

We estimated the number of hospital patients with ADRs in the United States by using the incidence of ADRs in US hospitals derived from our data and multiplying this value by the number of hospital admissions in 1994 in the United States, obtained from published statistics.¹⁸ In 1994, there were 83 125 492 hospital admissions in the United States. We calculated the 1994 fatal ADRins as follows:

$$\begin{aligned} \text{Number of Fatal ADRins in US Hospitals in 1994} &= (\text{Incidence of Fatal ADRins in Hospitals in the United States} \\ &(0.0019) \times \text{Number of Hospital Admissions in the United States} \\ &(83\,125\,492)). \end{aligned}$$

This estimate is based on the assumption that our sample is representative of the hospital population, and, hence, we examined representativeness at some length (see "Results" section).

RESULTS

Using our 5 selection criteria, 39 of the 153 studies found in the literature were included in our meta-analysis. Features

Table 1.—Studies on ADRs in Patients While in the Hospital (ADRIn)*

| Source, y | Wards Studied† | Study Size | Incidence of ADRs, %‡ | | |
|--|----------------|------------|-----------------------|---------|-------|
| | | | All Severities | Serious | Fatal |
| Bates et al, 1995 ¹⁹ | 1, 7 | 379 | 5.3 | 0.8 | 0 |
| Bates et al, 1995 ²⁰ | 1, 2 | 4031 | 4.4 | 1.5 | 0.08 |
| Bowman et al, 1994 ²¹ | 1 | 1024 | 10.3 | 1.1 | ... |
| Bates et al, 1993 ² | 1, 2, 6, 8 | 420 | 3.6 | 1.9 | 0 |
| Steel et al, 1981 ²² | 1 | 815 | 14.8 | 2.8 | ... |
| Mitchell et al, 1979 ²³ | 4 | 1669 | 16.8 | ... | ... |
| Bennett and Lipman, 1977 ²⁴ | 1, 2 | 152 | 7.2 | 1.4 | ... |
| May et al, 1977 ²⁵ | 1 | 334 | 10.2 | ... | ... |
| Miller, 1973 ²⁶ | 1 | 11 526 | 22.5 | 2.4 | 0.29 |
| McKenzie et al, 1973 ²⁷ | 4 | 658 | 12.2 | 2.3 | 0.15 |
| Wang and Terry, 1971 ²⁸ | 1, 2 | 8291 | 1.2 | ... | 0.01 |
| Gardner and Watson, 1970 ²⁹ | 1 | 939 | 10.5 | 2.1 | 0.85 |
| Borda et al, 1968 ³ | 1 | 830 | 24.1 | 6.0 | ... |
| Sidel et al, 1967 ³⁰ | 1 | 267 | 10.9 | ... | ... |
| Seidl et al, 1966 ⁴ | 1 | 714 | 13.6 | 0.9 | 0.42 |
| Smith et al, 1966 ⁵ | 1 | 900 | 10.8 | ... | 0.22 |
| Reichel, 1965 ¹ | 1 | 500 | 8.2 | ... | ... |
| Schimmel, 1964 ² | 1 | 1014 | 10.2 | 0.8 | 0.39 |

*ADR indicates adverse drug reaction; ADRIn, an ADR occurring in patients while in the hospital; and ellipses, data not available.

†Wards studied: 1, medical; 2, surgical; 3, geriatric; 4, pediatric; 5, psychiatric; 6, internal medicine; 7, intensive care; and 8, obstetric.

‡Incidence of ADRs = (number of patients with ADR/total patients studied) × 100.

§This study performed by the Boston Collaborative Drug Surveillance Program was categorized as United States in our analysis since only 1787 of the 11 526 patients were from hospitals outside the United States.

Table 2.—Studies on Patients Admitted to the Hospital Due to an ADR*†

| Source, y | Wards Studied‡ | Study Size | Incidence of ADRs, %§ | |
|---|----------------|------------|-----------------------|-------|
| | | | Serious | Fatal |
| Nelson and Talbert, 1986 ³³ | 6, 7 | 450 | 5.3 | ... |
| Coli et al, 1990 ³⁴ | 1 | 315 | 16.8 | ... |
| Mitchell et al, 1988 ³⁵ | 4, 6, 7 | 6546 | 1.0 | 0.03 |
| Bigby et al, 1987 ³⁶ | 1 | 686 | 6.9 | ... |
| Lakshmanan et al, 1985 ³⁷ | 1 | 834 | 4.2 | ... |
| Salari et al, 1984 ³⁸ | 5 | 41 | 12.2 | ... |
| Stewart et al, 1980 ³⁹ | 5 | 50 | 5.0 | ... |
| Frisk et al, 1977 ⁴⁰ | 1, 2, 3, 4, 8 | 442 | 6.8 | ... |
| McKenney and Harrison, 1976 ⁴¹ | 1 | 218 | 5.6 | 0 |
| McKenzie et al, 1976 ⁴² | 4 | 3558 | 1.9 | 0.11 |
| Caranias et al, 1974 ⁴³ | 1 | 6063 | 2.9 | 0.18 |
| Miller, 1974 ⁴ | 1 | 492 | 3.9 | ... |
| | 1 | 555 | 1.8 | ... |
| | 1 | 1025 | 3.0 | ... |
| | 1 | 1193 | 5.6 | ... |
| | 1 | 2065 | 2.9 | ... |
| McKenzie et al, 1973 ²⁷ | 4 | 658 | 2.9 | 0.15 |
| Gardner and Watson, 1970 ²⁹ | 1 | 939 | 5.1 | ... |
| Sidel et al, 1967 ³⁰ | 1 | 267 | 4.5 | ... |
| Seidl et al, 1966 ⁴ | 1 | 714 | 3.9 | 0.70 |
| Smith et al, 1966 ⁵ | 1 | 900 | 1.7 | ... |

*ADR indicates adverse drug reaction; ADRAd, an ADR causing admission to the hospital; and ellipses, data not available.

†Unlike Table 1, the column "All Severities" is missing from Table 2 because all ADRAds are classified as serious by definition.

‡Wards studied: 1, medical; 2, surgical; 3, geriatric; 4, pediatric; 5, psychiatric; 6, internal medicine; 7, intensive care; and 8, obstetric.

§Incidence of ADRs = (number of patients with ADR/total patients studied) × 100.

of these 89 studies are given in Tables 1 and 2.^{4,7,9,14-48} Fifty-seven studies were excluded from our meta-analysis by the 2 blinded investigators because they did not meet our criteria. In addition 57 of the remaining 96 studies were performed in countries other than the United States and were excluded from

our meta-analysis because one of our major goals was to determine representativeness of our sample in order to establish the accuracy of our summary statistics. Since we only had a sufficient number of studies from the United States to allow us to perform these tasks, we decided to exclude the remaining

countries from our meta-analysis since a proper analysis for representativeness for any other country would be impossible to perform.

Incidence of ADRs

As shown in Table 3, the incidence of serious ADRIn was 2.1% (95% CI, 1.9%-2.2%) of hospital patients, while the incidence of serious ADRAd was 4.7% (95% CI, 3.1%-6.2%). The incidence of fatal ADRIn was 0.19% (95% CI, 0.13%-0.26%) of hospital patients and the incidence of fatal ADRAds was 0.13% (95% CI, 0.04%-0.21%). Combining ADRIn and ADRAd, the overall incidence of serious ADR was 6.7% (95% CI, 5.2%-8.2%) of hospital patients and the overall incidence of fatal ADRs was 0.32% (95% CI, 0.23%-0.41%). The incidence of ADRIn of all severities (including nonserious and serious) was 10.9% (95% CI, 7.9%-13.9%) of hospital patients. The overall incidence of ADRIn plus ADRAd for ADRs of all severities was 15.1% (95% CI, 12.0%-18.1%) of hospital patients.

Eight ADRIn articles included the proportion of type A⁴⁴ (dose-dependent ADRs) and type B⁴⁴ (idiosyncratic and/or allergic ADRs). Of the "all severities" ADRIn, 76.2% (95% CI, 71.0%-81.4%) were type A reactions and 23.8% (95% CI, 18.6%-29.0%) were type B reactions. Unfortunately, none of these studies reported the proportion of type A and type B reactions for serious and fatal ADRs.

Number of Hospital Patients With ADRs

As shown in Table 4, we estimated that 702 000 (95% CI, 635 000-770 000) hospital patients in the United States experienced a serious ADRIn in 1994. We calculated that 1 547 000 (95% CI, 1 033 000-2 060 000) hospital patients experienced a serious ADRAd. Combining these values, overall 2 216 000 (95% CI, 1 721 000-2 711 000) hospital patients experienced a serious ADR in the United States in 1994. We calculated that there were 62 000 (95% CI, 41 000-85 000) fatalities due to ADRIn and another 43 000 (95% CI, 15 000-71 000) deaths occurred in association with ADRAd in the United States. Overall in 1994, we estimated that 106 000 (95% CI, 76 000-137 000) deaths were caused by ADRs in the United States, which could account for 4.6% (95% CI, 3.3%-6.0%) of the 2 286 000 recorded deaths from all causes during 1994 in the United States.¹⁸ Using the mean ADR incidence (106 000) or the more conservative lower 95% CI (76 000), we found that fatal ADRs ranked between the fourth and sixth leading cause of death in the United States in 1994.

Table 3.—ADR Incidence According to ADR Severity*

| ADR Group | No. of Studies | Total Patients Studied | Incidence of ADRs, % | 95% CI |
|---|----------------|------------------------|----------------------|-----------|
| ADRs in Patients While in the Hospital (ADRIn) | | | | |
| All severities | 18 | 34 463 | 10.9 | 7.9-13.9 |
| Serious | 12 | 22 502 | 2.1 | 1.3-2.3 |
| Fatal | 10 | 28 872 | 0.19 | 0.13-0.28 |
| Patients Admitted to the Hospital Due to an ADR (ADRAd) | | | | |
| Serious† | 21 | 28 017 | 4.7 | 3.1-6.2 |
| Fatal | 8 | 17 753 | 0.13 | 0.04-0.21 |
| Overall ADR Incidence (ADRIn + ADRAd)‡ | | | | |
| All severities | 39 | 82 480 | 15.1 | 12.0-18.1 |
| Serious | 33 | 50 519 | 6.7 | 5.2-8.2 |
| Fatal | 18 | 46 625 | 0.32 | 0.23-0.41 |

*ADR indicates adverse drug reaction; ADRIn, an ADR occurring in patients while in the hospital; CI, confidence interval; and ADRAd, an ADR causing admission to the hospital.
 †By definition, all ADRAds are serious, hence there is no "All Severities" category for ADRAd.
 ‡Overall incidence is adjusted to avoid double counting (see "Methods" section).

Table 4.—Estimated Number of Hospital Patients in 1994 With ADRs, in Thousands (95% CI)†

| | ADRIn | ADRAd | Overall |
|----------------|------------------|-------------------|------------------|
| All severities | 3607 (2618-4596) | 1547 (1033-2060)‡ | 4986 (3976-5995) |
| Serious | 702 (635-770) | 1547 (1033-2060) | 2216 (1727-2711) |
| Fatal | 83 (41-85) | 43 (15-71) | 106 (76-137)§ |

*ADR indicates adverse drug reaction; CI, confidence interval; ADRIn, an ADR occurring in patients while in the hospital; and ADRAd, an ADR causing admission to the hospital.
 †Based on 33 125 482 US admissions¹⁹ in 1994; estimates use values from Table 3 (eg, for all severities ADRIn: 33 125 482 × 0.1089 = 3 607 000 patients with an ADR).
 ‡By definition all ADRAds are serious, hence there are no data for nonserious ADRs in this category.
 §From these numbers, we estimated that ADRs were the fourth to sixth leading cause of death in the United States.

Representativeness of Our Sample

Among the many factors possibly influencing ADR incidence, considerable research has identified average length of stay,^{45,46} age,^{45,47} gender,^{48,49} and drug exposure.^{46,48} Therefore, as shown in Table 5, we checked to see whether the population that we sampled was representative of the US hospital population⁵⁰ vis-à-vis these 4 factors. We determined that the differences were significant for length of stay and gender but not for age. Unfortunately, we were unable to find values for the average number of drug exposures from national statistics. Possible biases in our ADR incidence that may have been caused by the differences in length of stay or gender are estimated in the "Comment" section.

Another possible source of sampling bias might be the year of study, as our meta-analysis spans 4 decades. Hence, we studied the relationship between ADR incidence and year of study using a random-effects linear regression model and found no significant correlation for ADRIn ($r=0.27$, $P=.14$, $n=18$) or for ADRAd ($r=0.23$, $P=.24$, $n=21$). The Figure shows these results graphically and indicates that no change in ADR incidence occurred over the span of our study. This result seems surprising since great changes have occurred over the last 4 decades in US hospitals that should have affected the incidence of ADRs. Perhaps, while length of hospital stay is decreasing,⁵¹ the num-

ber of drugs per day may be rising to compensate. Therefore, while the actual incidence of ADRs has not changed over the last 32 years, the pattern of their occurrence has, undoubtedly, changed.

It should be noted that additional factors have been proposed to have an effect on ADR rate: renal function, hepatic function, alcoholism, drug abuse, and severity of illness.^{52,53} Unfortunately, these factors were rarely reported in our sample of studies and, thus, could not be used to determine representativeness.

Medical wards are overrepresented in our database, and some articles in the literature suggest that ward type might have an effect on ADR incidence.^{54,55,56} Unfortunately, there is insufficient power in the 39 studies to calculate the incidence of ADRs for each ward type individually. Without these data, we cannot determine the possible effect that ward-type distribution might have on our ADR incidence. Nevertheless, in the "Comment" section, we estimate the possible bias due to ward type.

Similar to ward type, hospital type may also introduce bias into our results. It is thought that teaching hospitals contain more seriously ill patients than nonteaching hospitals, which may lead to a higher incidence of ADRs in teaching hospitals, but this has never been proven.^{55,56} Teaching hospitals are overrepresented in our sample. However, when we compared ADR incidences for teaching and nonteaching hospitals in

Table 5.—Is Our Sample Representative of US Hospitals?

| Factor | US Hospitals* | Our Sample† | No. of Studies‡ |
|---------------------------|---------------|-------------|-----------------|
| Average age, y§ | 50.4 | 54.1 | 11 |
| Average length of stay, d | 7.6 | 10.6 | 14 |
| Average drug exposure¶ | ... | 8.0 | 7 |
| Proportion female | 0.60 | 0.50 | 16 |

*Statistics in this column were derived from data by the National Hospital Discharge Survey.⁵⁰
 †Values in this column were derived from combining our ADRIn (adverse drug reaction [ADR] occurring in patients while in the hospital) and ADRAd (ADR causing admission to the hospital) studies to increase the sample size, except for average drug exposure, for which data were unavailable for the ADRAd group.
 ‡The number of studies among the 39 US articles that provided data on this factor.
 § $P = .53$ (Student t test).
 || $P < .001$ (Student t test).
 |||No statistic could be obtained for the average drug exposure in US hospital patients; ellipses indicate data not available.

our study, we found no significant differences. Thus, despite an overrepresentation of teaching hospitals in our sample, there may not be a major bias.

Finally, our letters to researchers in the field produced no evidence of publication bias.

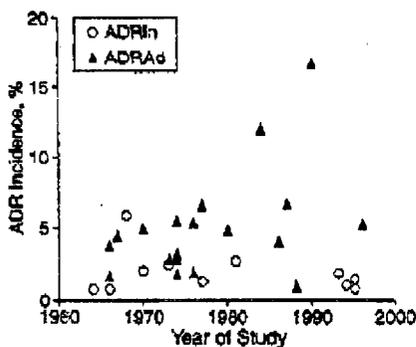
COMMENT

We have found that serious ADRs are frequent and more so than generally recognized. Fatal ADRs appear to be between the fourth and sixth leading cause of death. Their incidence has remained stable over the last 30 years.

There has been only one previous meta-analysis of ADR hospital studies,¹⁶ and it focused only on ADRAd. Our article differs from this report in many respects: (1) we studied incidence of ADRIn as well as ADRAd, (2) we combined ADRAd and ADRIn to obtain the overall incidence of ADRs, (3) we gave special emphasis to serious and fatal ADRs, (4) we improved the quality of the data by excluding retrospective studies and by excluding ADRs that were classified as "possible," (5) we examined the representativeness of our sample, and (6) we estimated the total number of patients in US hospitals experiencing ADRs.

Recent studies have focused on ADEs, which include errors in administration.^{3,19,20} One of the goals of ADE research is to alert physicians about the preventability of many ADEs.²⁰ In contrast, our study on ADRs, which excludes medication errors, had a different objective: to show that there are a large number of serious ADRs even when the drugs are properly prescribed and administered.

We found that a high proportion of ADRs (76.2%) were type A reactions. This may suggest that many ADRs are due to the use of drugs with unavoidably



Incidence of adverse drug reactions (ADRs) in 39 studies distributed over 32 years. All 39 points are not visible as several are superimposed on each other. Linear regression, using a random-effects model, showed no significant correlation for either those experiencing an ADR while in the hospital (ADRIn) ($r=0.27$, $P=.14$) or those admitted to the hospital due to an ADR (ADRAd) ($r=0.23$, $P=.34$).

high toxicity. For example, warfarin often results in bleeding. It has been shown that careful drug monitoring in hospitals leads to a reduction of many of these ADRs, suggesting that some type A and type B ADRs may be due to inadequate monitoring of therapies and doses.²⁶

Recent studies have shown that the costs associated with ADRs may be very high. Research to determine the hospital costs directly attributable to an ADR estimated that ADRs may lead to an additional \$1.56 to \$4 billion in direct hospital costs per year in the United States.^{27,28}

Heterogeneity

As outlined in the "Methods" section, we dealt with heterogeneity in numerous ways. After taking these measures, we examined the remaining heterogeneity. We determined whether 4 factors thought to affect ADR incidence (age, gender, drug exposure, and length of stay) contributed to the remaining heterogeneity in our data using a linear regression version of the random-effects model.¹⁵ For ADRIn, we found that number of drug exposures and length of hospital stay jointly accounted for 43% of the variance ($r=0.65$, $P=.009$, $n=13$). For the rate of ADRAd, when age was included in the model, the variance was reduced by 27% ($r=0.52$, $P=.04$, $n=14$). Gender did not contribute to the variance. Thus, a great deal of the heterogeneity could be attributed to factors well known to affect ADR rates: number of drug exposures per patient, length of hospital stay, and the age of patients. This result indicates that much of the heterogeneity is due to variation in the populations examined in the various ar-

ticles and, hence, only a portion of the variation could merely be attributed to inconsistent methods among the individual studies. For example, if the different investigators use different methods of ascertainment regarding what represents an ADR, they will find different rates. Another example of inconsistent methodology is the problem that some articles did not separate out administration errors. Methodological variation such as this is a limitation of meta-analysis.

Representativeness of Our Sample

In the "Results" section, we found that for the 5 factors examined 3 were possible sources of bias: length of stay, gender, and ward type. Thus, we have attempted to estimate the size of the sampling bias due to these 3 factors as follows. As seen in Table 5, we had a higher average length of hospital stay than the US national average (10.6 days vs 7.6 days).¹⁸ While the literature qualitatively reports a relationship between the incidence of ADRIn and length of stay,^{21,42,43} there are no quantitative estimates. Therefore, we performed a linear regression analysis on our own data using a random-effects model¹⁵ regressing the incidence of ADRIn of all severities on average length of stay to obtain a slope of 0.007 ($P=.008$) and deduced that increasing the length of hospital stay from 7.6 to 10.6 days would possibly cause the incidence of ADRIn of all severities to rise from the adjusted value of 8.7% to our value of 10.9%.

Also, as shown in Table 5, the proportion of female patients in our sample was lower than the national average (50% vs 60%). Using several studies reporting an increased incidence of ADRs among females, we were able to determine that, at most, the risk ratio for women vs men could be as high as 1.5 for both ADRIn and ADRAd. Assuming the worst-case scenario, the adjusted value for the overall incidence of ADRs of all severities in the United States becomes 15.7% (95% CI, 12.7%-18.8%) compared with our value of 16.1% (95% CI, 12.0%-18.1%).

Finally, with regard to ward type, there was insufficient power in 39 studies to determine precisely the effect of ward-type discrepancies. Instead, we made a crude determination of the worst-case scenario of ward bias. If we assumed (1) that obstetrical wards have zero ADRs and (2) that we sampled zero obstetrical patients, and, since there are about 4 million obstetrical ward patients each year in the United States⁴⁴ of 33 million total hospital admissions,⁴⁵ then the total number of ADRs occurring in the United States would be 4/33 lower than our estimates. Thus the overall

number of fatal ADRs in the United States would drop from 106 000 (95% CI, 76 000-137 000) to 93 000 (95% CI, 67 000-121 000), which would make ADRs between the fourth and seventh leading cause of death in the United States rather than between the fourth and sixth leading cause as reported above. Regarding other ward types, psychiatric wards tend to have a higher ADR incidence and pediatric wards a lower ADR incidence than medical wards,^{53,54} so these 2 biases might cancel out. Thus, altogether, there probably is a small net upward bias in our ADR incidence due to our overrepresentation of medical wards.

It is important to note that we have taken a conservative approach, and this keeps the ADR estimates low by excluding errors in administration, overdose, drug abuse, therapeutic failures, and possible ADRs. Hence, we are probably not overestimating the incidence of ADRs despite the 3 small sampling biases discussed earlier.

CONCLUSIONS

Perhaps, our most surprising result was the large number of fatal ADRs. We estimated that in 1994 in the United States 106 000 (95% CI, 76 000-137 000) hospital patients died from an ADR. Thus, we deduced that ADRs may rank from the fourth to sixth leading cause of death. Even if the lower confidence limit of 76 000 fatalities was used to be conservative, we estimated that ADRs could still constitute the sixth leading cause of death in the United States, after heart disease (743 460), cancer (529 904), stroke (150 108), pulmonary disease (101 077), and accidents (90 523); this would rank ADRs ahead of pneumonia (75 719) and diabetes (58 894).¹⁴ Moreover, when we used the mean value of 106 000 fatalities, we estimated that ADRs could rank fourth, after heart disease, cancer, and stroke as a leading cause of death. While our results must be viewed with some circumspection because of the heterogeneity among the studies and small biases in the sample, these data suggest that ADRs represent an important clinical issue.

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A complete list of the 164 papers excluded from our meta-analysis is available on request from the authors.

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